The Synthesis and Photochemistry of Pyrano[2,3-*c*]pyrazoles

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A Thesis
Submitted to the Faculty of the

WORCESTER POLYTECHNIC INSTITUTE

In partial fulfillment of the requirements for the
Degree of Master of Science
in
Chemistry

By

May 2006

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ABSTRACT

Two different synthetic approaches to the synthesis of pyrano[2,3-*c*]pyrazoles have been investigated. In one approach, dehydroacetic acid derivatives were treated with phenylhydrazine and methylhydrazine led to the formation of the phenylhydrazones and methylhydrazones, which undergo rearrangement in refluxing acetic acid to diketo-phenylpyrazoles and diketo-methylpyrazoles. Upon treatment with a mixture of acetic and sulfuric acid these compounds isomerize to the phenylpyrano[2,3-*c*]pyrazol-4-one and methylpyrano[2,3-*c*]pyrazol-4-one derivatives.

In a second approach, phenylhydrazine and methylhydrazine reacted with dimethyl(methoxymethylene)malonate **(34)** to give phenylpyrazole and methylpyrazole ester derivatives which were converted to phenylpyrazolone and methylpyrazolone by hydrolysis and decarboxylation. C-acylation of these compounds with trans-cinnamoyl chloride gave α,β-unsaturated-4-acetyl-5-hydroxypyrazoles. Bromination of these α,β-unsaturated-4-acetyl-5-hydroxypyrazoles with spontaneous cyclization, followed by dehydrobromination led to pyrano[2,3-*c*]pyrazol-4-one derivatives, respectively.

Phototochemical excitation of 1-phenyl and 1-methylpyrano[2,3-*c*]pyrazol-4-ones in acetonitrile led to the formation of cis-head-to-tail [2+2] cycloaddition products. Irradiation in ethanol solvent led to photodimerization and to photofragmentation to yield pyrazole ethylesters.

ACKNOWLEDGEMENT

I would like to express my sincere thanks to both of my supervisors, Professor James W. Pavlik and Professor Supawan Tantayanon who gave me the opportunity to conduct graduate research at Worcester Polytechnic Institute. Definitely, without the guidence of my supervisors, this thesis would not be complete.

I also want to thank Dr. Chuchawin Changtong, who taught me the value of hard work and supported me during the whole tenure of my research. In addition, I would like to thank Nantanit Wanichacheva, who gave me her loving support and understanding. The encouragement and inspiration were given to me to carry out my life in USA by Jessica A. Martinez, who is the best friend.

I will never forget IGSD and the Department of Chemistry and Biochemistry at Worcester Polytechnic Institute, since they provided me with financial aid assistant to support my studies.

I also enjoyed my work with the other graduate students, namely Dr. Somchoke Laohhasurayotin, Man Phewluangdee, Tharinee Vongnakorn, Marta Dabros, and Salimgerey Adilov.

Lastly, I would like to share this moment of happiness with my mother Pansupa Ervithayasuporn, who gave me enormous support and motivation during my entire life.

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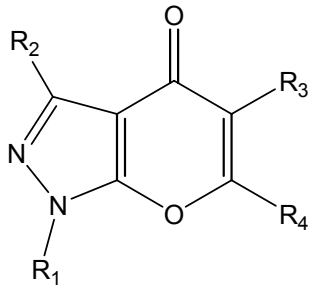
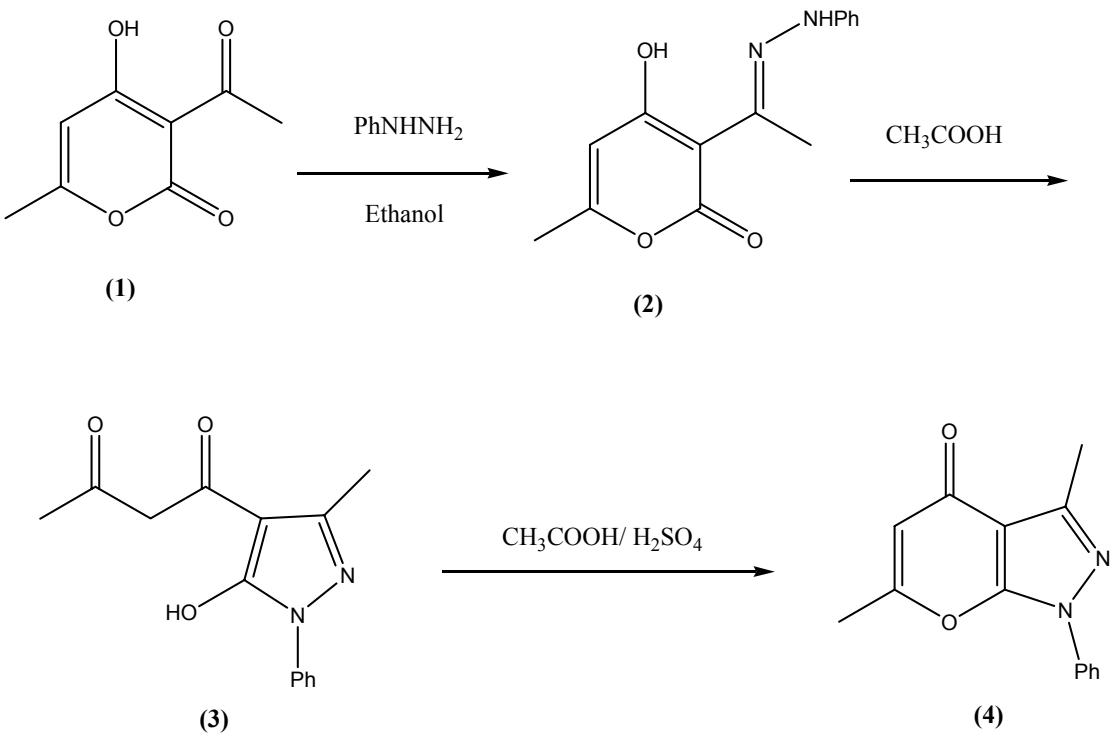
INTRODUCTION

Pyranopyrazoles are known to exhibit a wide range of biological activities.[1-2] Some pyrano[2,3-c]pyrazoles have been evaluated for their bovine brain adenosine A_1 A_{2A} receptor binding affinity and these pyranopyrazoles are also of interest because of their structural similarity to a wide variety of flavones and flavanones that exhibit interesting biological activity.[1-2] Although the synthesis[2-4] of pyranopyrazoles of type **A** has been known, the photochemical studies have not been reported.



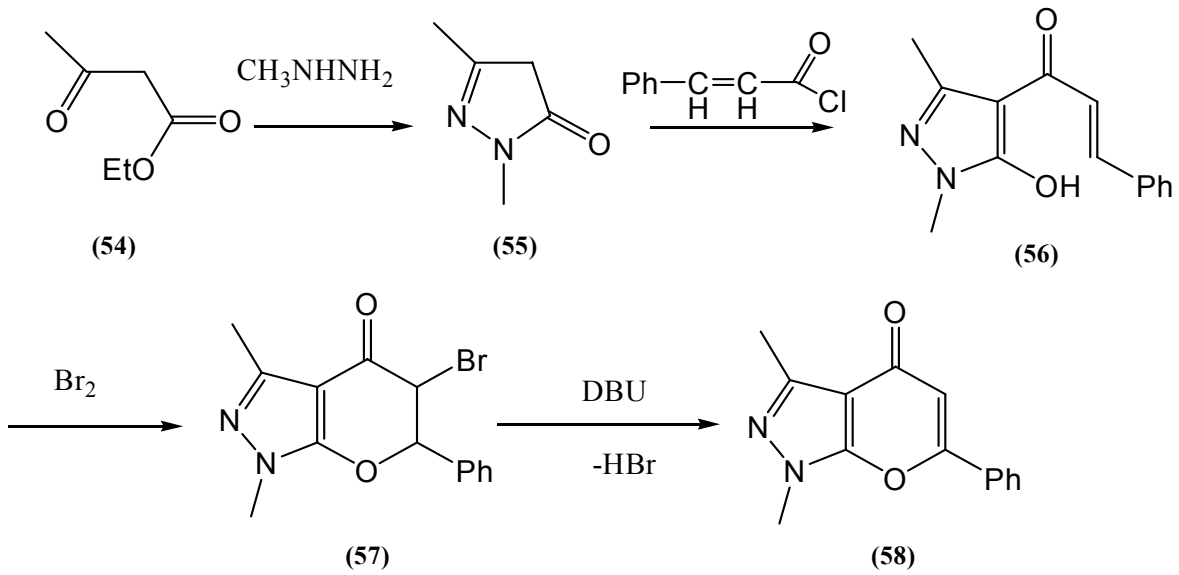
A

Previous work has shown that pyrano[2,3-*c*]pyrazol-4-ones can be synthesized by many different processes, depending upon the condition employed.[2-4] Dehydroacetic acid, 3-acetyl-4-hydroxy-6-methyl-2*H*-pyran-2-one **(1)**, has been reported to generate a number of heterocyclic compounds through ring opening and recyclization upon treatment with a variety of binucleophiles.[2-3] One such significant reaction was the synthesis of 3,6-dimethyl-1-phenylpyrano[2,3-*c*]pyrazole-4(1*H*)-one **(4)** by Gelin *et al.*[2] in 1983 and is shown in Scheme 1. These approaches will be studied in order to determine the synthetic scope and generality of the method for the synthesis of N-methyl and N-phenylpyranopyrazoles.



Scheme 1: Synthesis of 3,6-dimethyl-1-phenylpyrano[2,3-*c*]pyrazole-4(1*H*)-one by Gelin's method.

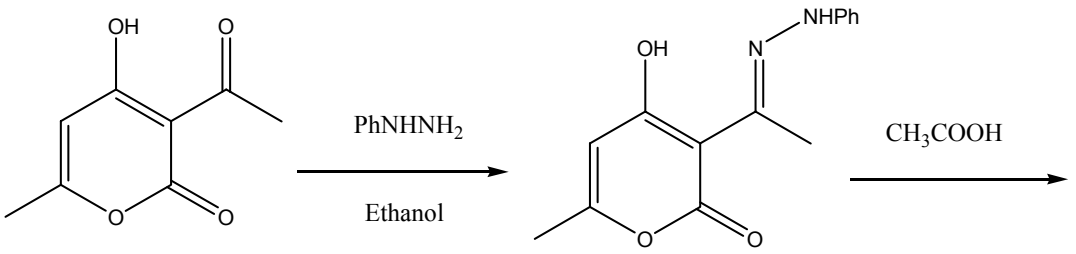
Carbon-carbon bond formation is basic to organic synthesis. Progress is made by extending the scope of already-known transformations. One of the most relevant methods for the synthesis of pyrano[2,3-*c*]pyrazol-4-ones consists in the transformation of pyrazolones into the corresponding α,β-unsaturated-4-acetyl-5-hydroxypyrazoles via base-induced acylation.[2,4] Bromination of the α,β-unsaturated-4-acetyl-5-hydroxypyrazoles with spontaneous cyclization, followed by dehydrobromination then leads to pyrano[2,3-*c*]pyrazol-4-ones.[2,4] For example, a synthetic approach to 1,3-dimethyl-6-phenylpyrano[2,3-*c*]pyrazole-4(1*H*)-one **(58)** has been published by Heinisch and colleagues[4] and is shown in Scheme 2.



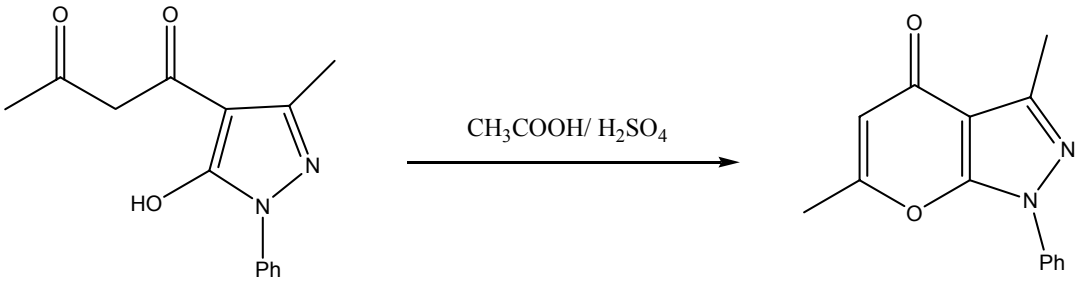
Scheme 2: Synthesis of 1,3-dimethyl-6-phenylpyrano[2,3-*c*]pyrazole-4(1*H*)-one by Heinisch's method.

RESULT AND DISCUSSION

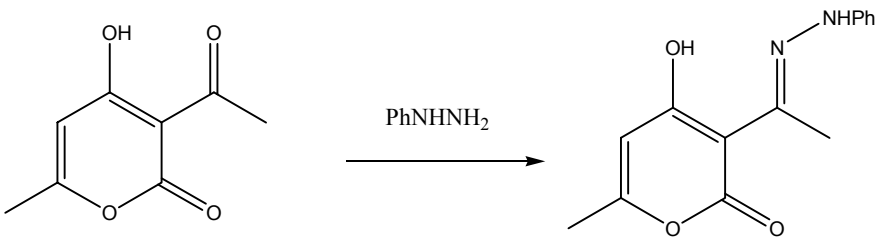
One approach to the synthesis of N-phenylpyranopyrazole **4** starts with the readily available dehydroacetic acid **1**. As shown below, according to the work of Gelin, S. and colleague,[3] dehydroacetic acid is first converted to its phenylhydrazone **3**. Upon treatment with acetic acid, phenylhydrazone **3** is reported[3] to undergo isomerization to diketo-N-phenylpyrazole **3**, which upon treatment with a mixture of acetic and sulfuric acid undergoes isomerization to the N-phenylpyranopyrazole **4**.[3]



(1) **(2)**



(3) **(4)**



(1) **(2)**

Scheme 3: Synthesis of 4-Hydroxy-6-methyl-3-(1-(2-phenylhydrazono)ethyl)-2*H*-pyran-2-one **(2)**.

In order to evaluate the literature procedure,[3] dehydroacetic acid **(1)** was treated with phenylhydrazine at 80°C for a few minutes. 4-Hydroxy-6-methyl-3-(1-(2-phenylhydrazono)ethyl)-2*H*-pyran-2-one **(2)** was obtained in a yield of 95%, mp 206-207°C (Lit.[3] mp 211-212°C) (Scheme 3).

(a)

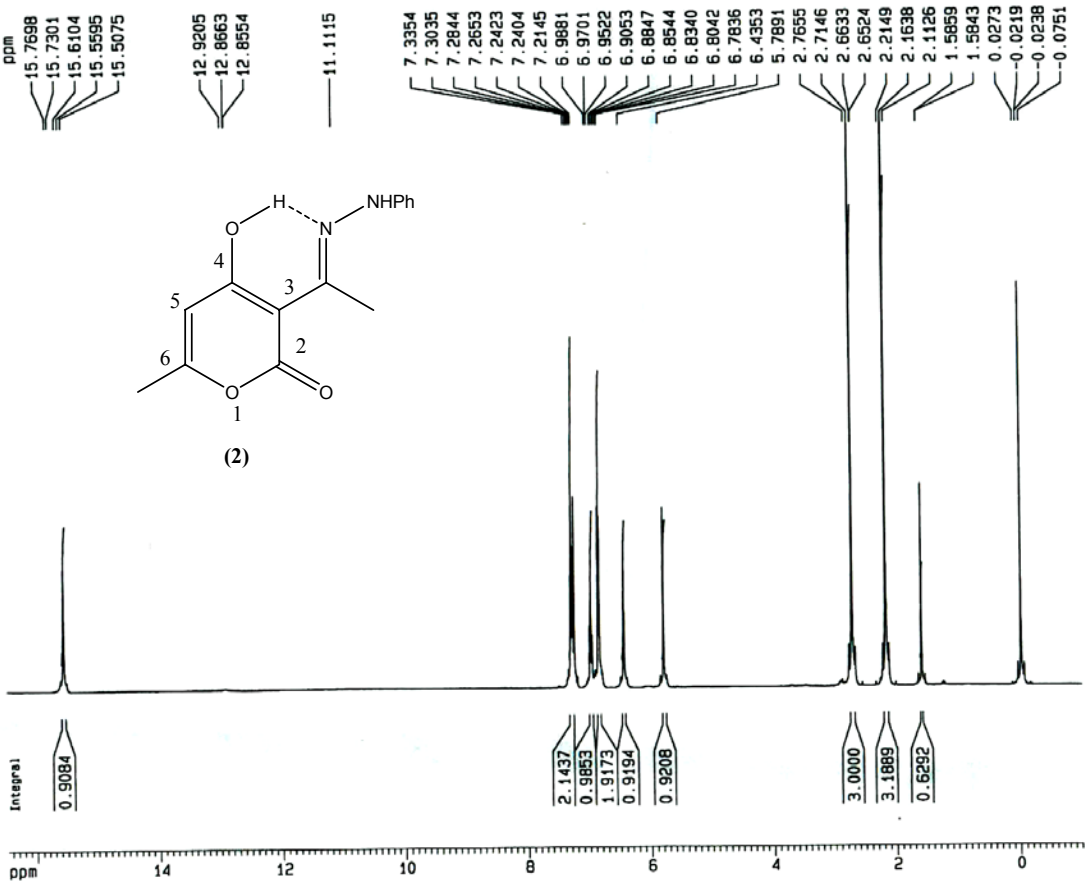
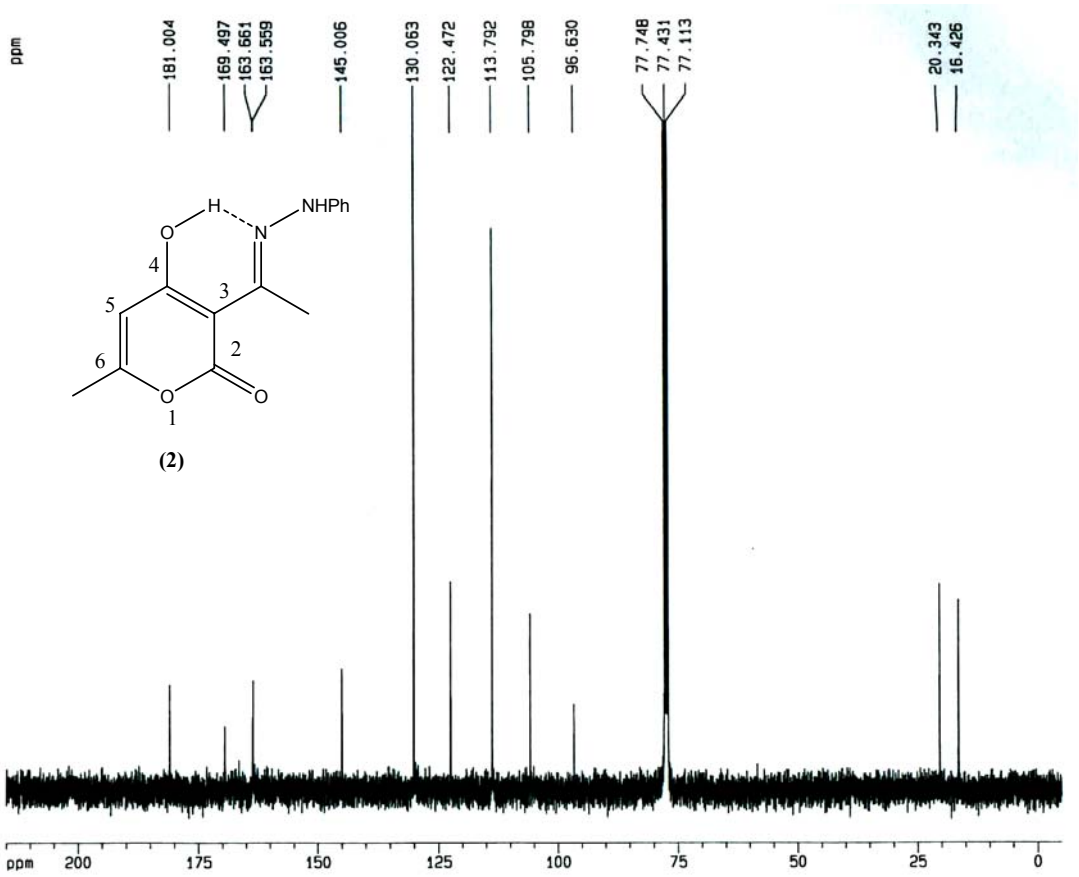


Figure 1(a) shows the ^{1}H-NMR spectrum of the yellow crystals which is consistent with the structure of **2.** The two methyl groups of the pyrone ring and hydrazone side chain appear as singlets at δ 2.16 (3H) and 2.71 (3H), respectively. In addition, the two triplets at δ 7.33 (2H; J = 7.6 Hz) and 6.98 (1H; J = 7.1 Hz) and the doublet at δ 6.90 (2H; J = 8.1 Hz) are due to absorptions of the phenyl ring protons at the meta, para, and ortho positions, respectively. Also, a key proton of the pyrone ring appears as a singlet at δ 6.43. The signals at δ 15.6 and 5.78 are due to the enol proton and the proton bonded to nitrogen in the hydrazone group, respectively. As expected for protons bonded to O and N, when compound **2** was treated with D_2O, these signals disappeared.

(b)



(2)

The ^{13}C-NMR spectrum (Figure 1(b)) is also consistent with the structure **2**. The enol carbon of the pyrone ring absorbs the furthest downfield at δ 181.0. The signal at δ 169.5 was assigned to the hydrazone carbon. The carbons at positions 2, 3, 5 and 6 of the pyrone ring appear at δ 163.7, 96.6, 105.8, and 163.6 respectively. The phenyl ring carbons attached to the nitrogen atom and at the para position absorb at δ 145.0 and 122.5 respectively, while the ortho and meta carbons of the phenyl ring appear as two singlets at δ 113.8 and 130.1, respectively. The methyl carbons of the pyrone ring and hydrazone functional group are observed at δ 20.3 and 16.4, respectively. These assignments are consistent with the ^{13}C-DEPT 135 spectrum (Figure 1(c)).

(c)

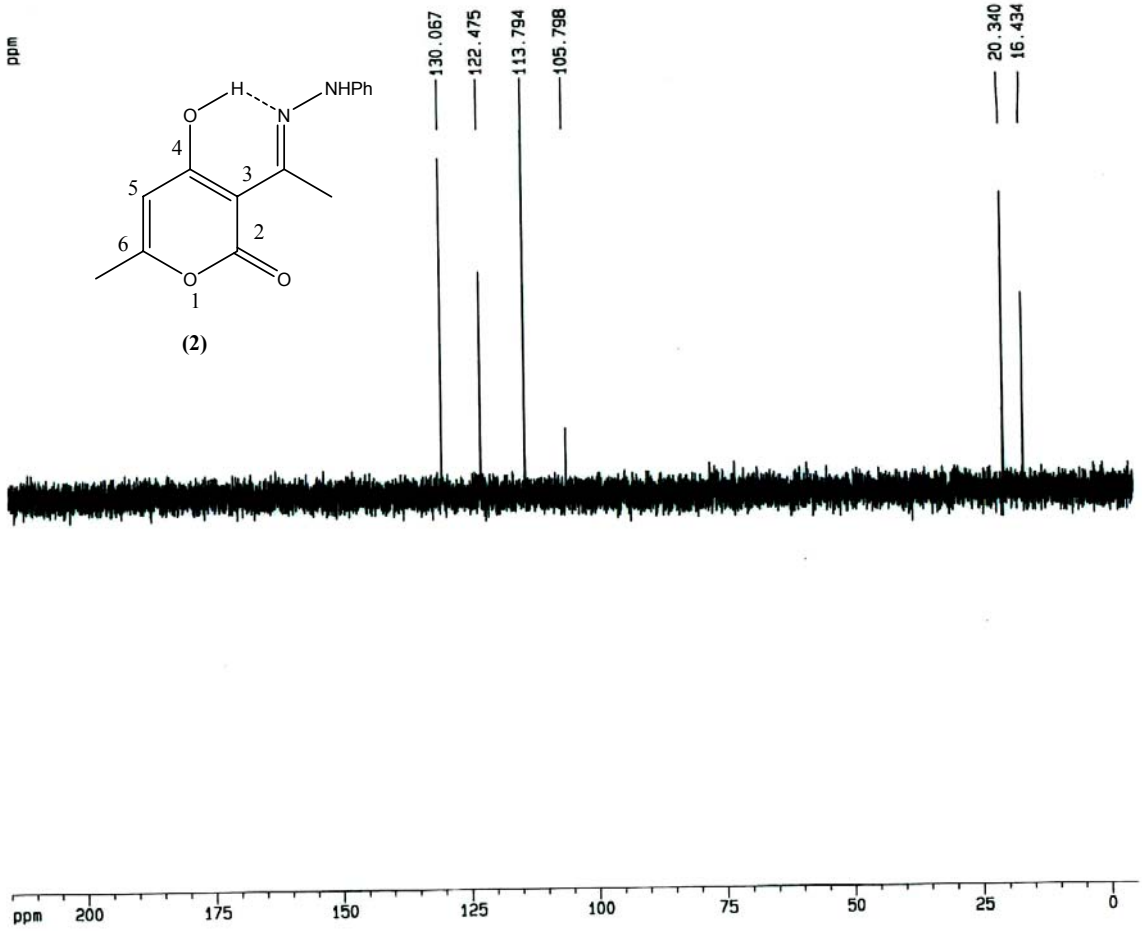
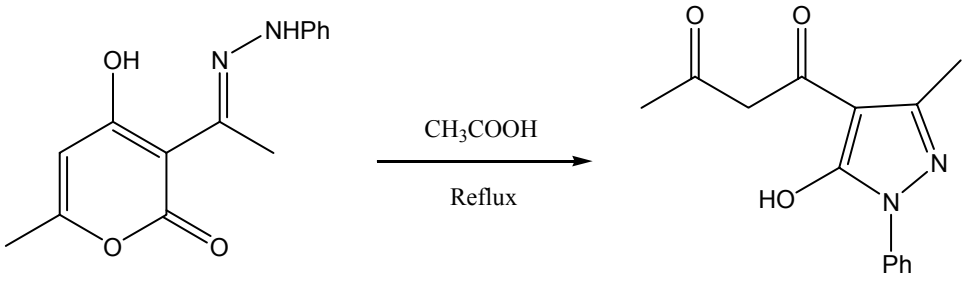


Figure 1: (a) ^{1}H-NMR of compound **2**; (b) ^{13}C-NMR of compound **2**; (c) ^{13}C-NMR DEPT 135 of compound **2**.

The six signals at δ 181.0, 169.5, 163.7, 163.6, 145.0, and 96.6 disappeared which is consistent with their assignment to the six quaternary carbons at position 1 of the phenyl ring, the four carbons of the pyrone ring, and the hydrazone carbon. In contrast, the signals at δ 130.1, 122.5, 113.8, 105.8, 20.3, and 16.4 still appear in the positive direction which is consistent with their assignment to the three CH type carbons of the phenyl ring, the CH type carbon of the pyrone ring, and the methyl carbons of the pyrone ring and the hydrazone group.



(2) **(3)**

Scheme 4: Synthesis of 1-(5-hydroxy-3-methyl-1-phenyl-1*H*-pyrazol-4-yl)butane-1,3-dione **(3)**.

The literature reported[3] the conversion of **2** to 1-(5-hydroxy-3-methyl-1-phenyl-1*H*-pyrazol-4-yl)butane-1,3-dione **(3)**, a rearrangement involving a nitrogen nucleophilic attack at the C-2 lactone carbonyl with ring opening to **3**.[3] As reported in the literature,[3] when **2** was refluxed in acetic acid for one hour, **3** was formed in 72% yield, mp 95-97^{o}C (Lit.[3] mp 101^{o}C) (Scheme 4).

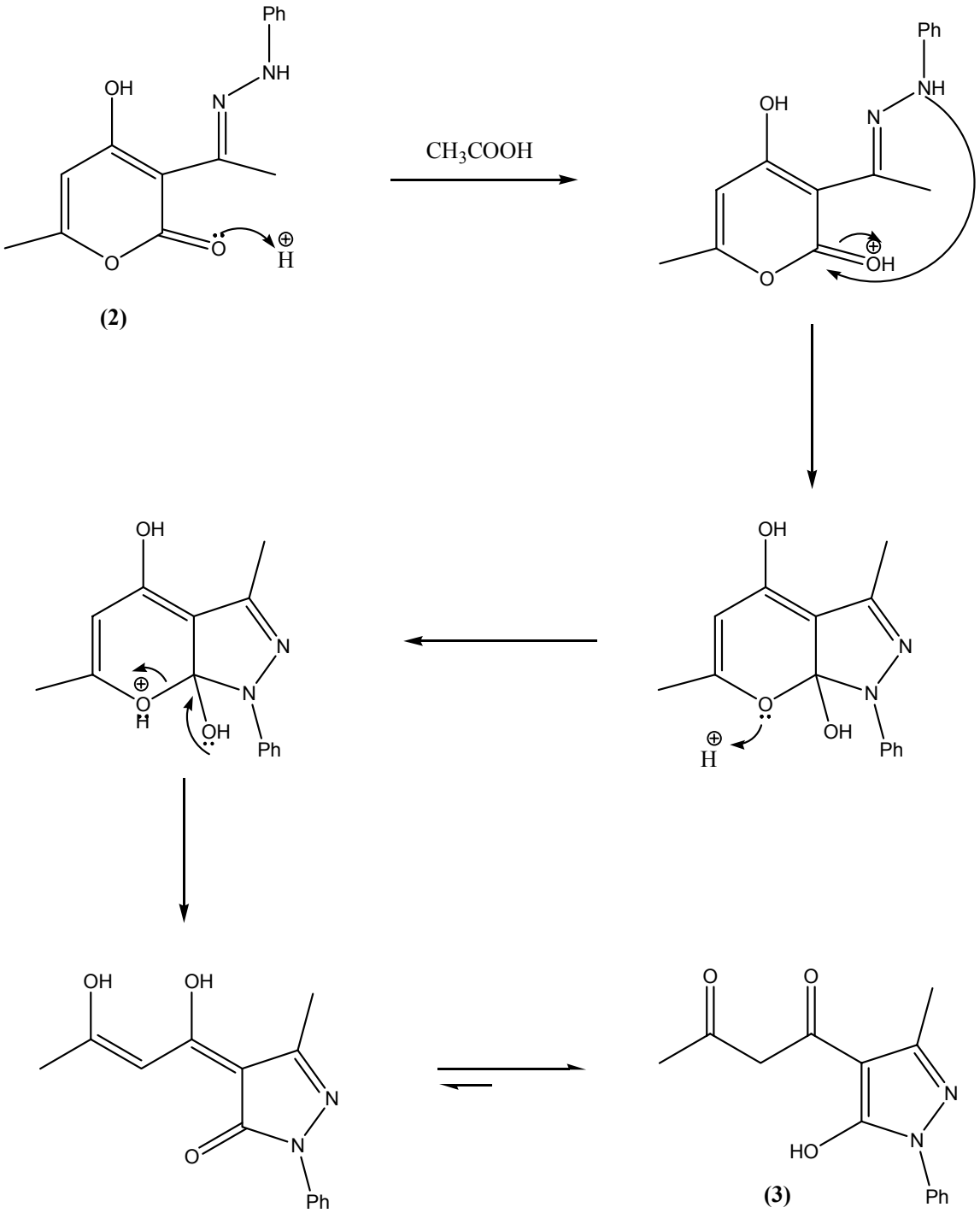


Figure 2: Mechanism of the formation **3**.

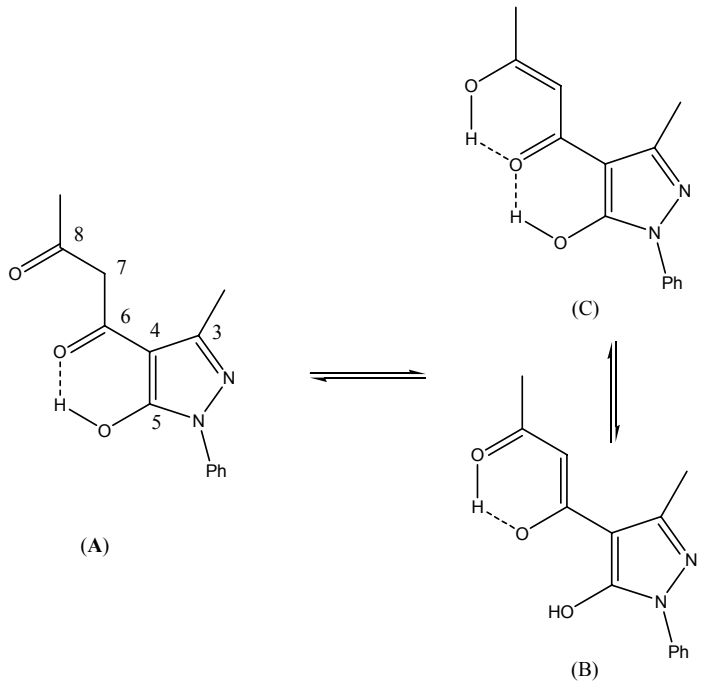
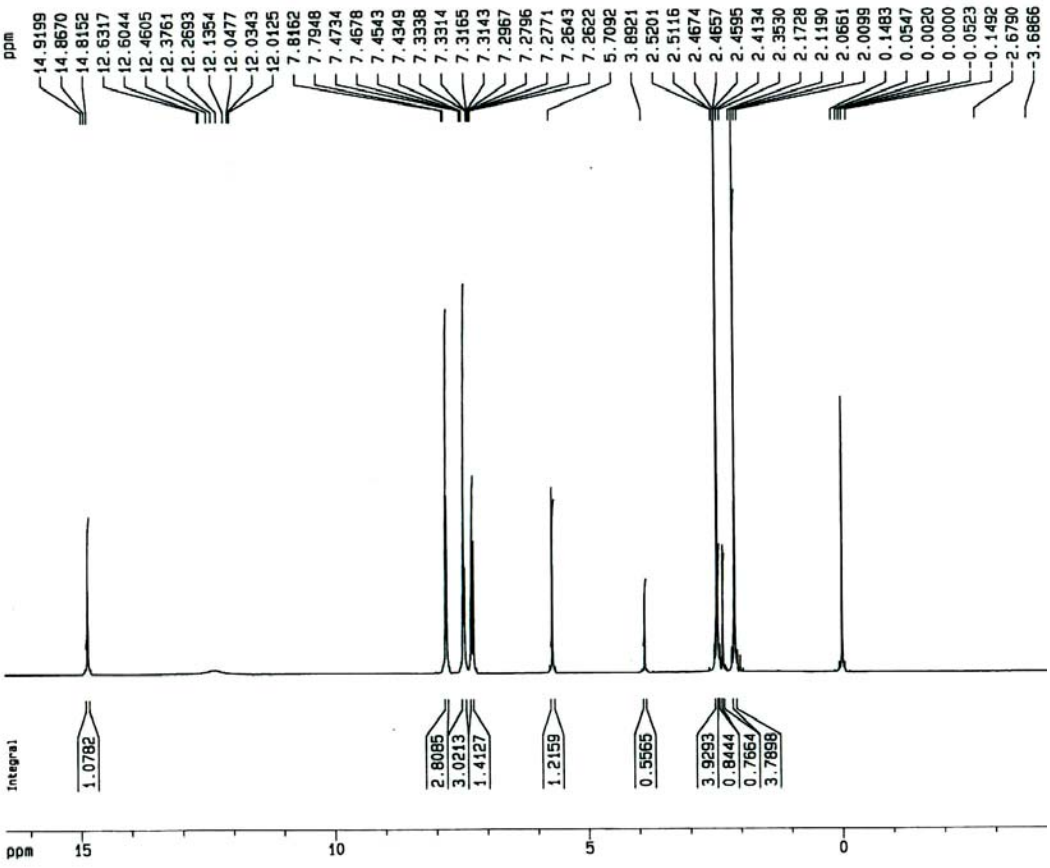


Figure 3: Tautomerization of compound **3**.

(a)

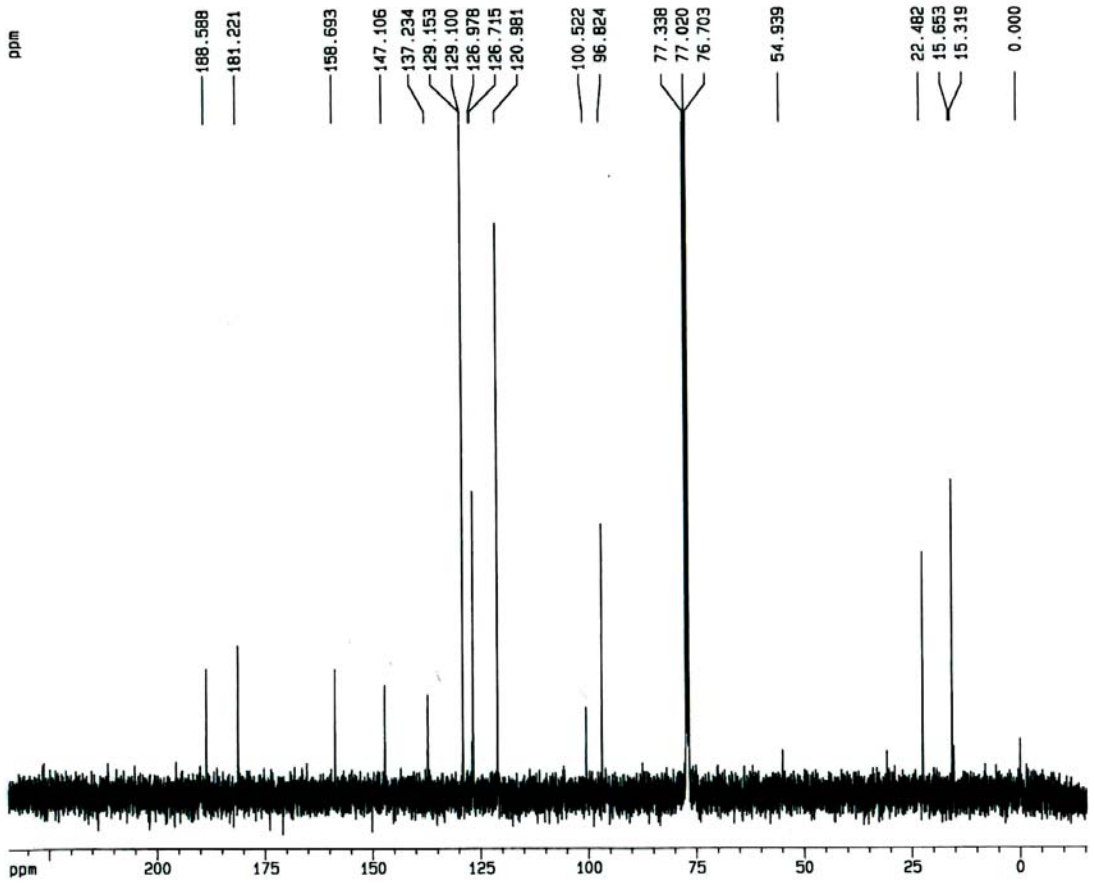


The ^{1}H-NMR spectrum (Figure 4(a)) shows that **3** is an equilibrium mixture of conformers A, B, and C. The equilibrium between keto form A and the two enol forms B and C is expected to be slow on the NMR time scale so that both the keto and enol forms are expected to be detected as distinct species. The equilibrium between B and C, however, is expected to be very fast and the NMR will detect one enol structure which would be an average of B and C.

The enol and keto forms are most easily detected by the signal at δ 5.71 for the vinyl proton in the enol structure and the signal at δ 3.89 for the methylene protons in the keto structure. Based on the integral rises of 1.22 and 0.556 respectively for these signals, and noting that they are due to 1H and 2H signals respectively, the enol to keto ratio is calculated to be 4.37 to 1.

The sharp peak down field at δ 14.9 (D_2O exchangeable) is consistent with the intramolecularly H-bonded enolic proton in enol tautomer (B $\rightleftharpoons$ C), while the very broad signal at δ 12.2 is more consistent with the more acidic, C-5 hydrogen bonded hydroxyl proton in tautomers A, B, and C. The singlet signals at δ 2.46 (3H) and 2.35 (3H) were assigned to the C-3 and C-8 methyl protons in tautomer A, respectively, while the singlet signals at δ 2.47 (3H) and 2.11 (3H) were assigned to the C-3 and C-8 methyl protons in tautomer B and C, respectively. In addition, the doublet at δ 7.81 (2H; J = 8.3 Hz), the two triplets at δ 7.47 (2H; J = 7.6 Hz), and 7.33 (1H; J = 6.8 Hz) are characteristic of the phenyl ring protons of all tautomers A, B, and C at ortho, meta, and para positions, respectively.

(b)



The ^{13}C-NMR spectrum (figure 4(b)) in $CDCl_3$ solution of compound **3** gives rise to two resonances for all the carbon atoms corresponding to the enol and keto tautomers. It is known that a hydrogen-bonded carbonyl carbon resonates at lower field than a corresponding free carbonyl carbon and that an enolic carbon atom resonates at higher field than a corresponding keto carbon atom, according to literature reported.[3] The C-6 resonance of the enol form (B $\rightleftharpoons$ C) would be at a lower field than the C-8 carbon atom. From the chemical shift values, respectively at δ 188.6 and 181.2, it can be reasonably concluded the enol tautomer contributes mainly to the tautomeric population in $CDCl_3$ solution. The characteristic ^{13}C-NMR spectrum of the enol tautomer at δ 188.6, 181.2, 96.8 and 22.5 is consistent with C-6, C-8, C-7, and methyl

C-8 on the side chain of the pyrazole ring, respectively. The carbons of the pyrazole ring at δ 158.7, 147.1 and 100.5 were assigned to C-5, C-3 and C-4, respectively. The phenyl ring carbons at the quaternary and para positions absorb at δ 137.2 and 126.9, while the ortho and meta positions in the phenyl ring appear as two singlets at δ 120.9 and 129.2 respectively. Thus, the C-3 methyl of the pyrazole ring was assigned to at the signal δ 15.6. On the other hand, the keto tautomer A could not be completely assigned in the ^{13}C-NMR spectrum because of the low intensity of the signals of this minor tautomer. However, the ^{13}C-NMR spectrum exhibits some key signals which could be assigned to the keto tautomer A. The signals at δ 54.9 and 30.8 are due to at C-7 methylene carbon and C-8 methyl group on the side chain, respectively. Also, the signal at δ 15.3 can be assigned to the C-3 methyl of the pyrazole ring.

These assignments are consistent with the NMR CH-correlation of compound **3** (Figure 4(c)).

(c)

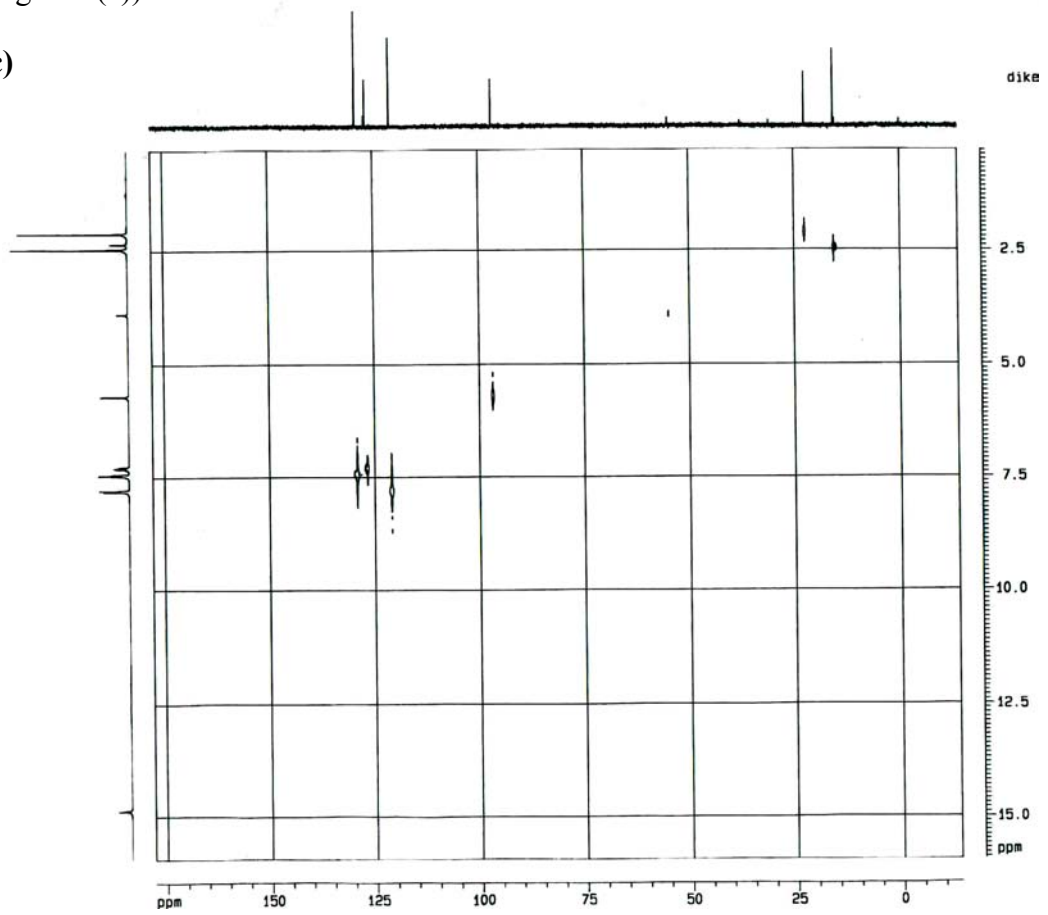
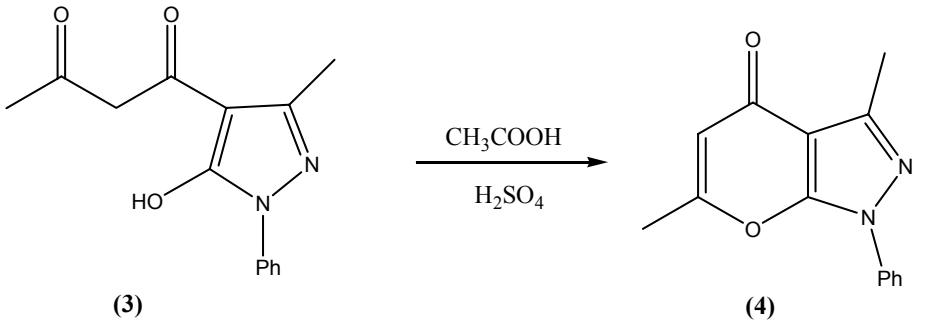


Figure 4: (a) ^{1}H-NMR of compound **3**; (b) ^{13}C-NMR of compound **3**; (c) NMR CH-correlation of compound **3**.

In order to confirm the ^{1}H and ^{13}C-NMR spectral assignments, the two dimensional CH correlation spectrum (Figure 4(c)) was recorded. The ^{13}C-NMR spectrum of the enol tautomer reveals that the two carbon signals at δ 22.5 and 15.6, which were assigned to the non-equivalent methyl carbon atoms and correlating with the two singlets of non-equivalent methyl groups at δ 2.11 and 2.47 in the ^{1}H spectrum, respectively. The signal in the ^{13}C spectrum at δ 96.8, which was assigned to the vinyl carbon, correlates with the singlet at δ 5.71, which was previously assigned to the vinyl proton. As expected, the three carbon signals at δ 129.2, 126.9, and 120.9, which were assigned to the carbons of the phenyl ring, correlate with the phenyl protons at δ 7.47, 7.33, and 7.81. In contrast, in the two dimensional spectrum the signals due to the keto tautomer A are of very low intensity and are not all observed. Some observed signals could be assigned. The ^{13}C spectrum at δ 54.9 correlates with C-7 methylene protons at δ 3.89, while the small signal at δ 15.3 correlates with the singlet proton at δ 2.46 which was assigned to the C-3 methyl group of the pyrazole ring.



(3) **(4)**

Scheme 5: Synthesis of 3,6-dimethyl-1-phenylpyrano[2,3-*c*]pyrazole-4(1*H*)-one **(4)**.

The ring closure of **3** to 3,6-dimethyl-1-phenylpyrano[2,3-*c*]pyrazole-4(1*H*)-one **(4)** which was reported in the literature,[3] was easily achieved by refluxing compound **3** in acetic acid in the presence of sulfuric acid as a catalyst to obtain **4** in a yield of 80 % , mp 148-149^{o}C (Lit.[3] mp 150^{o}C) (Scheme 5). This route allowed the conversion of dehydroacetic acid **1** to N-phenyl pyranopyrazole **4** in an overall yield of 55 %.

(a)

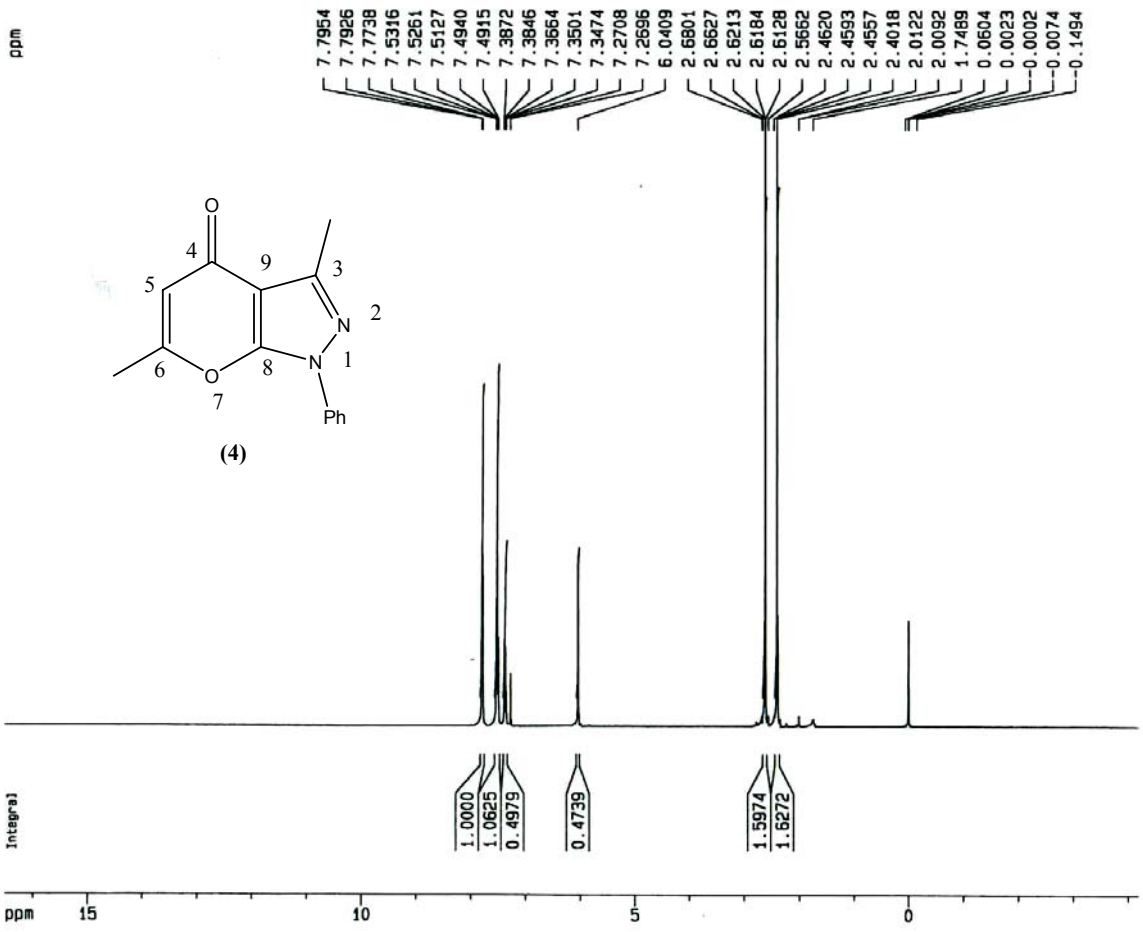
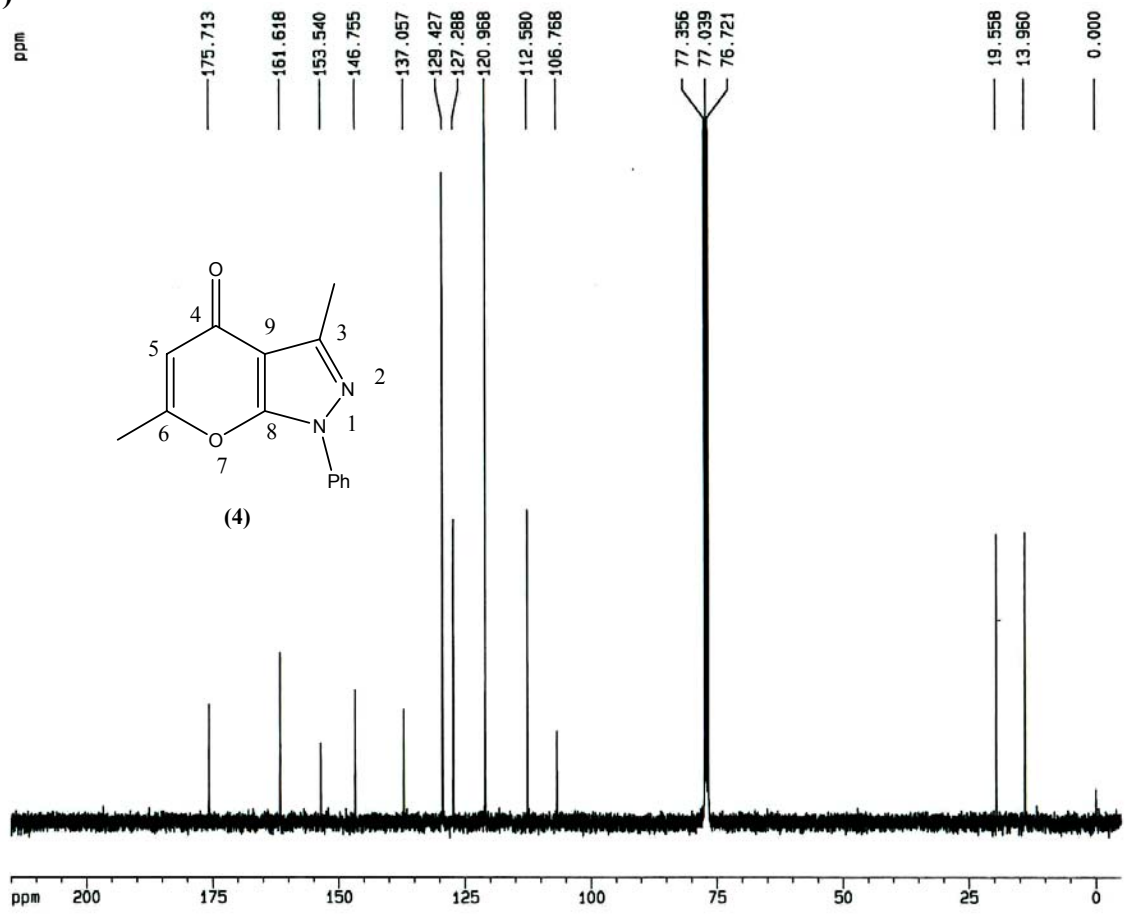


Figure 5(a) shows that the ^{1}H-NMR spectrum of the colorless crystals obtained in the previous experiment is consistent with the structure of **4.** The methyl protons of the pyrone and pyrazole rings are shown as singlets at δ 2.40 (3H) and 2.62 (3H), respectively. The two triplets at δ 7.36 (1H; J = 7.6 Hz) and 7.49 (2H; J = 7.6 Hz) and

the doublet at δ 7.77 (2H; J = 8.6 Hz) are due to absorptions of the protons at the para, meta and ortho positions of the phenyl ring, respectively. A key signal due to the proton of the pyrone ring appears as a singlet at δ 6.04.

(b)



(4)

The ^{13}C-NMR spectrum (Figure 5(b)) is also consistent with the structure **4**. The carbonyl carbon of the pyrone ring absorbs the furthest downfield at δ 175.7. The signals at δ 153.5 and δ 106.8 were assigned to the bridgehead carbons at positions 8 and 9, respectively. The pyrone ring carbons in positions 5 and 6 appear at δ 112.6 and 161.6, respectively. The imine carbon of the pyrazole ring was assigned to the signal at δ 146.8. The phenyl ring carbon attached to the nitrogen atom and at the para carbon absorb at δ 137.1 and 127.3 respectively, while the ortho and meta carbons in the

phenyl ring appear as two singlets at δ 120.9 and 129.4, respectively. The methyl carbons of the pyrazole and pyrone rings are shown at δ 13.9 and 19.6 respectively.

(c)

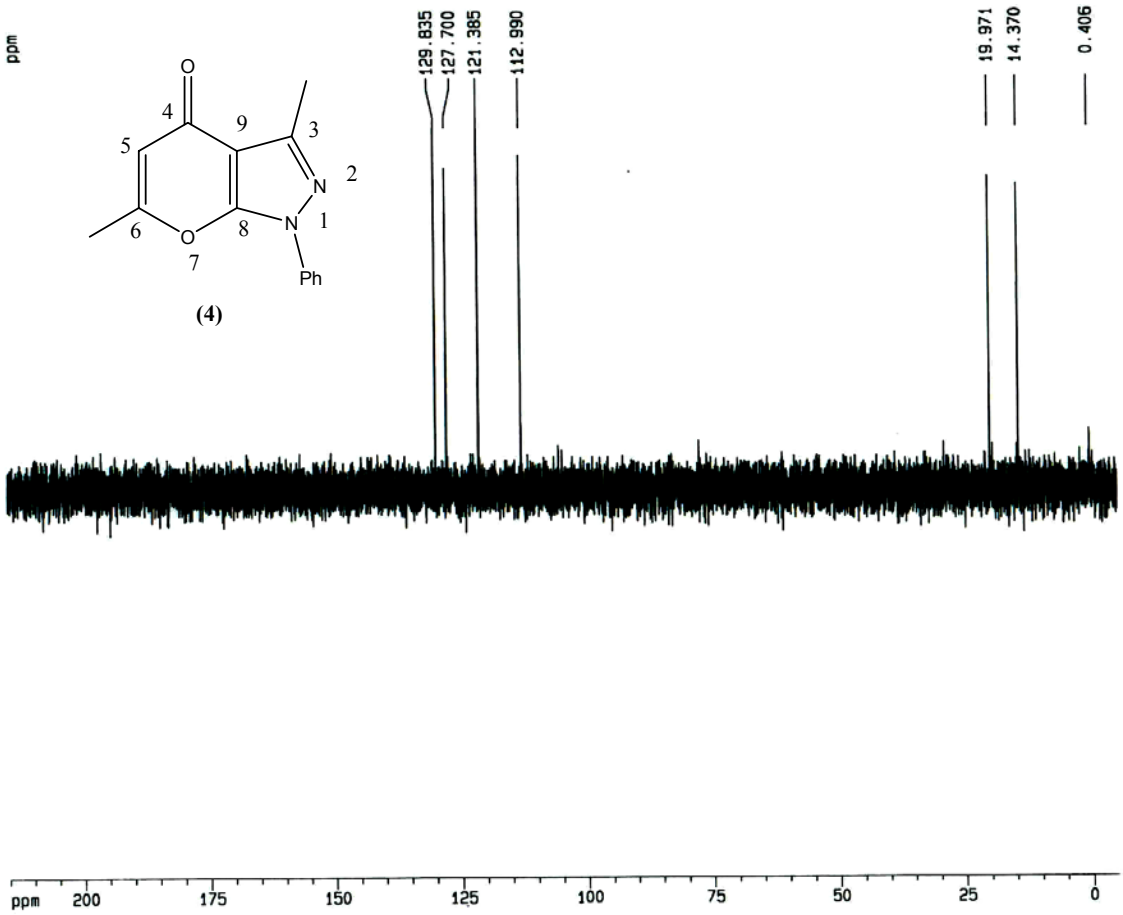
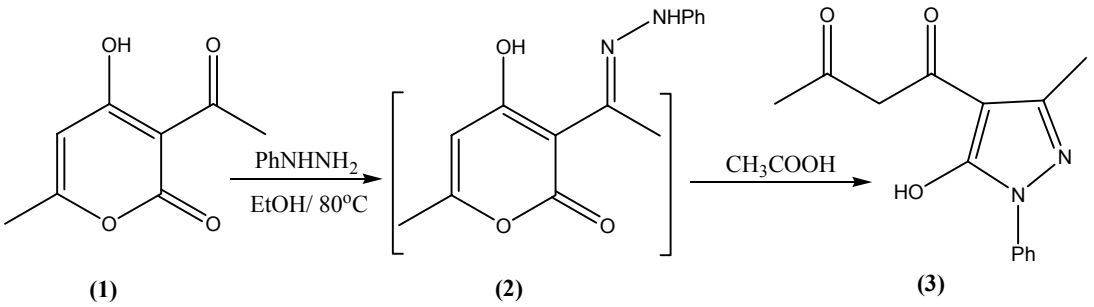


Figure 5: (a) ^{1}H-NMR of compound **4**; (b) ^{13}C-NMR of compound **4**; (c) ^{13}C-NMR DEPT 135 of compound **4**.

These assignments are consistent with the ^{13}C-DEPT 135 spectrum (Figure 5(c)). The six signals at δ 175.7, 161.6, 153.5, 146.8, 137.1 and 106.8 disappeared which is consistent with their assignment to the six quaternary carbons found in

positions 3,4,6,8, and 9 of the pyranopyrazole ring and at position 1 of the phenyl ring. In addition, the signals at δ 129.4, 127.3, 120.9, 112.6, 13.9 and 19.6 still appear in the positive direction which is consistent with their assignment to the three CH type carbons of phenyl ring, the CH type carbon of the pyrone ring, and the two methyl carbons of the pyrone and pyrazole rings.

These published procedures[2-3] allow the conversion of dehydroacetic acid to N-phenylpyranopyrazole **4** in an overall yield of 55 %. According to this synthetic approach, both intermediates **2** and **3** were isolated and purified before their use in the subsequent reaction. In an attempt to condense this synthetic procedure, experiments were carried out without isolating intermediates **2** and **3**.

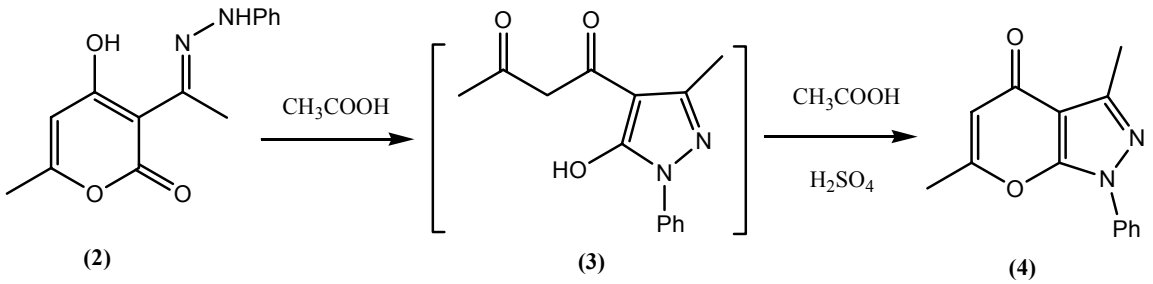


(1) **(2)** **(3)**

Scheme 6: Synthesis of 1-(5-hydroxy-3-methyl-1-phenyl-1*H*-pyrazol-4-yl)butane-1,3-dione **(3)**.

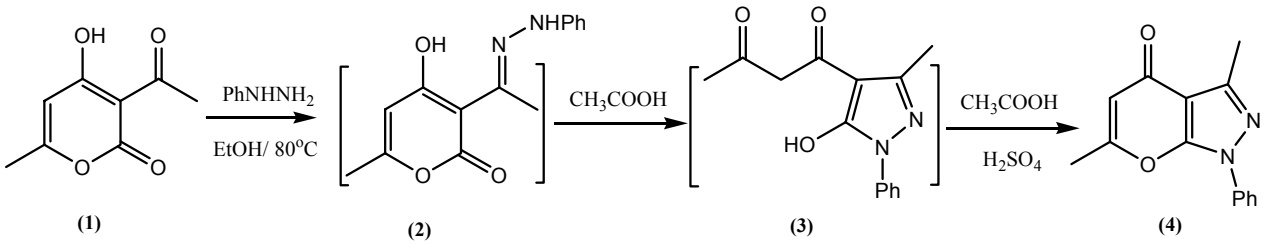
In the first experiment, the conversion of **1** to **3** was attempted without isolation and purification of N-phenylhydrazone **2**. Thus, **1** was treated with phenylhydrazine

and the crude N-phenylhydrazone **2** was refluxed in acetic acid. This allowed the formation of **3** in a yield of 72% (Scheme 6).



Scheme 7: Synthesis of 3,6-dimethyl-1-phenylpyrano[2,3-*c*]pyrazole **(4)**.

In the second experiment, the conversion of **2** to **4** without isolation of **3** was attempted. To accomplish this, phenylhydrazone **2** was refluxed in acetic acid for one hour. Concentrated sulfuric acid was then added dropwise and the mixture was refluxed for one additional hour to give **4** in a yield of 73%. This approach allowed the conversion of dehydroacetic acid **1** to N-phenylpyranopyrazole **4** in an overall yield of 69% (Scheme 7).

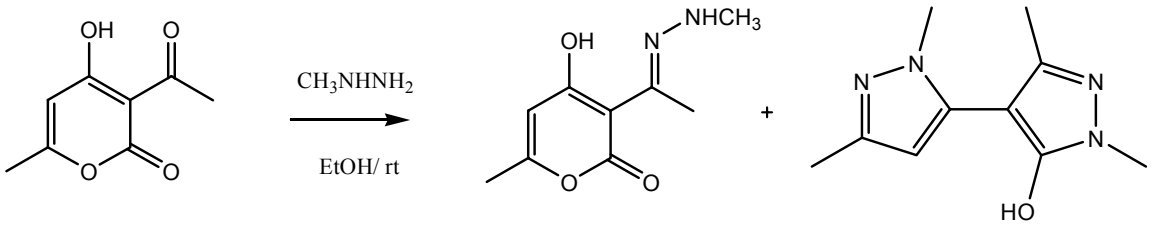


Scheme 8: Synthesis of 3,6-dimethyl-1-phenylpyrano[2,3-*c*]pyrazole **(4)**.

In the final experiment, the conversion of dehydroacetic acid **1** to N-phenylpyranopyrazole **4** was attempted without the isolation and purification of both **2** and **3**. Thus, **1** was treated with phenylhydrazine for a few minutes and after evaporation of the solvent, the crude N-phenylhydrazone **2** was refluxed in acetic acid for one hour. Concentrated sulfuric acid was then added and the mixture was refluxed for one additional hour. This approach led to the isolation of **4** in an overall yield of 70 % (Scheme 8) which is this substantially higher than the yield of 55% which was obtained when intermediates **2** and **3** were isolated and purified.

This work clearly establishes that dehydroacetic acid (**1**) can be converted to N-phenylpyranopyrazole (**4**) in good yield. The next goal of this research was to explore the generality of this synthetic approach to prepare other pyranopyrazole derivatives.

Since the substituent on nitrogen in **4** originates in the hydrazine reagent, it was first attempted to use other hydrazine reagents in order to vary the substituent on the pyrazole ring nitrogen. Although the N-methylhydrazone of dehydroacetic acid is a known compound,[5] no attempt has been made to determine if this compound can be isomerized to the N-methylpyranopyrazole derivative.



(1) **(5)** major **(8)** minor

Scheme 9: Synthesis of 4-Hydroxy-6-methyl-3-(1-(2-methylhydrazono)ethyl)-2*H*-pyran-2-one **(5)**.

In order to explore this possibility, dehydroacetic acid (**1**) was allowed to react with methylhydrazine in ethanol solution at room temperature for two hours. 4-Hydroxy-6-methyl-3-(1-(2-methylhydrazono)ethyl)-2*H*-pyran-2-one **(5)** was observed as the major product in 51 % yield, mp 95-97°C (Lit.[5] mp 100-102°C) and 5-hydroxy-1,3-dimethyl-4-(1,3-dimethyl-pyrazol-5-yl)pyrazole **(8)** was obtained as a minor product in 14 % yield, mp 201-202°C (Lit.[5] mp 203-204°C) (Scheme 9). These compounds were easily separated due to their solubility difference in ethyl acetate solvent.

(a)

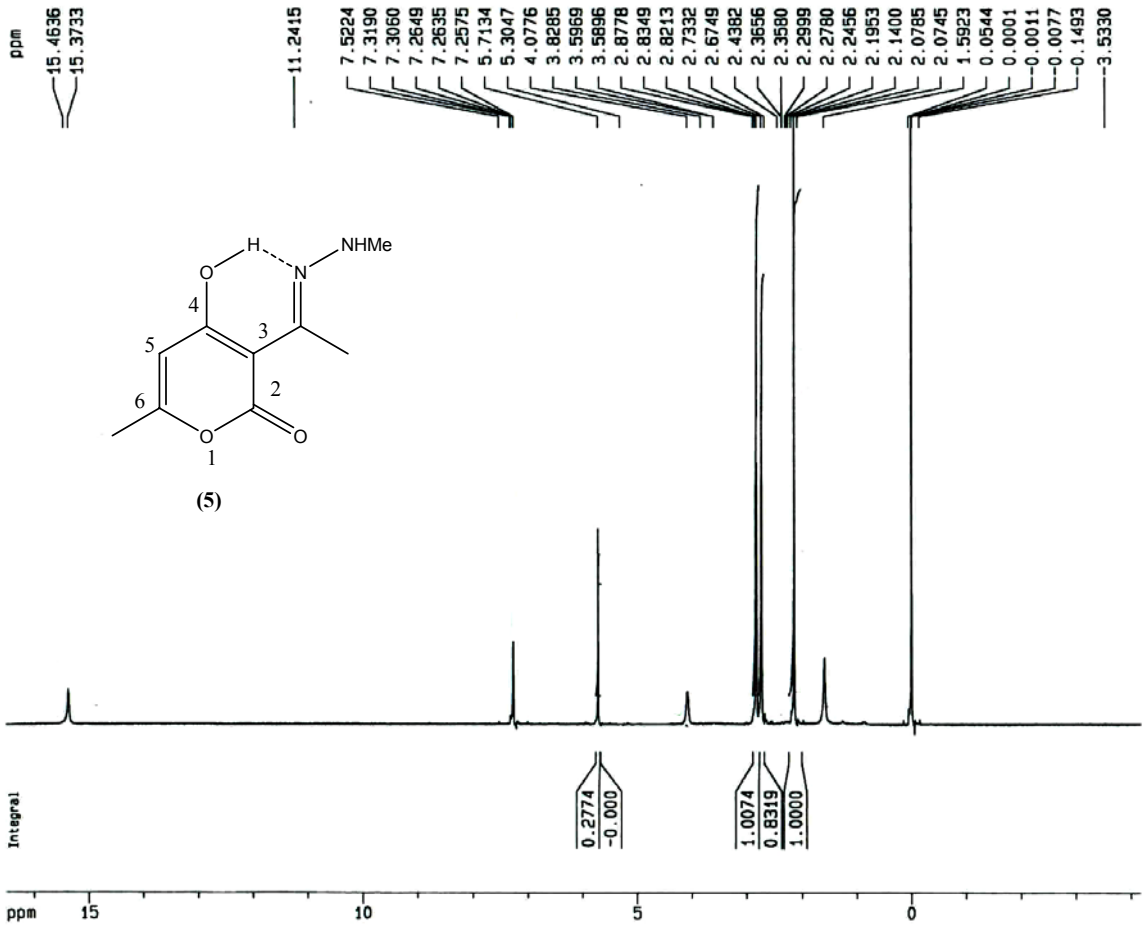
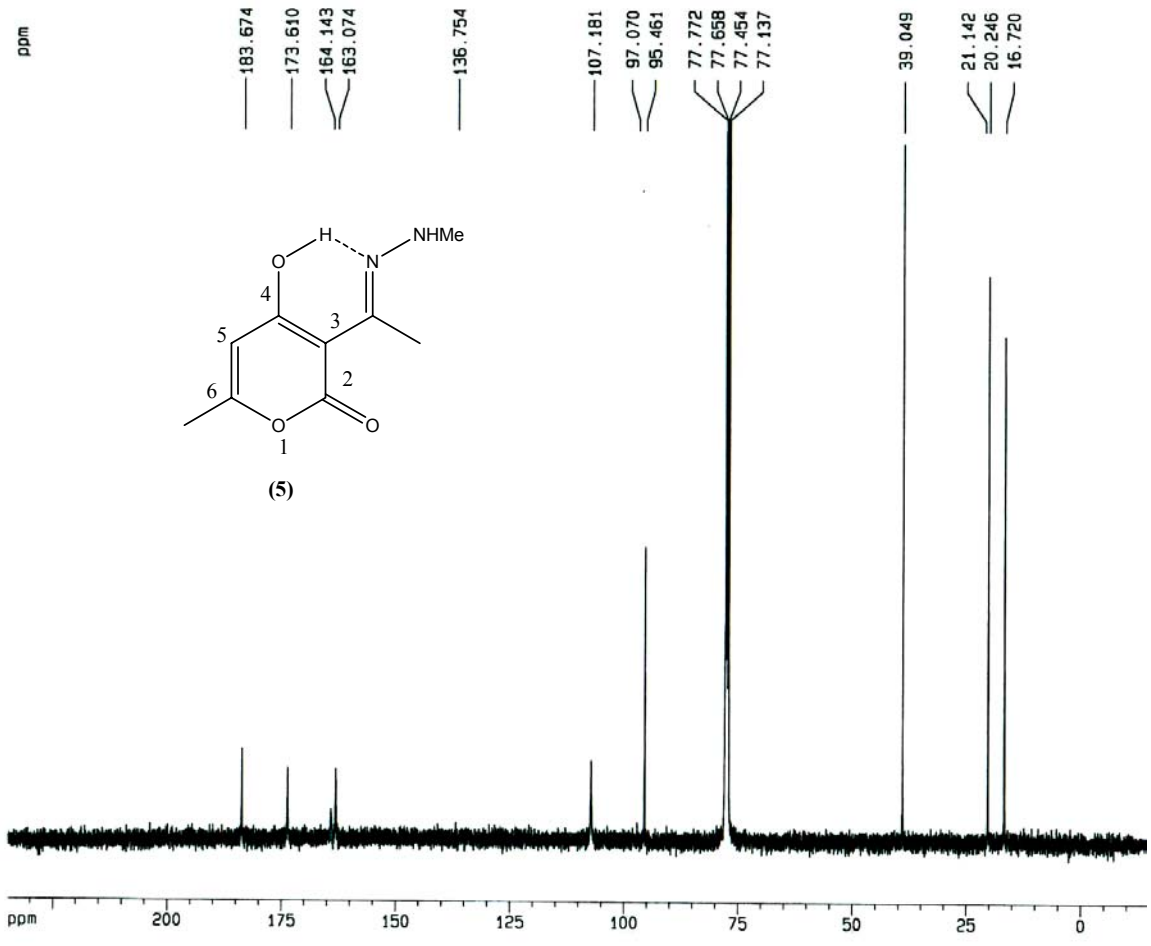


Figure 6(a) shows that the ^{1}H-NMR spectrum of the white crystalline major product is consistent with the structure of **5.** The N- and C- methyl groups of the hydrazone functional group and the methyl group on the pyrone ring appear as singlets at δ 2.83 (3H), 2.73 (3H) and 2.19 (3H), respectively. A key proton on the pyrone ring appears as a 1H singlet at δ 5.71. The signals at δ 15.4 and 4.07 are due to the protons of the enol and hydrazine groups, respectively. When compound **5** was treated with D_2O, these signals disappeared.

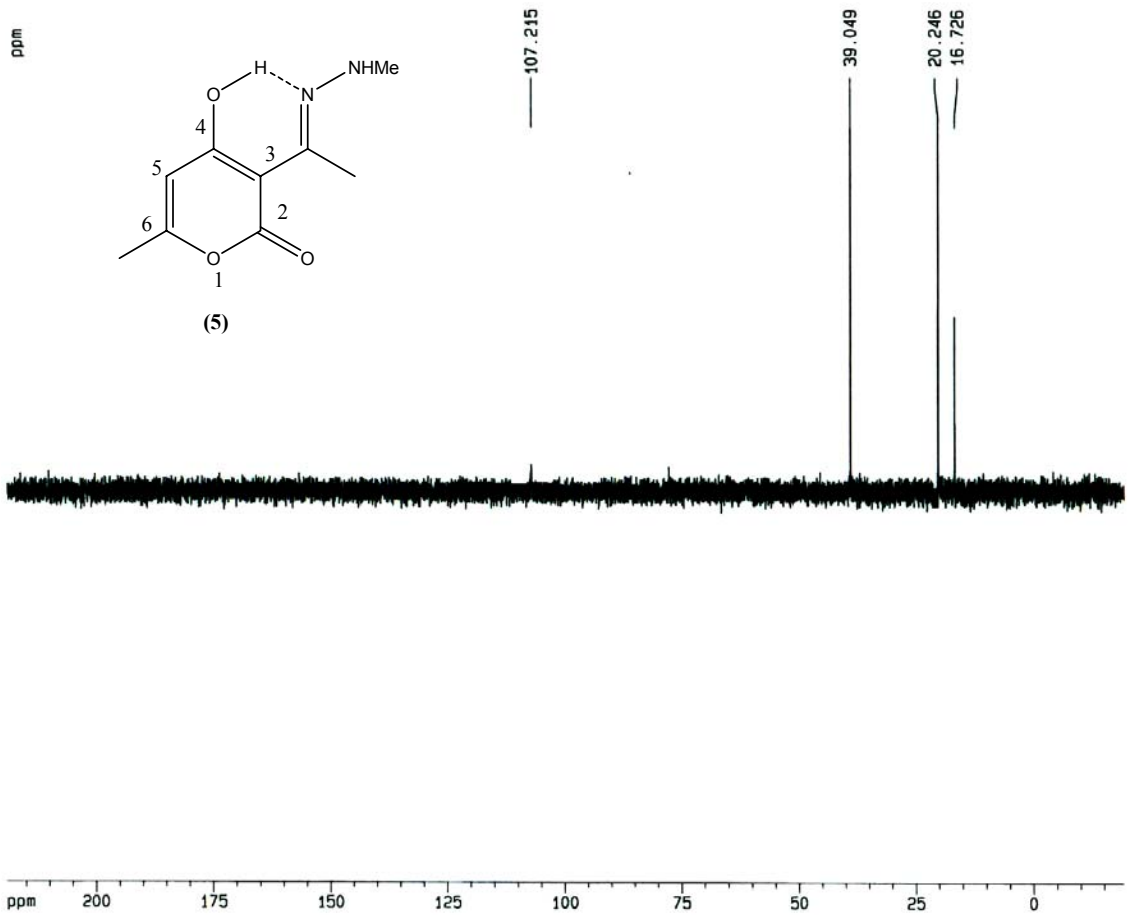
(b)



(5)

The ^{13}C-NMR spectrum (Figure 6(b)) is also consistent with the structure of **5**. The hydroxyl carbon of the lactone ring absorbs furthest downfield at δ 183.7. The signal at δ 173.6 was assigned to the hydrazone carbon. The carbons at position 2, 3, 5, and 6 of the pyrone ring appear at δ 164.1, 95.5, 107.2, and 163.1, respectively. In addition, the signals at δ 39.0, 20.3, and 16.6 are due to carbons of the methyl groups on the nitrogen atom, the pyrone ring, and the hydrazone moiety, respectively.

(c)



(5)

Figure 6: (a) ^{1}H-NMR of compound **5**; (b) ^{13}C-NMR of compound **5**; (c) ^{13}C-NMR DEPT 135 of compound **5**.

These assignments are consistent with the ^{13}C-DEPT 135 spectrum (Figure 6(c)). The five signals at δ 183.7, 173.6, 164.1, 163.1, and 95.4 disappeared which is consistent with their assignment to the four quaternary carbons of the pyrone ring and the carbon of the hydrazone group. In addition, the signal at δ 107.2 still appears as a positive signal which is consistent with a CH type carbon of the pyrone ring. Also, the signals at δ 39.0, 20.2, and 16.7 are due to carbons of the methyl groups on the nitrogen atom, the pyrone ring, and the hydrazone moiety, respectively.

(a)

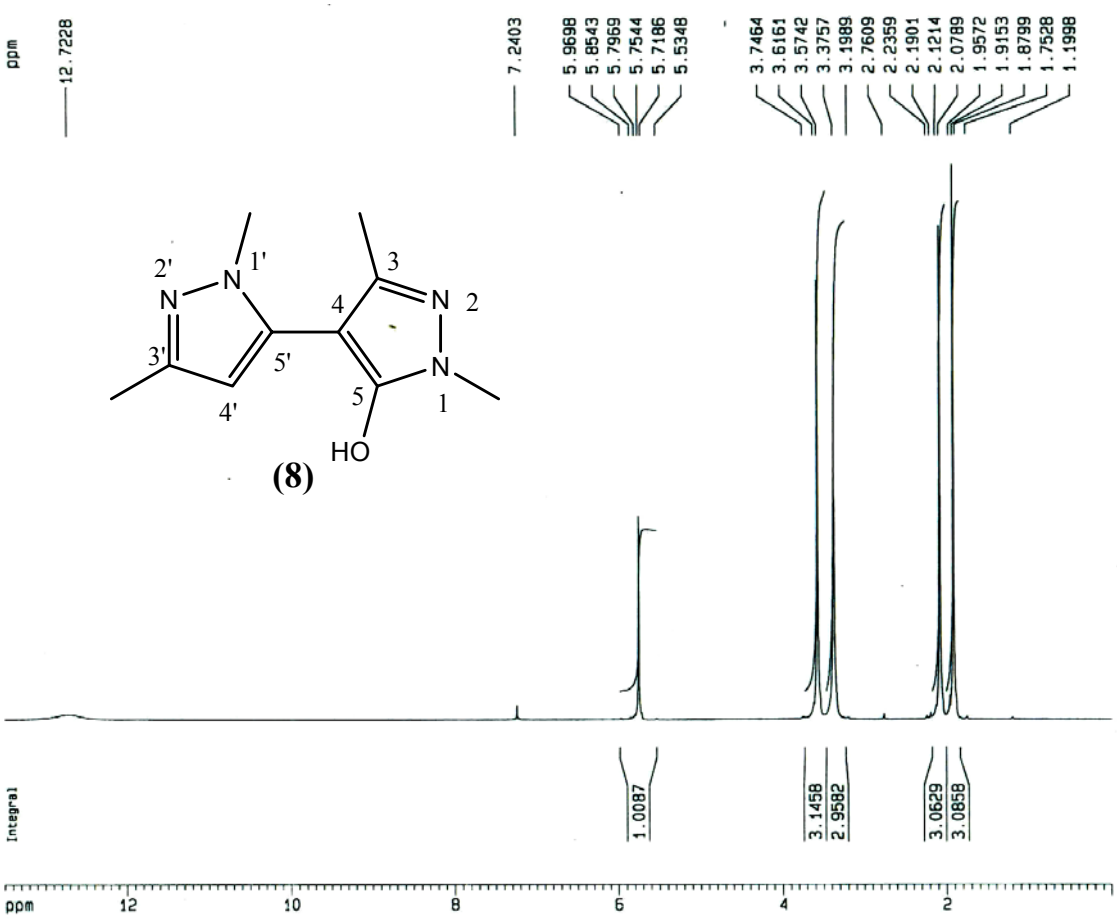
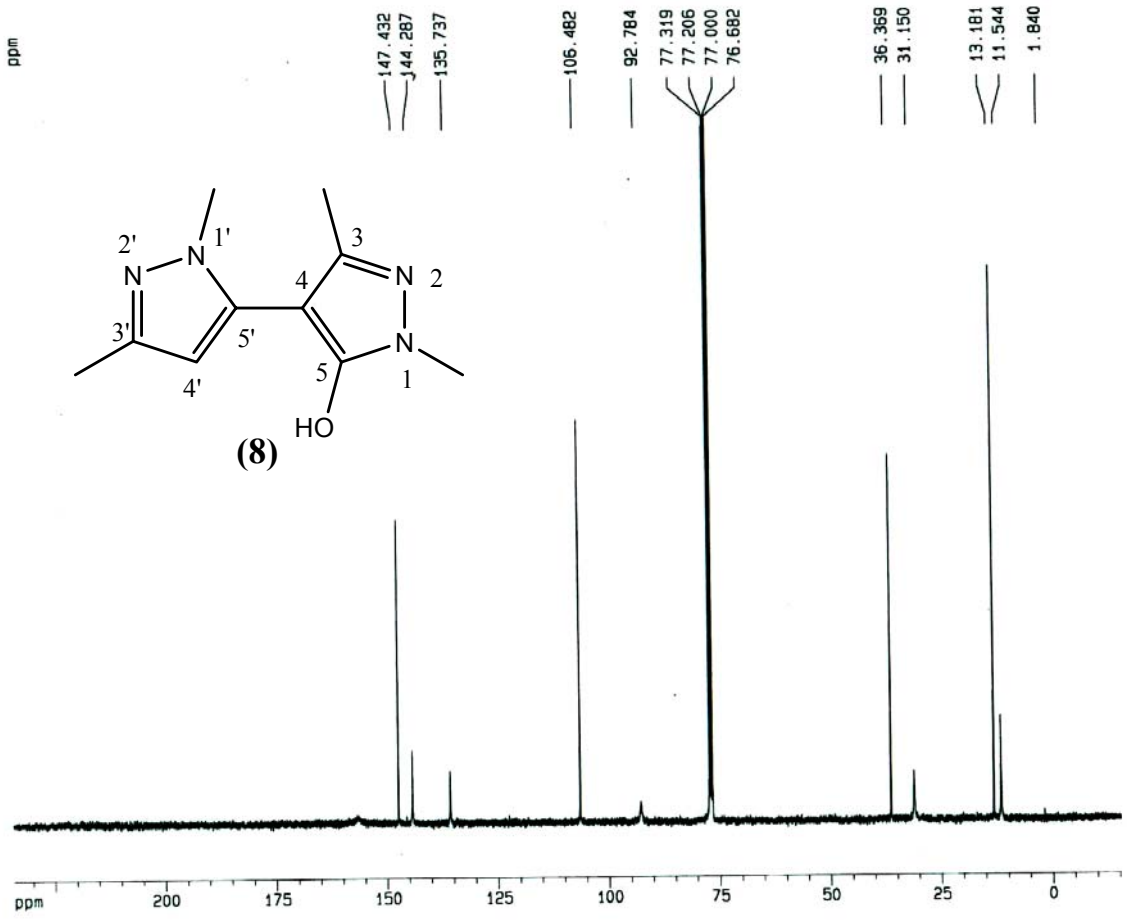


Figure 7(a) shows that the ^{1}H-NMR spectrum of the white crystalline minor product is consistent with the structure of **8.** The key proton at C-4' of the pyrazole ring appears as a singlet at δ 5.80. The N- methyl protons of C-1 and C-1' appear as singlets at δ 3.42 (3H) and 3.62 (3H), respectively. In addition, the C- methyl protons of C-3 and C-3', appear as singlets at δ 1.96 (3H) and 2.12 (3H), respectively. The signal at δ 12.7 is due to the proton of the hydroxyl proton. When compound **8** was treated with D_2O, this signal disappeared.

(b)



The ^{13}C-NMR spectrum (Figure 7(b)) is also consistent with the structure of **8**. The hydroxyl carbon of the pyrazole ring absorbs furthest downfield at δ 156.5. The signal at δ 135.7 is due to the carbon at C-5 position. The signals at δ 147.4 and 144.3 were assigned to the carbons at C-3' and C-3 positions, respectively, while the carbons at C-4' and C-4 appear at δ 106.5 and 92.8, respectively. In addition, the signals at δ 36.4, 31.1, 13.2, and 11.5 are due to carbons of the methyl groups on the nitrogen atom at C-1 and C-1' positions and on the pyrazole rings at C-3 and C-3' positions, respectively.

According to the ^{13}C-NMR spectrum, the carbons due the hydroxyl pyrazole ring gave the weaker signals than the other ring. This may be due to different relaxation times of the carbon atoms in the two rings.

(c)

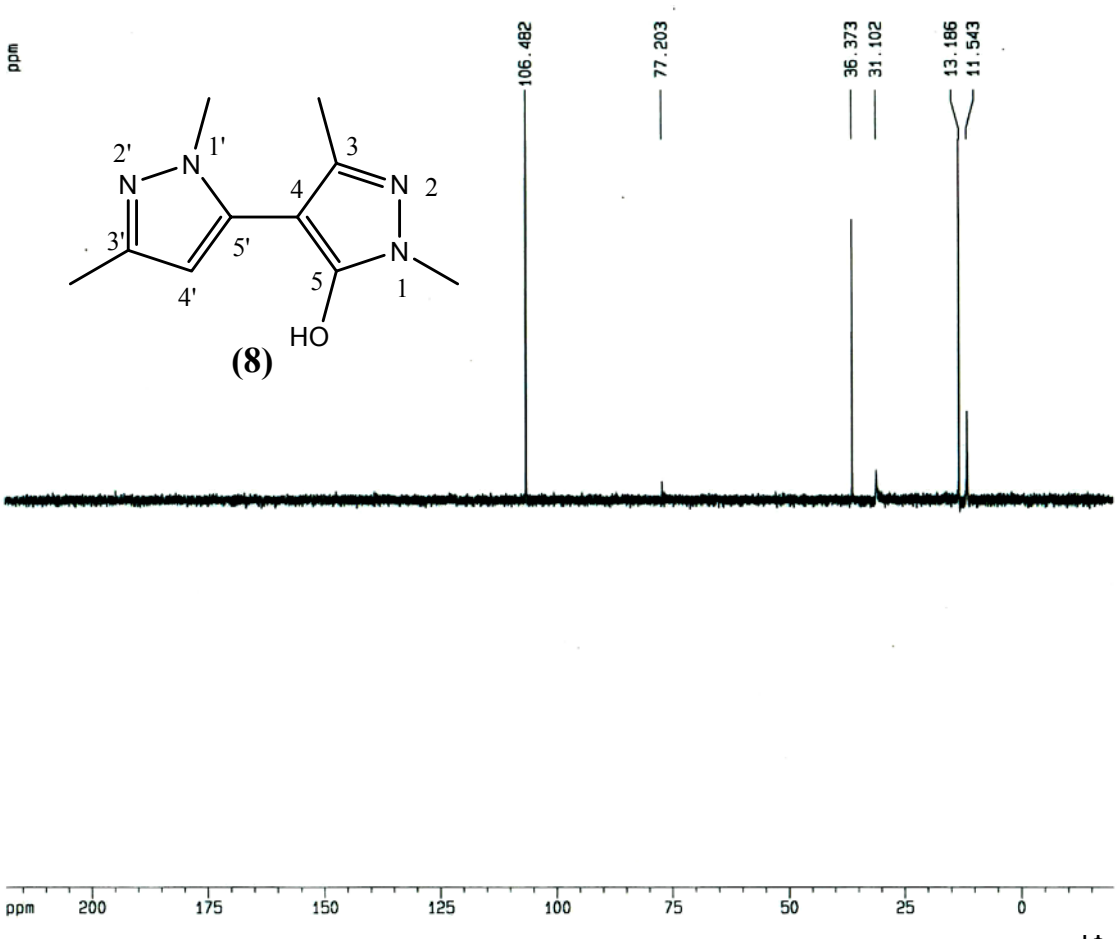
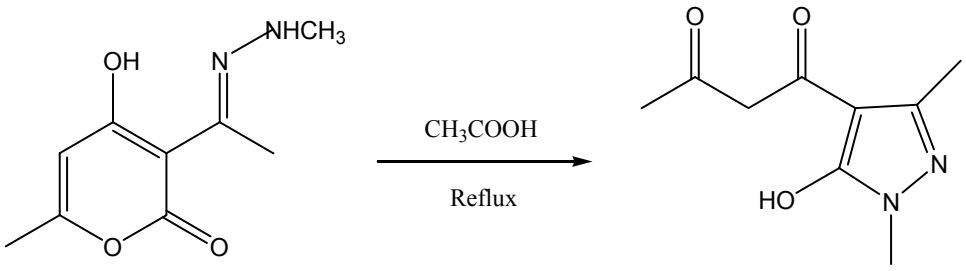


Figure 7: (a) ^{1}H-NMR of compound **8**; (b) ^{13}C-NMR of compound **8**; (c) ^{13}C-NMR DEPT 135 of compound **8**.

These assignments are consistent with the ^{13}C-DEPT 135 spectrum (Figure 7(c)). The five signals at δ 156.5, 147.4, 144.3, 135.7 and 92.8 disappeared which is consistent with their assignment to the five quaternary carbons of the bipyrazole **8**. In addition, the signal at δ 106.5 still appears as a positive signal which is consistent with a CH type of carbon of pyrazole ring. Also, the signals at δ 36.4, 31.1, 13.2 and 11.5 are due to the carbons of the N-methyl groups, C-3, and C-3' positions.



(5) **(6)**

Scheme 10: Synthesis of 1-(5-hydroxy-1,3-dimethyl-1*H*-pyrazol-4-yl)butane-1,3-dione **(6)**.

1-(5-hydroxy-1,3-dimethyl-1*H*-pyrazol-4-yl)butane-1,3-dione **(6)** is a new compound and has not never been synthesized by isomerization of the hydrazone **5**. In this study, however, it was observed that refluxing **5** in acetic acid for one hour led to the formation of 1-(5-hydroxy-1,3-dimethyl-1*H*-pyrazol-4-yl)butane-1,3-dione **6** in 75% yield, mp 136-137^{o}C (Scheme 10).

As was the case with the N-phenyl derivative **3**, NMR analysis indicates that compound **6** exists in $CDCl_3$ as a mixture of tautomers.

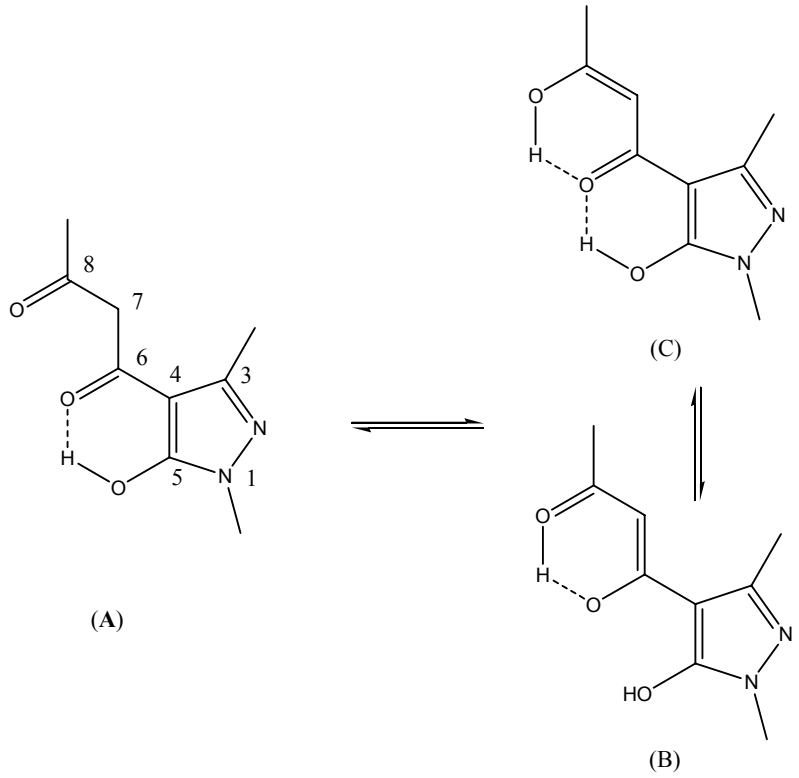
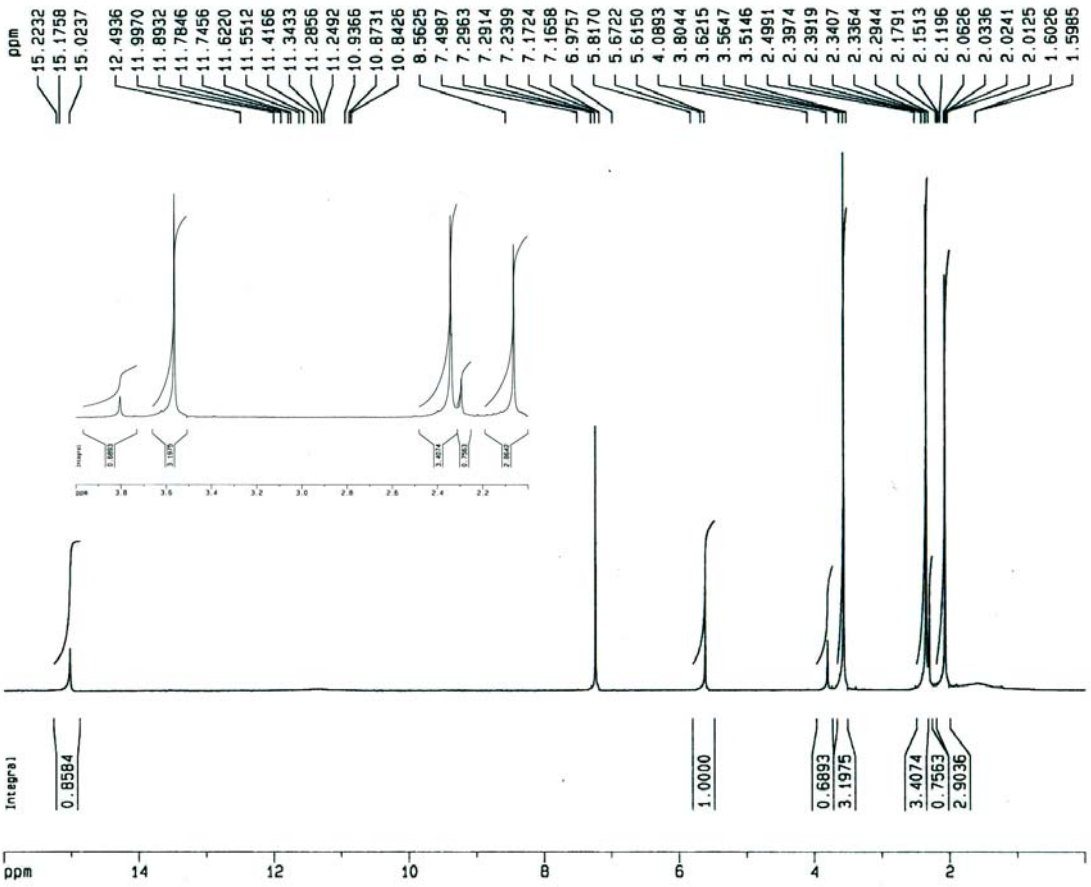


Figure 8: Tautomerization of compound **6**.

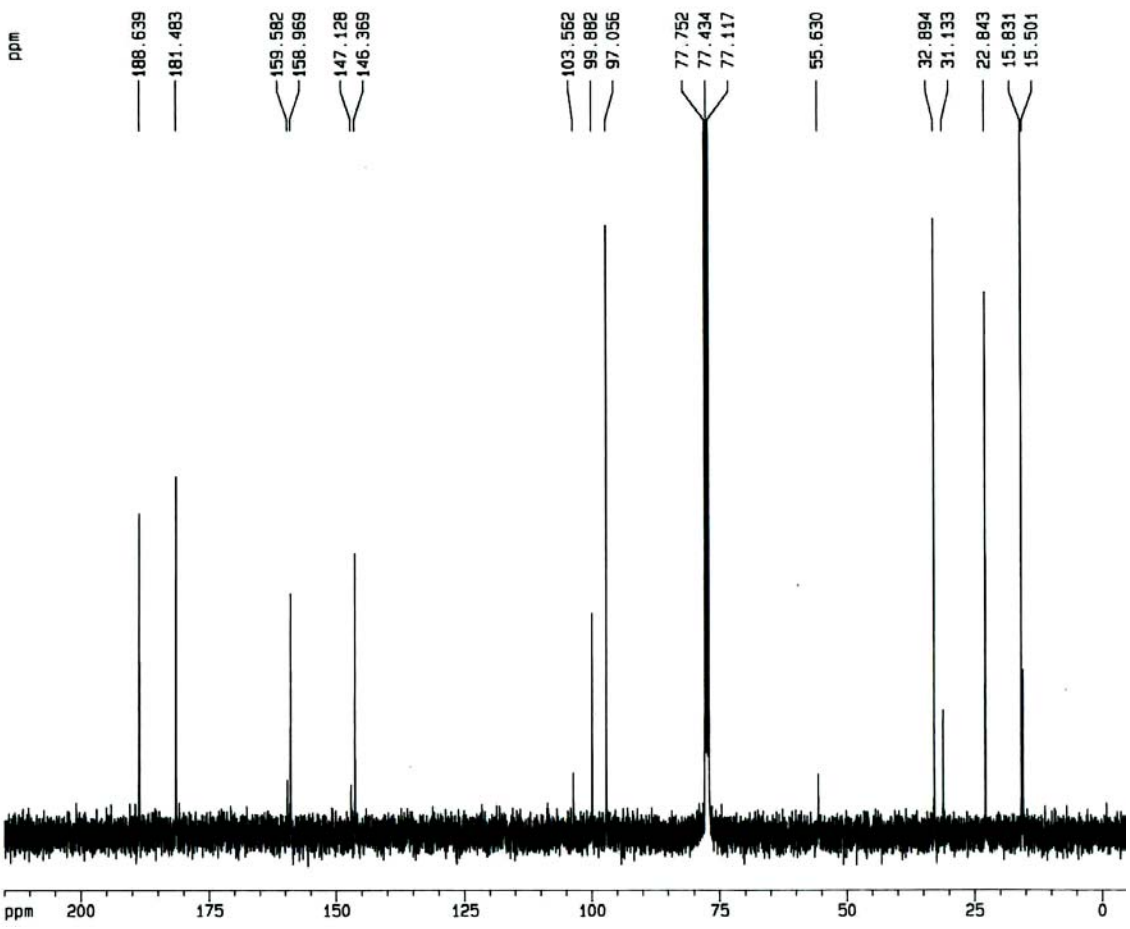
According to the ^{1}H-NMR spectrum (Figure 9(a)) the enol and keto forms are most easily detected by the signal at δ 5.61 for the vinyl proton in the enol structure and the signal at δ 3.80 for the methylene protons in the keto structure. Based on the integral rises of 1.00 and 0.689 respectively for these signals, and noting that they are due to 1H and 2H signals respectively, the enol to keto ratio is calculated to be 2.90 to 1.

(a)



The sharp peak down field at δ 15.0 (D_2O exchangeable) is consistent with the intramolecularly H-bonded enolic proton in conformer B and C, while the very broad signal at 11.3 is more consistent with the more acidic, C-5 hydrogen bonded hydroxyl proton in tautomers A, B, and C. The singlet protons at δ 2.33 (3H) and 2.29 (3H) are assigned to the C-3 and C-8 methyl protons in the keto tautomer A, respectively, while the 3H singlet signals at δ 2.34 and 2.11 were assigned to the C-3 and C-8 methyl protons in the enol tautomer (B ⇌ C), respectively. In addition, the singlet signal at δ 3.56 is due to the N-methyl protons in tautomeres A, B, and C.

(b)



The upfield portion of the ^{13}C-NMR spectrum (figure 9(b)) of compound **6** in $CDCl_3$ solution shows evidence of two sets of methyl carbon atoms. The signals at δ 15.83 and 15.50 were assigned to the C-3 methyl groups of the pyrazole ring of the major and minor tautomers, respectively. These signals correlate with the high intensity methyl proton signal at δ 2.34 and the low intensity methyl proton signal at δ 2.33 as shown in the ^{1}H-^{13}C correlation spectrum Figure 9(c). The terminal methyl groups of the side chain of the major and minor tautomers absorb at δ 22.84 and 31.13, respectively and are observed to correlate with the high intensity ethyl signal at δ 2.11

and low proton signal at δ 2.29. The signal at δ 32.89 was assigned to the carbons of the N-methyl groups of both tautomers, and was observed to correlate with the signal in the ^{1}H-NMR spectrum at δ 3.56 which was previously assigned to the protons of the N-methyl group.

(c)

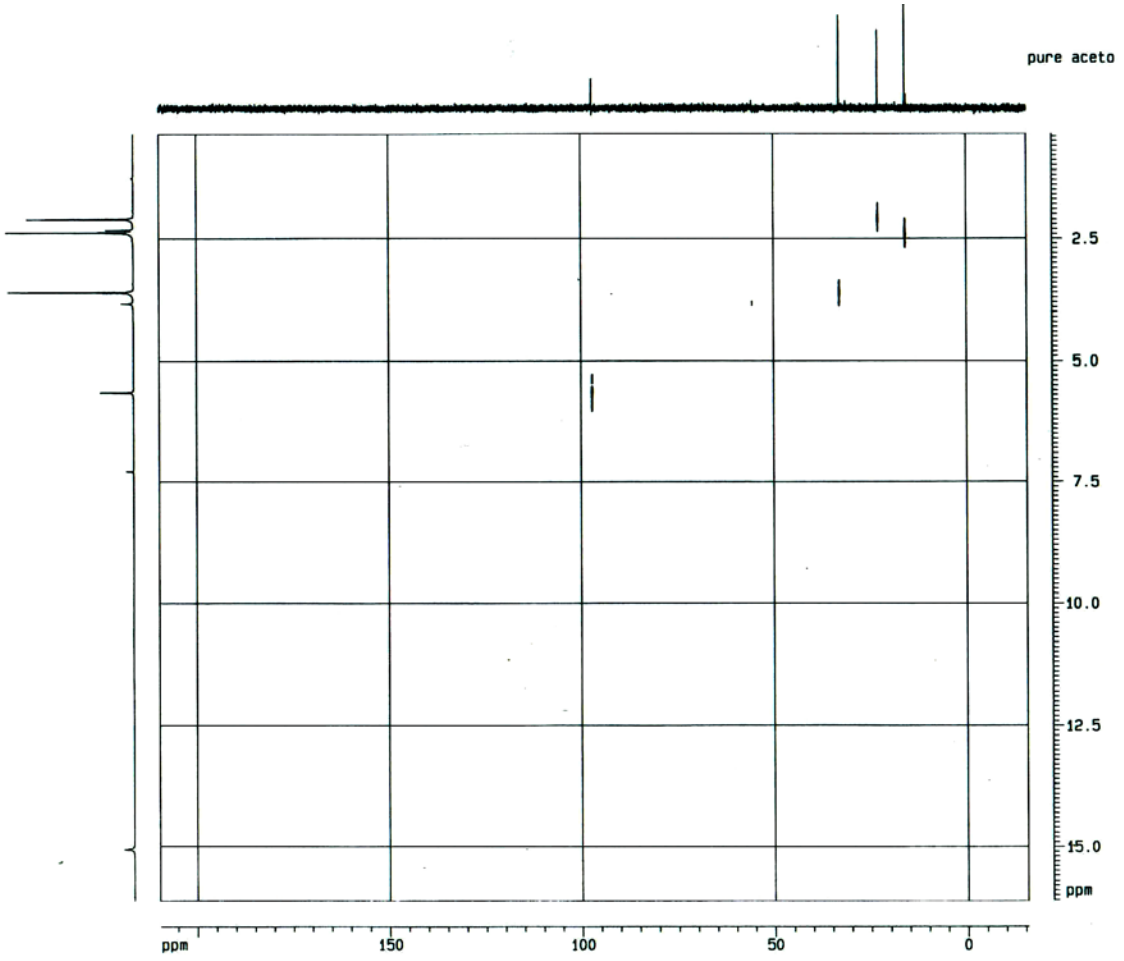
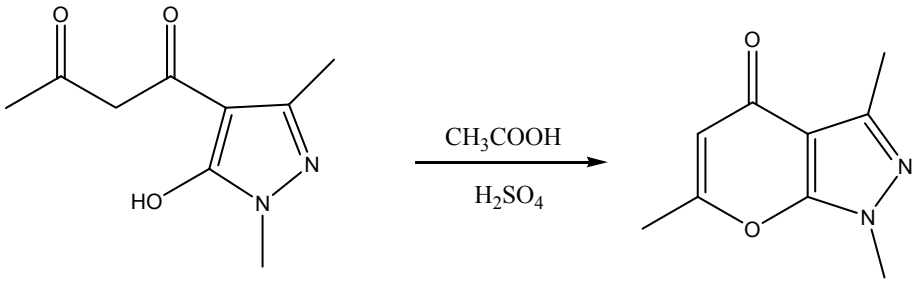


Figure 9: (a) ^{1}H-NMR of compound **6**; (b) ^{13}C-NMR of compound **6**; (c) NMR-CH-correlation of compound **6**.

The signal at δ 55.63 was assigned to the C-7 carbon of the keto tautomer A. As expected for this assignment, the ^{1}H-^{13}C correlation spectrum reveals that this signal correlates with the absorption in the ^{1}H-NMR spectrum at δ 3.81 which was previously assigned to the CH_2 group of the keto tautomer A. The signals in the ^{13}C-NMR spectrum δ 188.6 and 181.5 were assigned to the C-6 and C-8 carbonyl carbons of the keto-enol side chain of tautomers B and C. As expected, the ^{1}H-^{13}C correlation spectrum shows that these signals do not correlate with any signals in the ^{1}H-NMR spectrum. The ^{13}C-NMR spectrum exhibits two sets of signals, which were shown to be quaternary carbons by the ^{1}H-^{13}C correlation spectrum and were therefore assigned to the carbon atoms of the pyrazole rings in the enol and keto tautomers. The signals at δ 158.9, 146.4, and 99.88 were assigned to the C-5, C-3, and C-4 carbon atoms of the major enol tautomers, while the signals at δ 159.6, 147.1, and 103.6 were assigned to the same ring carbon atoms of the minor keto tautomer. Finally, the ^{13}C-NMR exhibits a signal at δ 97.06 which correlates with the signal at δ 5.80 in the ^{1}H-NMR spectrum and was therefore assigned to the C-7 vinyl carbon in the side chain of the major enol tautomer.



(6) **(7)**

Scheme 11: Synthesis of 1,3,6-trimethyl-[2,3-*c*]pyrazole-4(1*H*)-one **(7)**.

Although, compounds **5** and **6** are known,[5,6] no attempt has been reported for the isomerization of **6** to compound **7**. The ring closure of **6** to the new compound 1,3,6-trimethyl-[2,3-*c*]pyrazole-4(1*H*)-one **(7)** was easily achieved by refluxing compound **6** in acetic acid in the presence of sulfuric acid as a catalyst. **7** was obtained in a yield of 73%, mp 154-155^{o}C (Scheme 11). This route allowed the conversion of dehydroacetic acid **1** to N-methyl pyranopyrazole **7** by procedures involving the isolation and purification of **5** and **6** in an overall yield of 28 %.

(a)

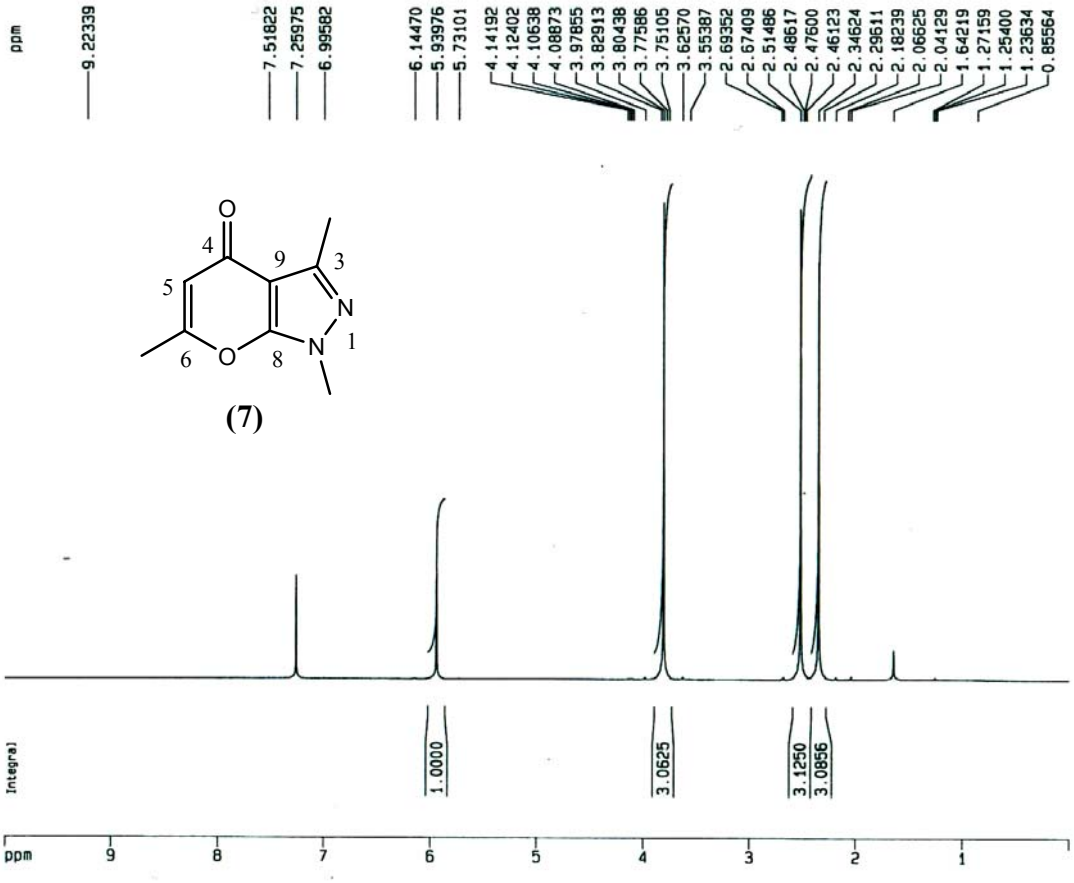
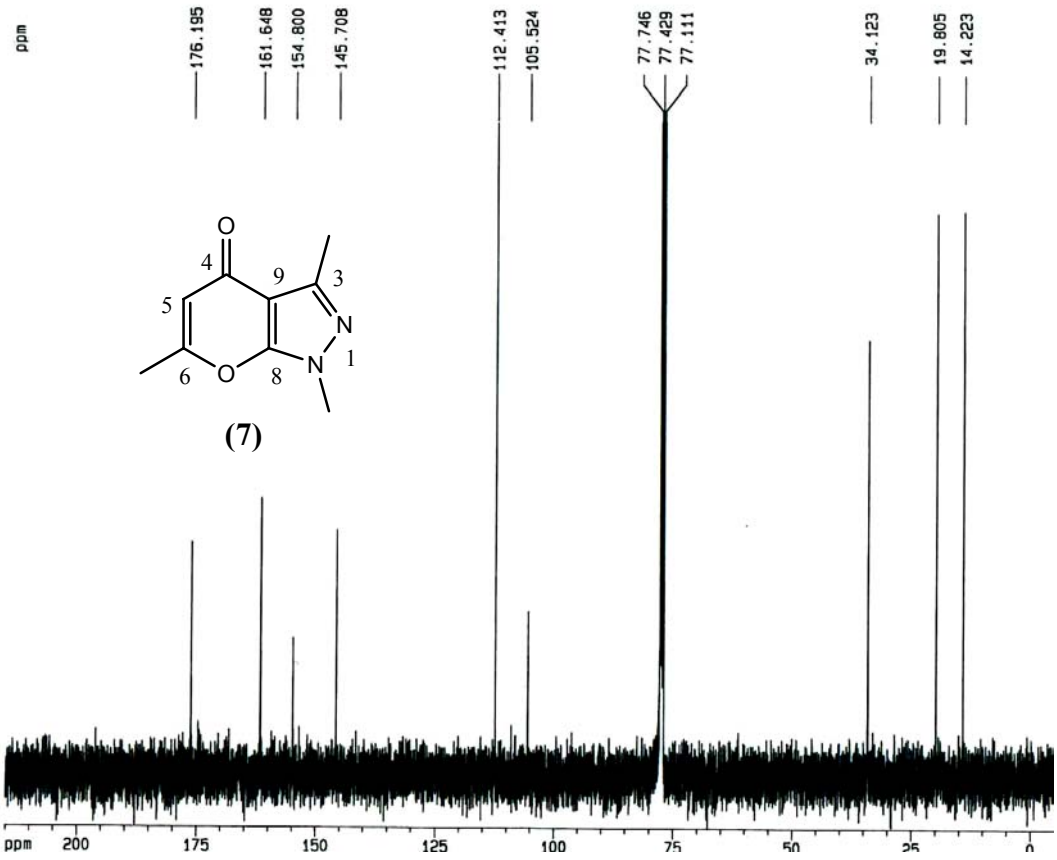


Figure 10(a) shows that the ^{1}H-NMR spectrum of the colorless crystalline product is consistent with the structure of **7**. In addition to the 3H singlets at δ 2.35,

2.51, and 3.80 for the three methyl groups, the spectrum exhibits a key 1H singlet at δ 5.94 for the vinyl proton of the pyrone ring α to the carbonyl group.

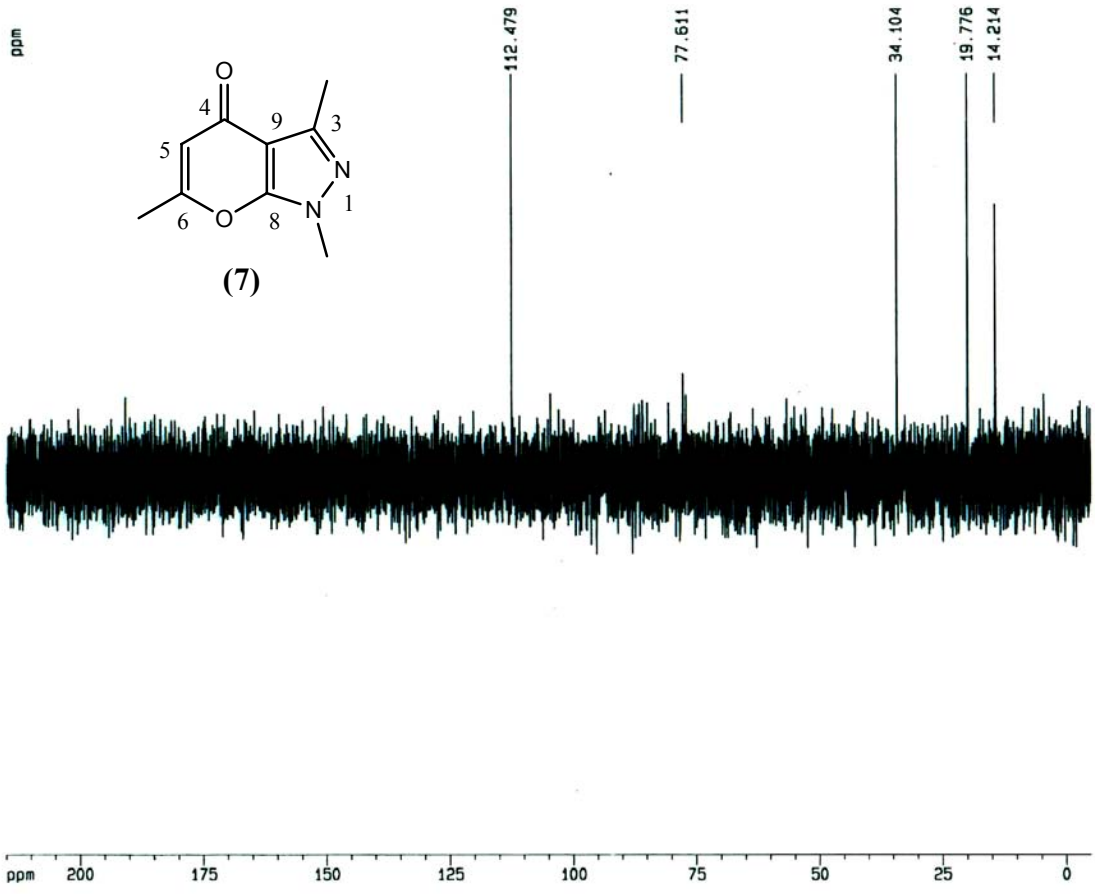
(b)



(7)

The ^{13}C-NMR spectrum (Figure 10(b)) is also consistent with the structure of **7**. Of the signals that absorb below δ 100, only the signal at δ 112.5 is not a quaternary carbon. This signal was therefore unambiguously assigned to the C-5 carbon atom. The signals at δ 176.2, 161.6, 134.8, 145.7, and 105.5 were assigned to the quaternary carbons at ring positions 4, 6, 8, 3, and 9, respectively. Finally, the signals at δ 34.2, 19.8, and 14.2 were assigned to the carbon atoms of the methyl groups at ring positions 1, 6, and 3, respectively.

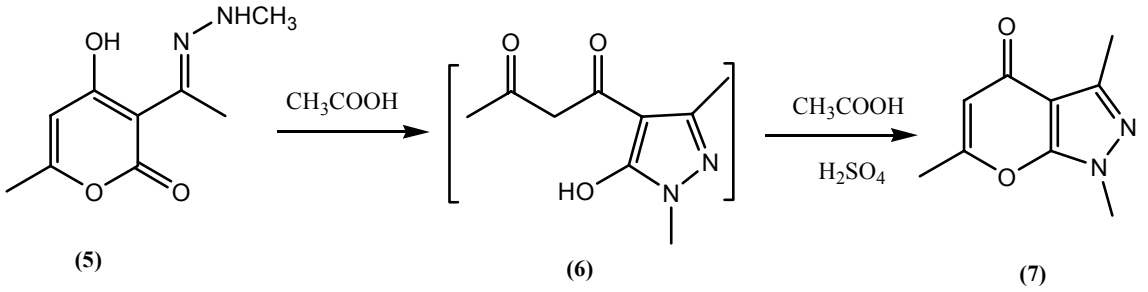
(c)



(7)

Figure 10: (a) ^{1}H-NMR of compound **7**; (b) ^{13}C-NMR of compound **7** and (c) ^{13}C-NMR DEPT 135 of compound **7**.

These assignments are consistent with the ^{13}C-DEPT 135 spectrum (Figure 10(c)). The five signals at δ 176.2, 161.6, 154.8, 145.7, and 105.5 disappeared which is consistent with their assignment to the five quaternary carbons of the pyrazole and pyrone rings. In addition, the signals at δ 112.5, 34.1, 19.8, and 14.2 absorb in the positive direction which is consistent with their assignment to the CH type carbon of the pyrone ring, the methyl carbon of the pyrone ring, and the two methyl carbons of the pyrazole ring.

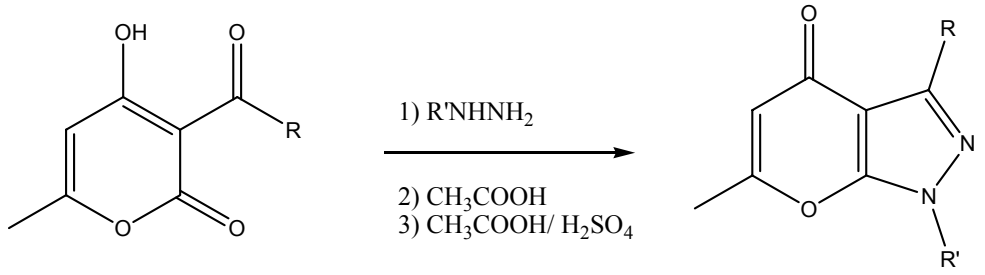


(5) (6) (7)

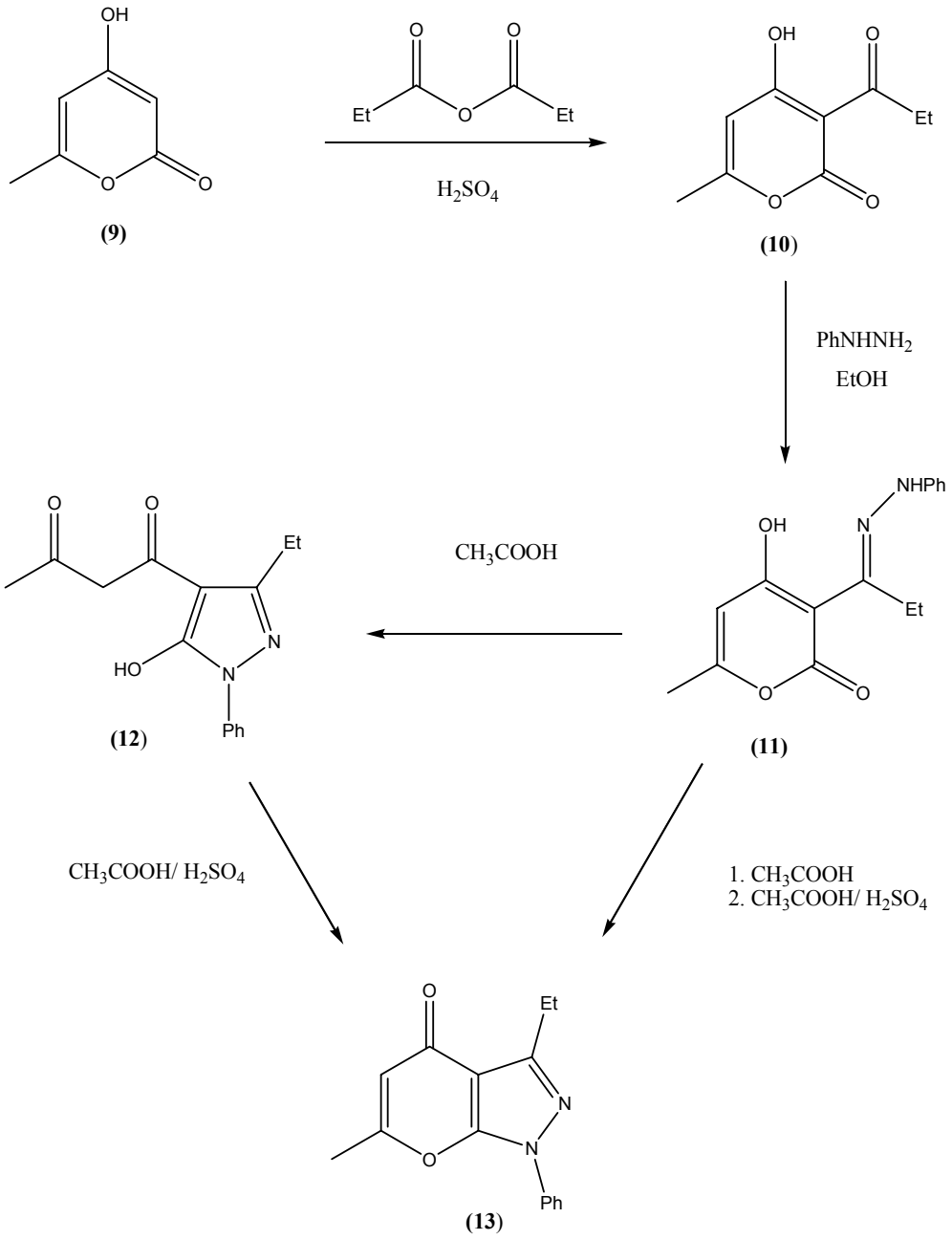
Scheme 12: Synthesis of 1,3,6-trimethylpyrano[2,3-*c*]pyrazole-4(1*H*)-one **(7)**.

The formation of the new compound 1,3,6-trimethylpyrano[2,3-*c*]pyrazole-4(1*H*)-one **(7)** was also achieved without the isolation of 6. Thus, after refluxing hydrazone **5** in acetic acid to give **6,** sulfuric acid was added dropwise and the crude mixture was refluxed for an additional hour. This led to the isolation of **7** in a yield of 54 % (Scheme 12). Therefore, this experiment led to the isolation of **7** in an overall yield of 36 % which is this substantially higher than the yield of 28 % which was obtained when intermediate **6** was isolated and purified.

According to this synthetic approach, the substituent at C-3 of the pyrazole ring of the pyranopyrazole is controlled by the R group in the acyl side chain of dehydroacetic acid as shown below. In order to synthesize pyranopyrazoles with different R

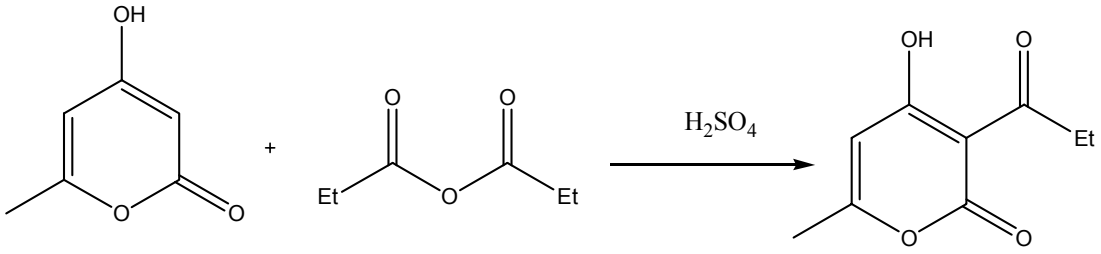


groups at C-3 of the pyrazole ring thus required the synthesis of dehydroacetic acid derivatives with different R groups in the acyl side chain.



In order to accomplish this, the method of Marcus, E. and colleague[7] was used. As an example (Scheme 13) of this method, the commercially available 4-hydroxy-6-

methyl-2-pyrone **(9)** was acylated with propionic anhydride in the presence of a catalytic amount of sulfuric acid.



(9) **(10)**

Scheme 13: Synthesis of 4-Hydroxy-6-methyl-3-propionyl-2*H*-pyran-2-one **(10)**.

4-Hydroxy-6-methyl-3-propionyl-2*H*-pyran-2-one **(10)** was obtained in a yield of 68%, mp 104-105^{o}C (Lit.[7] mp 105-107^{o}C).

(a)

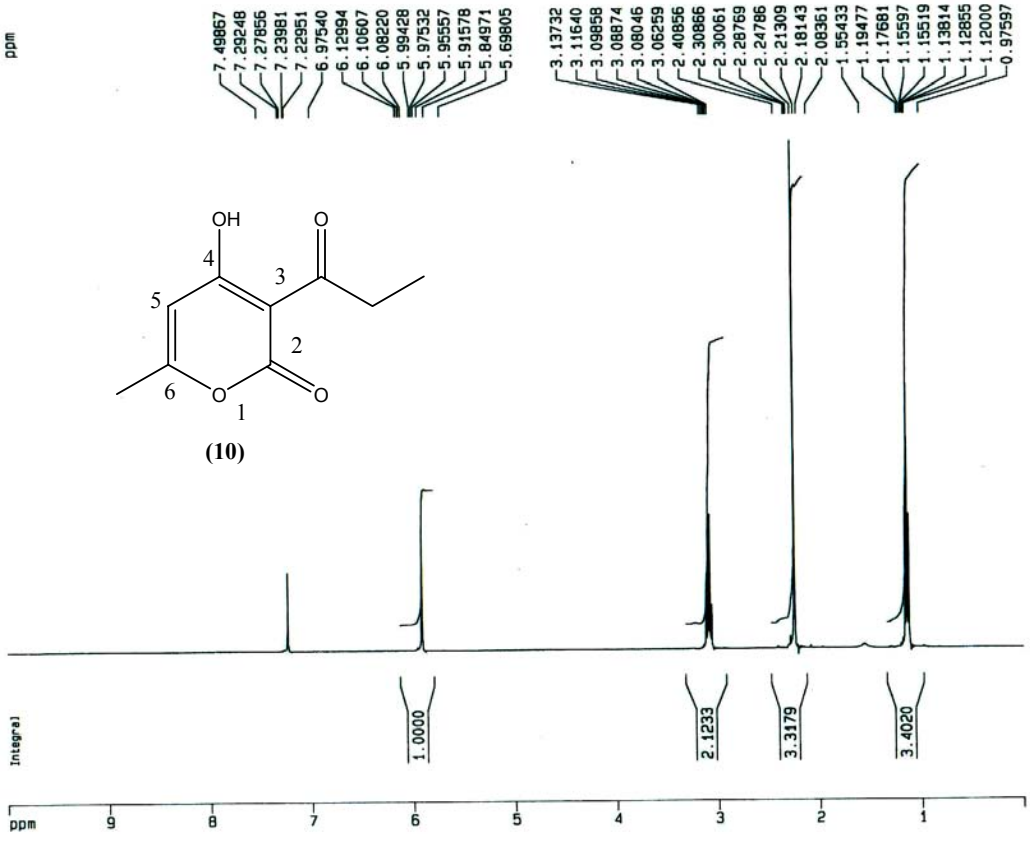
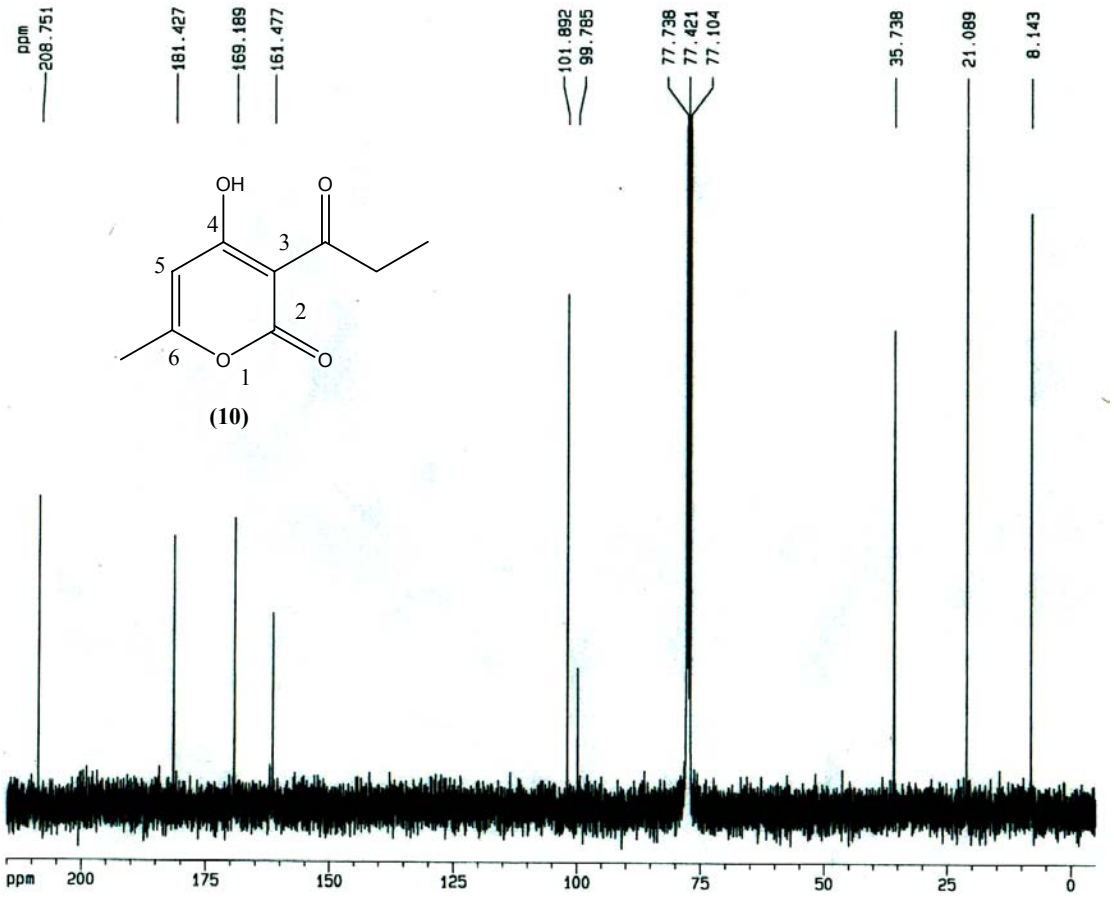


Figure 11(a) shows that the ^{1}H-NMR spectrum of the white solid compound is consistent with the structure of **10.** The key proton at C-5 of the 2-pyrone ring of compound **10** appears as a singlet at δ 5.92 (1H). The protons of the C-6 methyl group appear as a 3H singlet at δ 2.25. The ethyl group of the propionyl side chain appears as a 2H quartet (J = 7.1 Hz) at δ 3.06 due to the methylene group while the methyl group appears as a 3H triplet (J = 7.3 Hz) at δ 1.12. This confirms that the 2-pyrone ring has been propionylated.

(b)



The ^{13}C-NMR spectrum (Figure 11(b)) is also compatible with the structure of **10**. The carbonyl carbon of the acyl side chain absorbs the furthest downfield at δ

208.6. The pyrone ring carbons at positions 2, 3, 4, 5, and 6 absorb the signals at δ 169.2, 99.8, 181.4, 101.9, and 161.5, respectively. In addition, the two methyl carbons in the pyrone ring and acyl side chain are observed the signals at δ 21.1 and 8.14, respectively. Finally, the CH_2 of the propionyl side chain appears at δ 35.7.

(c)

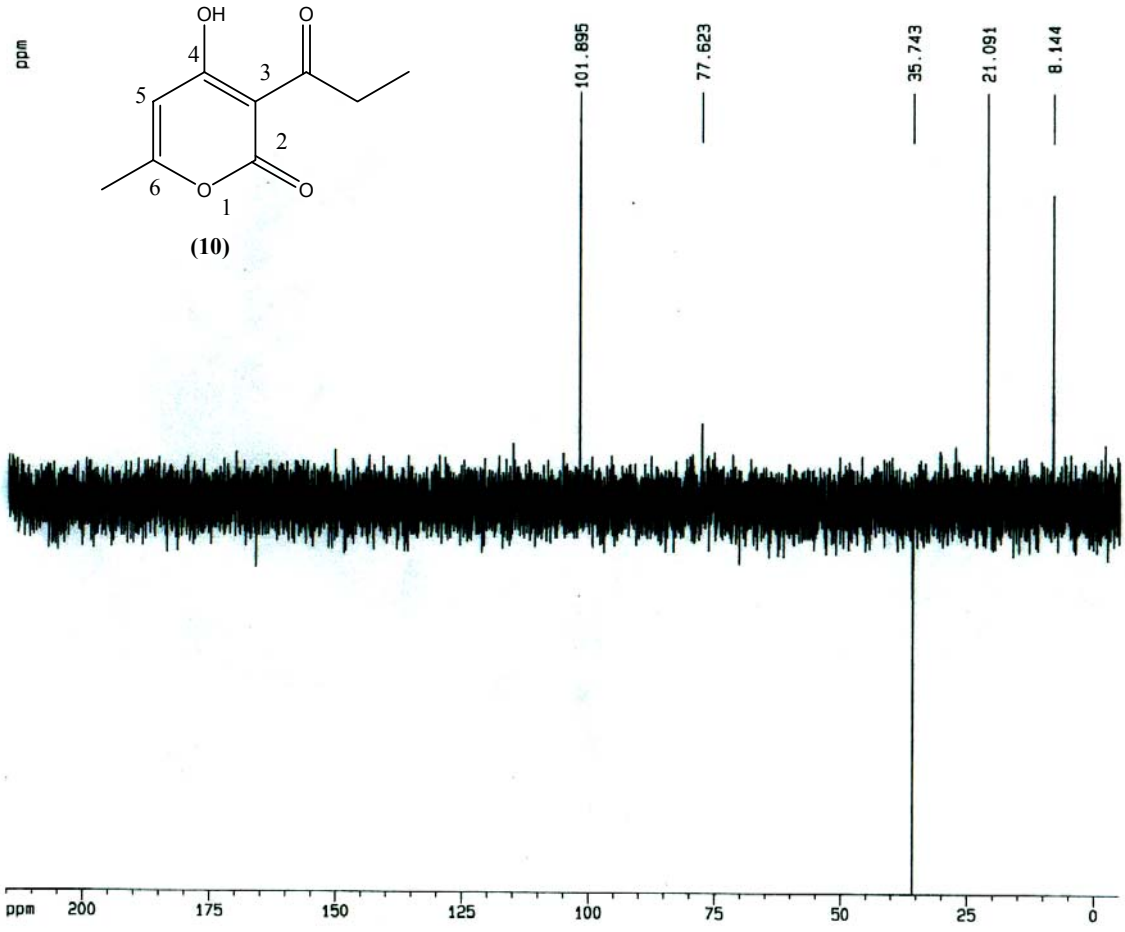
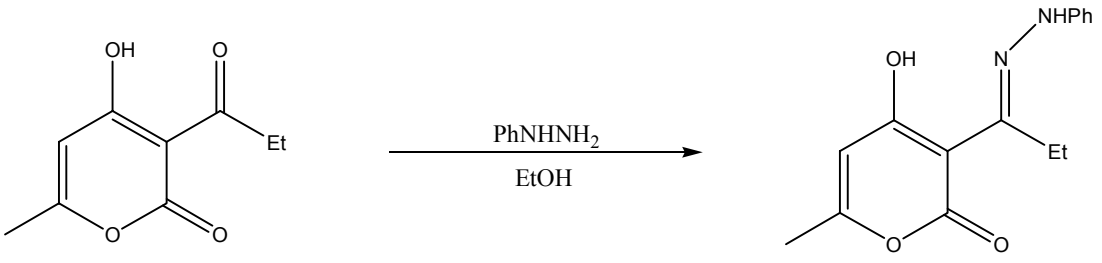


Figure 11: (a) ^{1}H-NMR of compound **10**; (b) ^{13}C-NMR of compound **10**, and (c) ^{13}C-NMR DEPT 135 of compound **10**.

These assignments are consistent with the ^{13}C-DEPT 135 spectrum (Figure 11(c)). The six signals at δ 208.6, 181.4, 169.2, 161.5, and 99.8 disappeared which is consistent with their assignment to the four quaternary carbons of the pyrone ring and

the quaternary hydrazone carbon. In addition, the signals at δ 101.9, 21.1, and 8.14 still appear in the positive direction, which is consistent with their assignment to the CH type carbon of the pyrone ring, the methyl carbon of the pyrone ring, and the methyl carbon in the acyl side chain. The signal at δ 22.4, however, appears in the negative direction confirming that this signal is due to a CH_2 type carbon.



(10) **(11)**

Scheme 14: Synthesis of 4-hydroxy-6-methyl-3-(1-(2-phenylhydrazono)propyl)-2*H*-pyran-2-one **(11)**.

As reported by Gelin, S. and colleague,[3] when 4-hydroxy-6-methyl-3-propionyl-2*H*-pyran-2-one **(10)** was treated with phenylhydrazine in ethanol at 80°C, the yellow crystalline, N-phenylhydrazone, 4-hydroxy-6-methyl-3-(1-(2-phenylhydrazono)propyl)-2*H*-pyran-2-one **(11)** was formed in a yield of 77%, mp 154-155°C (Lit.[3] mp 155°C) (Scheme 14).

(a)

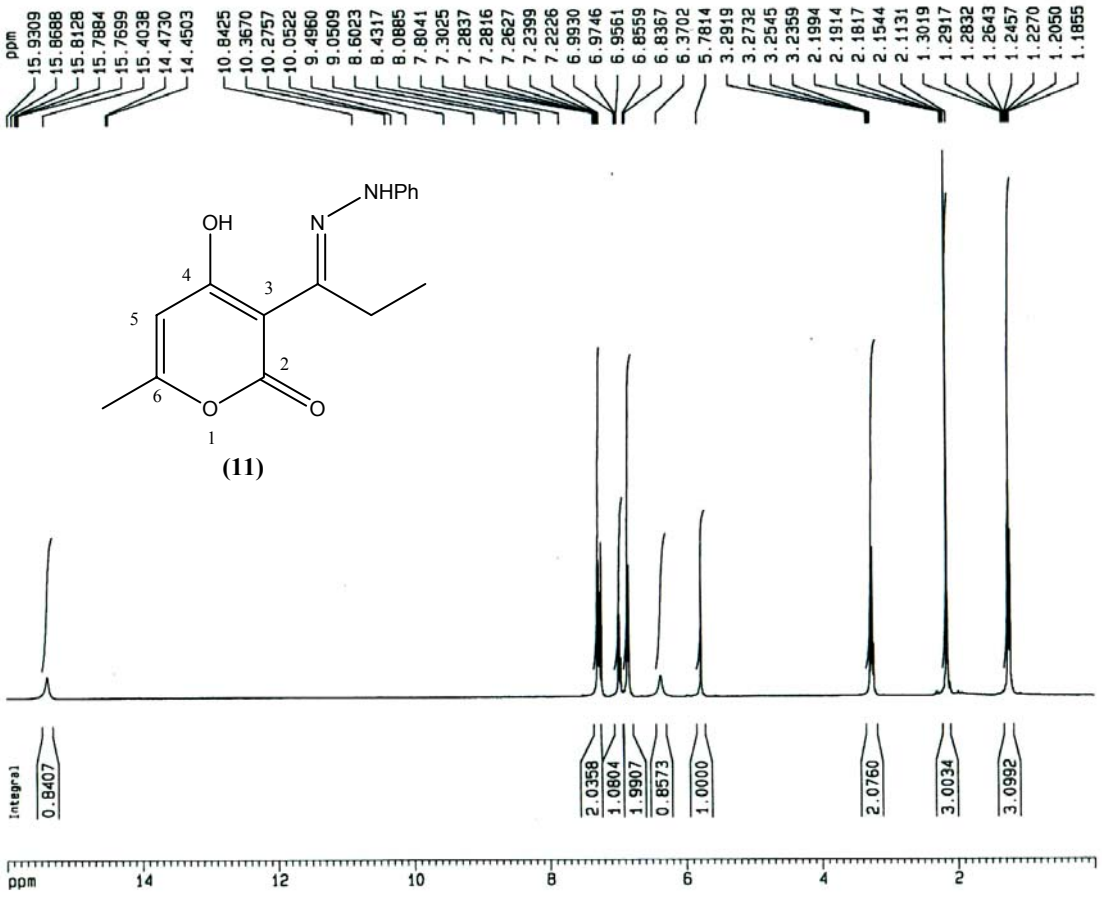
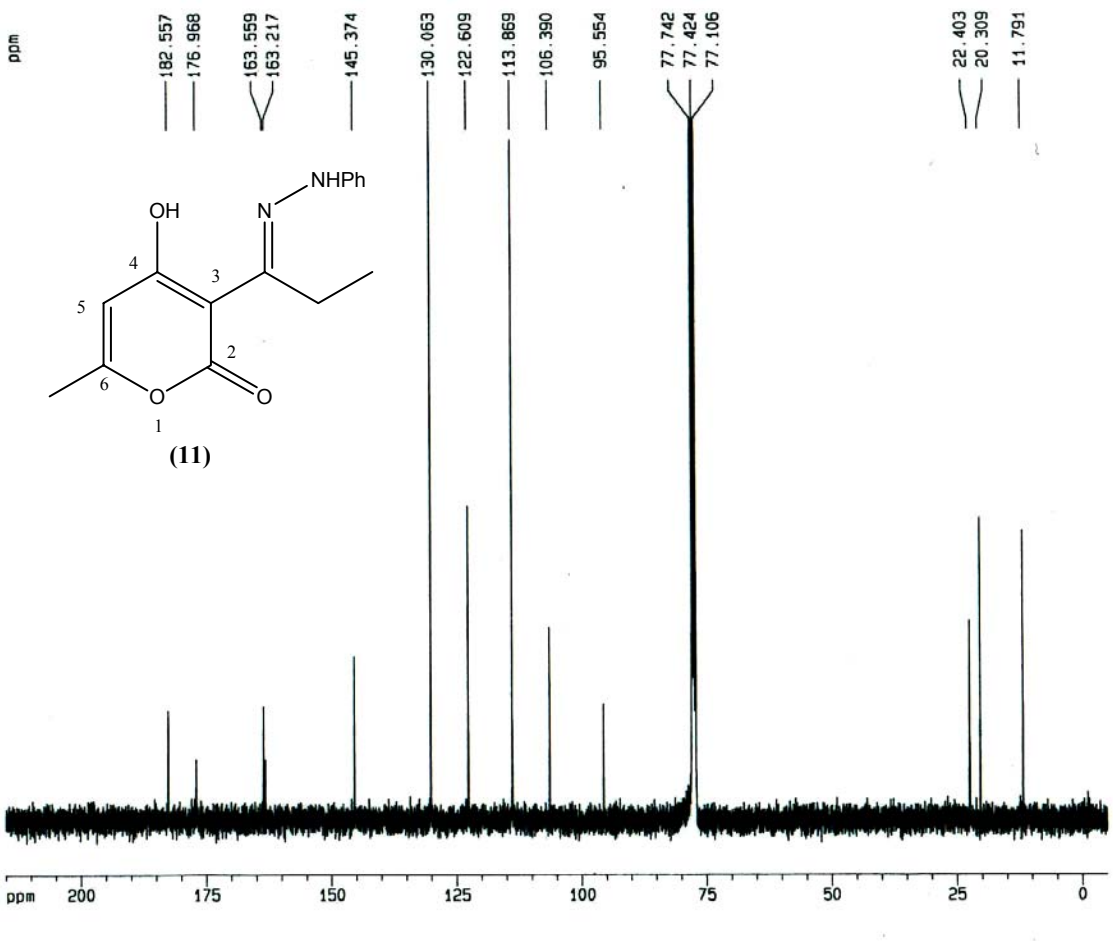


Figure 12(a) shows that the ^{1}H-NMR spectrum of the yellow crystalline product is consistent with the structure of **11.** The key signal for compound **11** is due to the proton at C-5 of the pyrone ring. This was observed as a 1H singlet at δ 5.28. In addition, the C-6 methyl group of the pyrone ring was observed as a 3H singlet at δ 2.15 while the ethyl side chain was observed as a 2H quartet (J = 7.6 Hz) at δ 3.24 and a 3H triplet (J = 7.6 Hz) at δ 1.23. Furthermore, the two triplets at δ 7.27 (2H; J = 7.6 Hz) and 6.96 (1H; J = 7.3 Hz) and a doublet at δ 6.84 (2H; J = 8.1 Hz) are due to absorptions of the phenyl ring protons at the meta, para, and ortho positions, respectively. The signals at δ 15.4 and 6.37 are due to protons of the hydroxyl group

and hydrazine group, respectively. When compound **11** was treated with the D_2O, these signals disappeared.

(b)

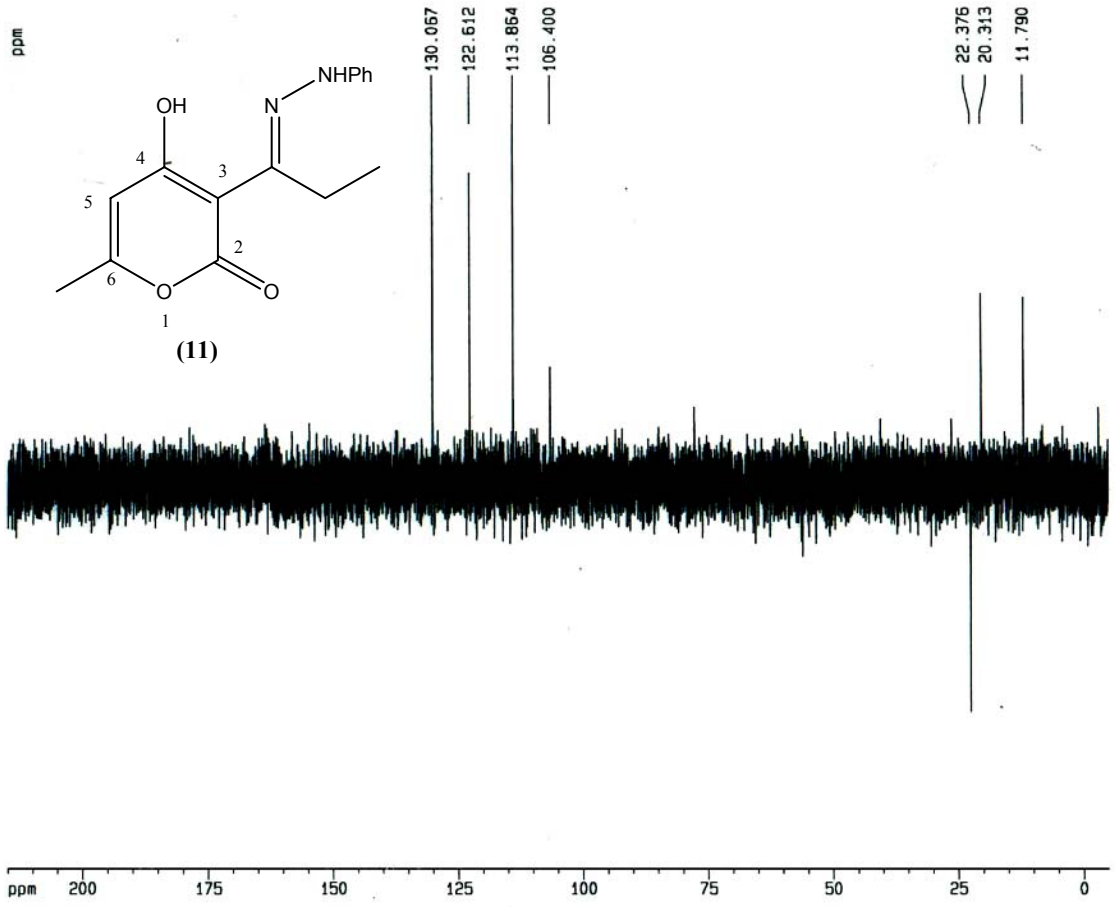


(11)

The ^{13}C-NMR spectrum (Figure 12(b)) is also consistent with the structure of **11**. The hydroxyl carbon in the lactone ring absorbs the furthest downfield at δ 182.6. The signal at δ 176.9 was assigned to the hydrazone carbon, while the carbon at positions 2, 3, 5, and 6 of the pyrone ring exhibit the signals at δ 163.6, 95.6, 106.4, and 163.2, respectively. The quaternary carbon of the phenyl group and the carbon at the

para position absorb at δ 145.4 and 122.6 while the ortho and meta carbons appear as the two singlets at δ 113.9 and 130.1, respectively. In addition, the signal due to the methyl carbon of the pyrone ring appears at δ 20.3 while the signals at δ 22.4 and 11.8 were assigned to the carbon atoms of the ethyl side chain of the hydrazone group.

(c)

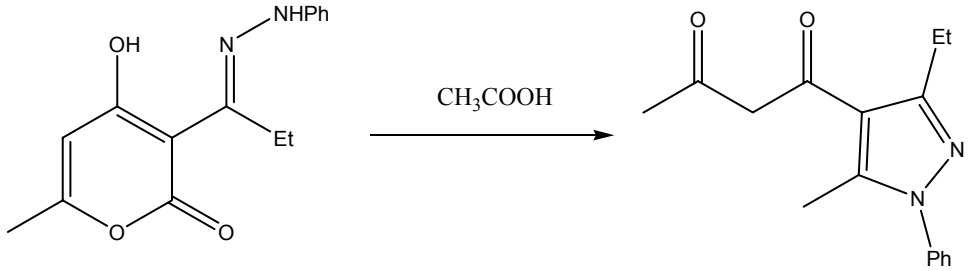


(11)

Figure 12: (a) ^{1}H-NMR of compound **11**; (b) ^{13}C-NMR of compound **11**; (c) ^{13}C-NMR DEPT 135 of compound **11**.

These assignments are consistent with the ^{13}C-DEPT 135 spectrum (Figure 12(c)). The six signals at δ 182.6, 176.9, 163.6, 163.2, 145.4, and 95.6 disappeared,

which is consistent with their assignment to the six quaternary carbons at the position 1 of the phenyl ring, the four positions of the pyrone ring, and the hydrazone carbon. But the signals at δ 130.1, 122.6, 113.9, 106.4, 20.3, and 11.8 still appear in the positive direction which is consistent with their assignment to the CH type carbons of the phenyl ring, the CH type carbon of the pyrone ring, the methyl carbon of the pyrone ring, and the methyl carbon in the ethyl side chain of the hydrazone group. The signal at δ 22.4, however, appears in the negative direction which confirms that it is due to CH_2 type carbon of the ethyl side chain of the hydrazone group.



(11) **(12)**

Scheme 15: Synthesis of 1-(3-ethyl-5-methyl-1-phenyl-1*H*-pyrazol-4-yl)butane-1,3-dione **(12)**.

The literature reported[3] the conversion of **11** to 1-(3-ethyl-5-methyl-1-phenyl-1*H*-pyrazol-4-yl)butane-1,3-dione **(12),** a rearrangement involving a nitrogen nucleophilic attack at the C-2 lactone carbonyl with ring opening to **12**. As reported in the literature,[3] when **11** was refluxed in acetic acid for one hour, **12** was formed in a yield of 66 %, mp 94-95^{o}C (Lit.[3] mp 95^{o}C), (Scheme 15).

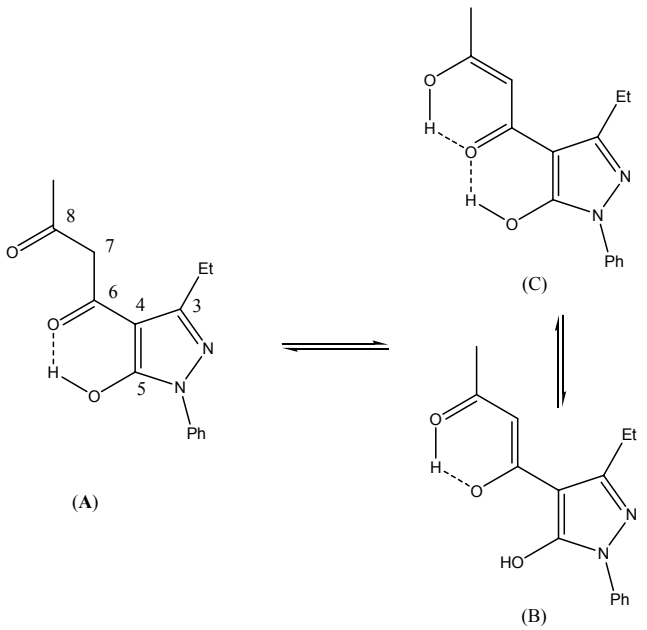
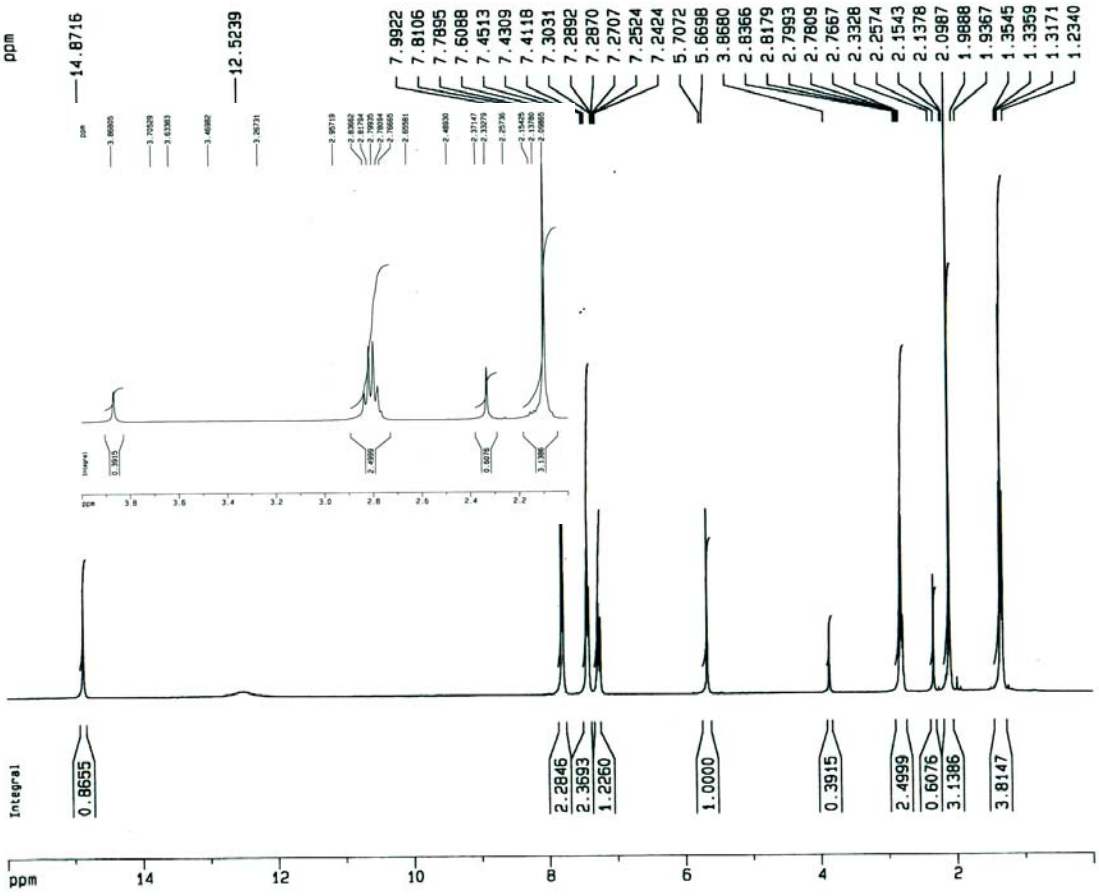


Figure 13: Tautomerization of compound **12**

(a)

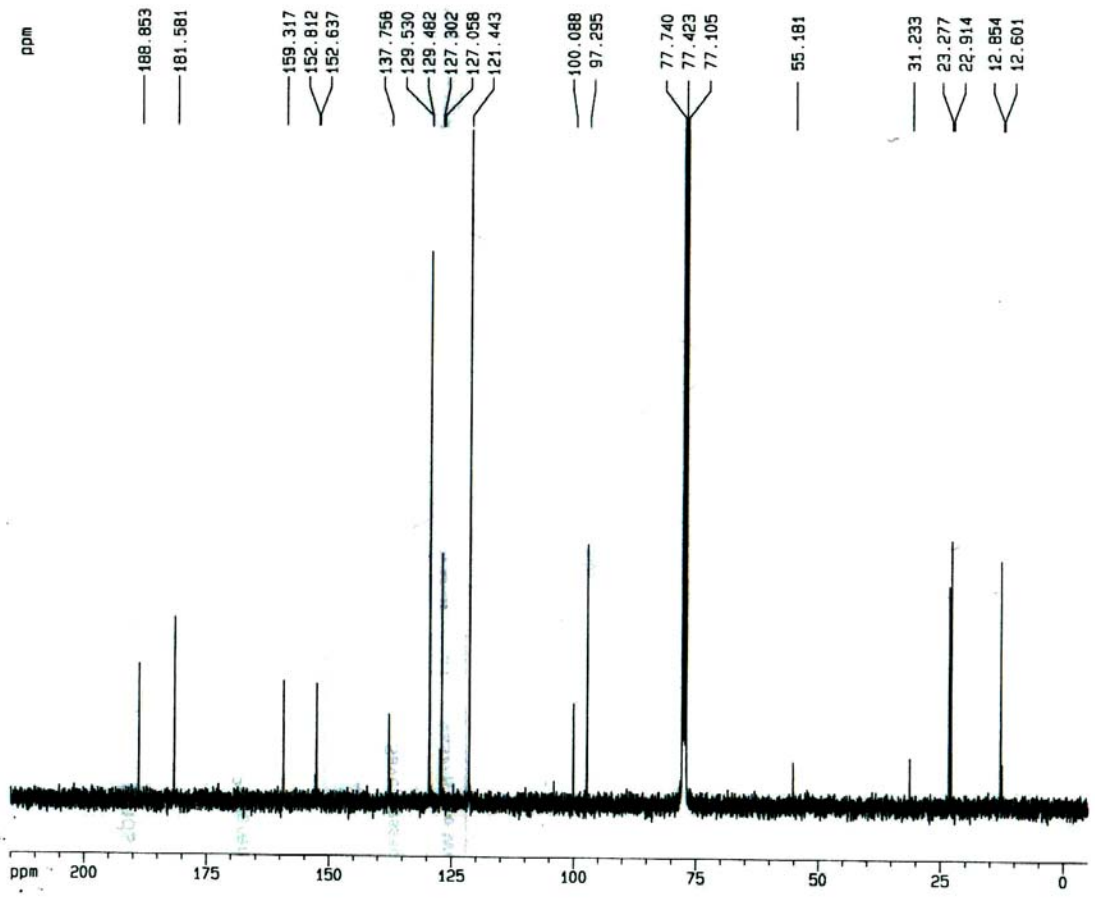


The ^{1}H-NMR in Figure 14(a) shows that compound **12** in deuteriochloroform exists as an equilibrium mixture of keto form A and an enol form which is the average of B and C. The enol form (B $\rightleftharpoons$ C) can be detected by the singlets at δ 5.67 and 2.10 due to the C-7 vinyl and C-8 methyl group while the singlets at δ 3.87 and 2.33 result from the C-7 methylene and C-8 methyl protons of the keto tautomer A. Based on the integral rises of 1.00 and 0.391 respectively for the vinyl and methylene proton signals, the enol to keto ratio was calculated to be 5.1 to 1.

The signals at δ 14.9 and 12.5 are due to protons bonded to oxygens. The sharp enolic signal at δ 14.9 is consistent with the strongly chelated hydroxyl proton on the side chain of the enol tautomer (B $\rightleftharpoons$ C), while the broad signal at δ 12.5 is consistent with the more acidic proton at the C-5 hydroxyl group.

In addition, the ^{1}H-NMR also shows a 2H doublet (J = 8.6 Hz) at δ 7.79, a 2H triplet at δ 7.41 (J = 7.6 Hz), and a 1H multiplet at δ 7.25 (J = 7.3 Hz) characteristic of protons in the ortho, meta, and para positions respectively of the phenyl ring. As expected, the spectrum also exhibits a 2H quartet (J = 7.3 Hz) at δ 2.78 and a 3H triplet (J = 7.6 Hz) at δ 1.32 for the ethyl group at C-3 of the pyrazole ring.

(b)



The ^{13}C-NMR spectrum (figure 14(b)) in $CDCl_3$ solution of compound **12** gives rise to two resonances for all the carbon atoms corresponding to the enol and keto tautomers. It is known that a hydrogen-bonded carbonyl carbon resonates at lower field than a corresponding free carbonyl carbon and that an enolic carbon atom resonates at higher field than a corresponding keto carbon atom, according to literature reported.[3] The C-6 resonance of the enol form (B $\rightleftharpoons$ C) would be at a lower field than the C-8 carbon atom. From the chemical shift values, respectively at δ 188.9 and 181.6, it can be reasonably concluded the enol tautomer contributes mainly to the tautomeric

population in $CDCl_3$ solution. The characteristic ^{13}C NMR spectrum of the enol tautomer at δ 188.9, 181.6, 97.3 and 22.9 is consistent with C-6, C-8, C-7, and methyl C-8 on the side chain of the pyrazole ring, respectively. The carbons of the pyrazole ring at δ 159.3, 152.6 and 100.1 were assigned to C-5, C-3 and C-4, respectively. The phenyl ring carbons at positions 1 and 4 absorb at δ 137.8 and 127.1, while the ortho and meta carbons of the phenyl ring appear as two singlets at δ 121.4 and 129.5, respectively. The two carbons of the ethyl side chain of the pyrazole ring appear at δ 23.3 and 12.9. On the other hand, the A tautomer could not be completely assigned in the ^{13}C-NMR spectrum because of the low intensity of the signals of the minor A tautomer. However, the ^{13}C-NMR spectrum exhibits some key signals of the A tautomer which could be assigned. These include the signals at δ 55.18 for C-7 methylene carbon and at δ 31.23 for the methyl C-8 on the side chain, while the signal at δ 152.8 appears for C-3 of the pyrazole ring. Also, the signal at δ 12.60 appears for the methyl carbon of the ethyl side chain.

These assignments are consistent with the ^{13}C-NMR DEPT 135 of compound **12** (Figure 14(c)).

(c)

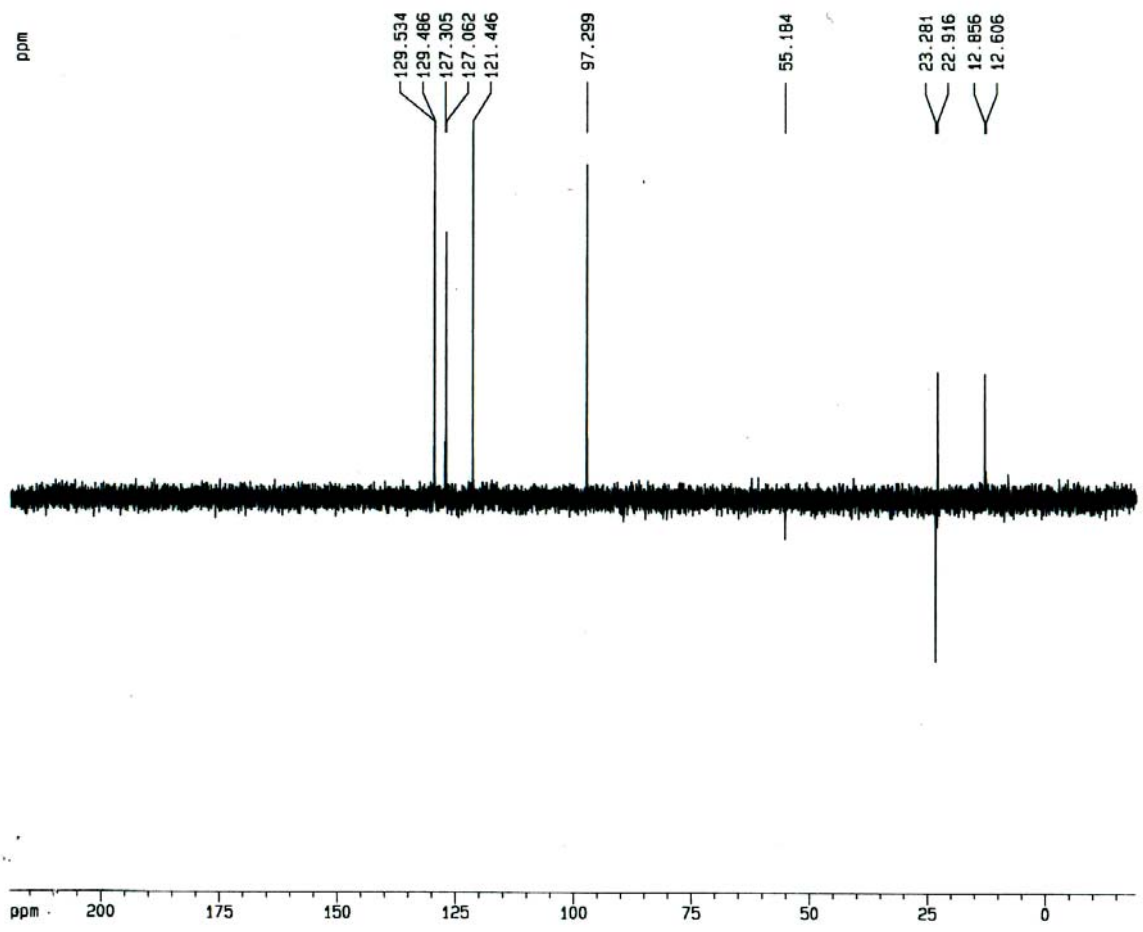
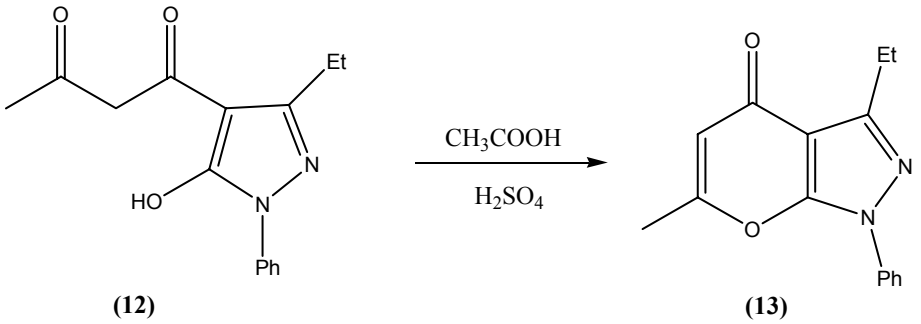


Figure 14: (a) ^{1}H-NMR of compound **12**; (b) ^{13}C-NMR of compound **12**; (c) ^{13}C-NMR DEPT 135 of compound **12**.

As expected the ^{13}C-NMR DEPT 135 (figure 14(c)) of compound **12** shows that the seven signals at δ 188.9, 181.6, 159.3, 152.6, 152.8, 137.8, and 100.1 disappeared which is consistent with their assignment to the two sets of the quaternary signals of the keto A and the enol B and C tautomers. These signals are due to the keto and enol carbons on the C-6 and 8 side chain, the quaternary carbon of the phenyl ring, and the quaternary carbons of the pyrazole ring at C-3, C-4, and C-5 positions. But, the signals

at δ 129.5, 127.1, 121.4, 97.3, 22.9, and 12.9 appear in the positive direction which is consistent with their assignment to the CH type carbons at ortho, meta, and para positions of the phenyl ring, the CH vinyl side chain, and the two methyl types at C-8 and the ethyl side chain. Thus, the signal at δ 12.6 appears for the methyl of the ethyl side chain for the minor keto tautomer. On the other hand, the negative signal is observed at δ 55.18 which is due to the methylene carbon of the diketo side chain ring in keto tautomer. Also, the signal at δ 23.28 appears for the CH_2 type carbon of the ethyl side chain.



(12) **(13)**

Scheme 16: Synthesis of 3-ethyl-6-methyl-1-phenylpyrano[2,3-*c*]pyrazole-4(1*H*)-one **(13)**.

The ring closure of **12** to 3-ethyl-6-methyl-1-phenylpyrano[2,3-*c*]pyrazole-4(1*H*)-one **(13)**, which was reported in the literature,[3] was achieved by refluxing compound **12** in acetic acid in the presence of sulfuric acid as a catalyst to obtain **13** in a yield of 82%, mp 132-133^{o}C (Lit.[3] mp 132^{o}C) (Scheme 16).

(a)

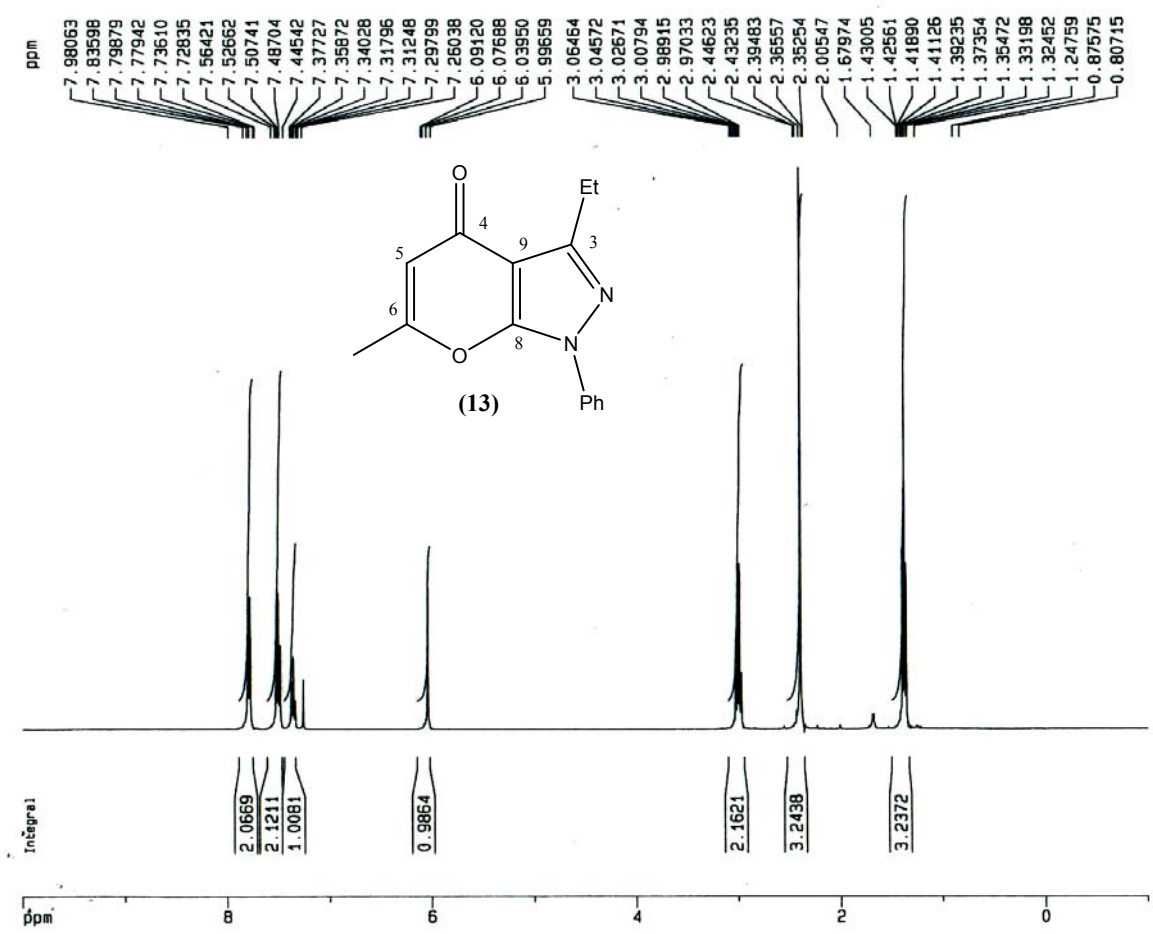
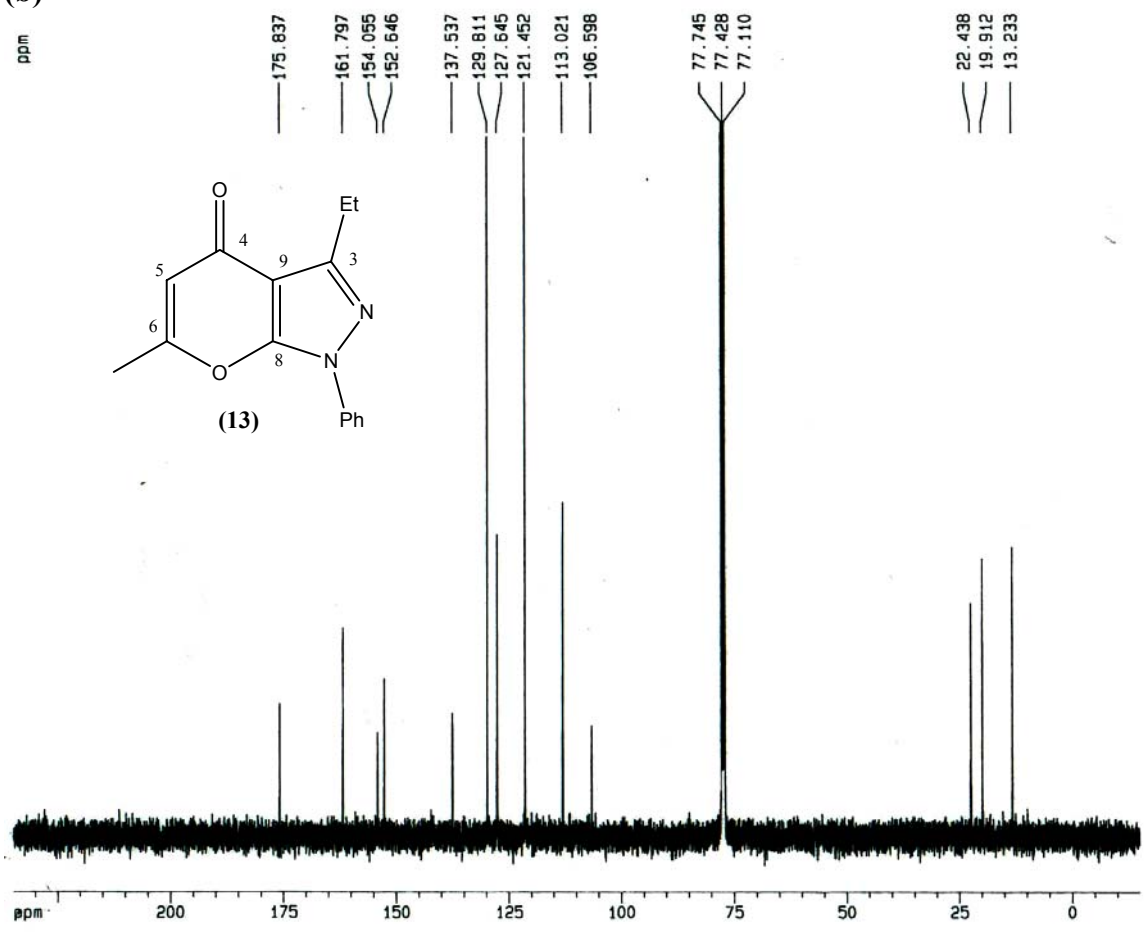


Figure 15(a) shows that the ^{1}H-NMR spectrum of the colorless crystals obtained in the previous experiment is consistent with the structure of **13**. A key signal due to the proton of the pyrone ring appears as a 1H singlet at δ 6.02 while the methyl protons of the pyrone ring is shown as a 3H singlet at δ 2.34. The two triplets at δ 7.28 (1H; J = 7.6 Hz) and 7.47 (2H; J = 7.6 Hz) and one doublet at δ 7.71 (2H; J = 8.6 Hz) are due to absorptions of the protons at the para, meta and ortho positions of the phenyl ring, respectively. Finally, the ethyl side chain was observed as a 2H quartet (J = 7.1 Hz) at δ 2.95 and a 3H triplet (J = 7.3 Hz) at δ 1.30.

(b)



The ^{13}C-NMR spectrum (Figure 15(b)) is also consistent with the structure **13**. The carbonyl carbon of the pyrone ring absorbs the furthest downfield at δ 175.8. The signals at δ 154.1 and δ 106.6 were assigned to the bridgehead carbons at positions 8 and 9, respectively. The pyrone ring carbons in positions 5 and 6 appear at δ 113.0 and 161.8, respectively. The imine carbon of the pyrazole ring is assigned to the signal at δ 152.6. The phenyl ring carbon attached to the nitrogen atom and at the para carbon absorb at δ 137.5 and 127.6 respectively. While the ortho and meta carbons in the phenyl ring appear as two singlets at δ 121.5 and 129.8, respectively. The methyl

carbon of the pyrone ring is shown at δ 19.9 while the signals at δ 22.4 and 13.2 were assigned to the carbon atoms of the ethyl side chain of the pyrazole ring.

(c)

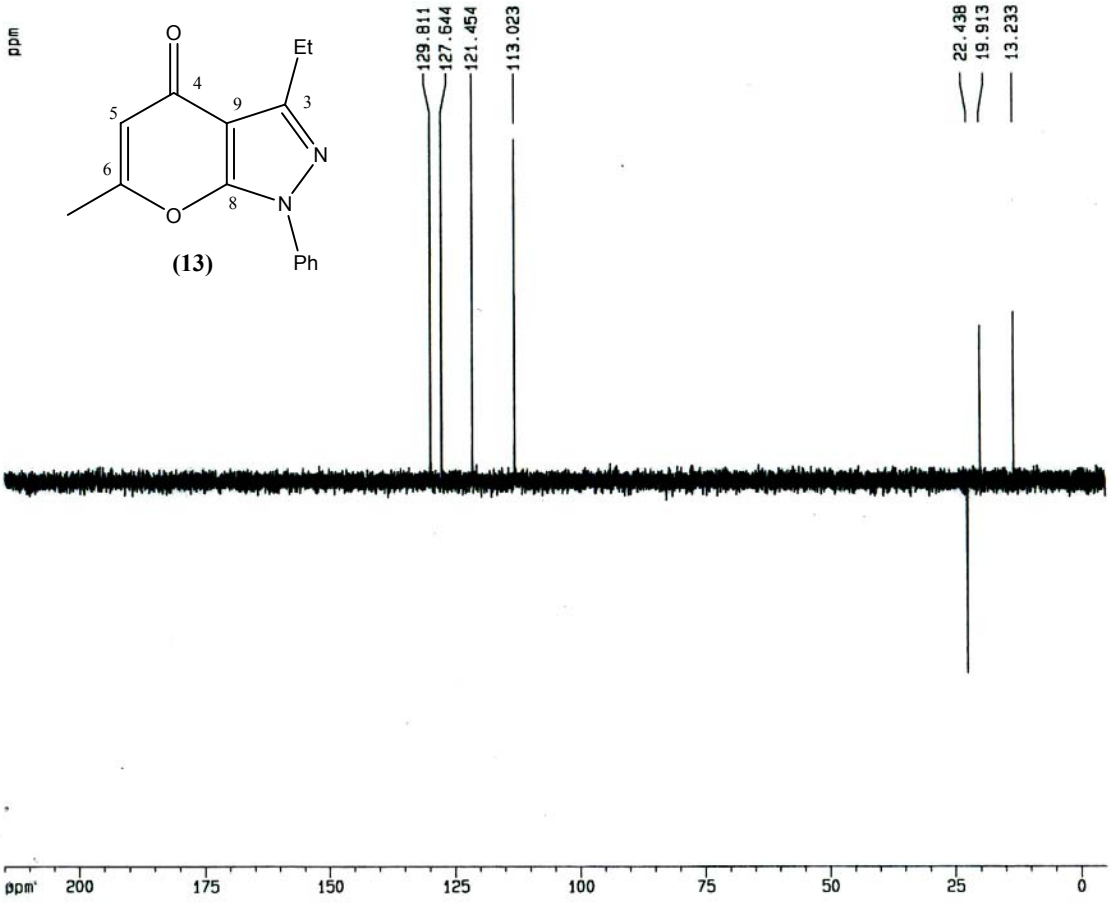
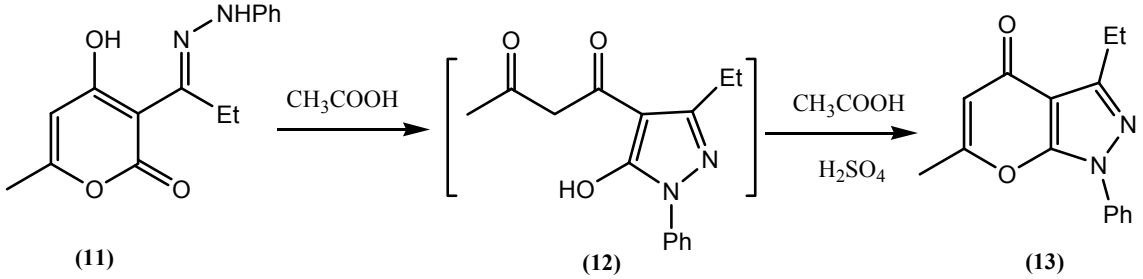


Figure 15: (a) ^{1}H-NMR of compound **13**; (b) ^{13}C-NMR of compound **13**; (c) ^{13}C-NMR DEPT 135 of compound **13.**

These assignments are consistent with the ^{13}C-DEPT 135 spectrum (Figure 15(c)). The six signals at δ 175.8, 161.8, 154.1, 152.6, 137.5, and 106.6 disappeared which is consistent with their assignment to the six quaternary carbons of the pyranopyrazole and phenyl rings. In addition, the signals at δ 129.8, 127.6, 121.5,

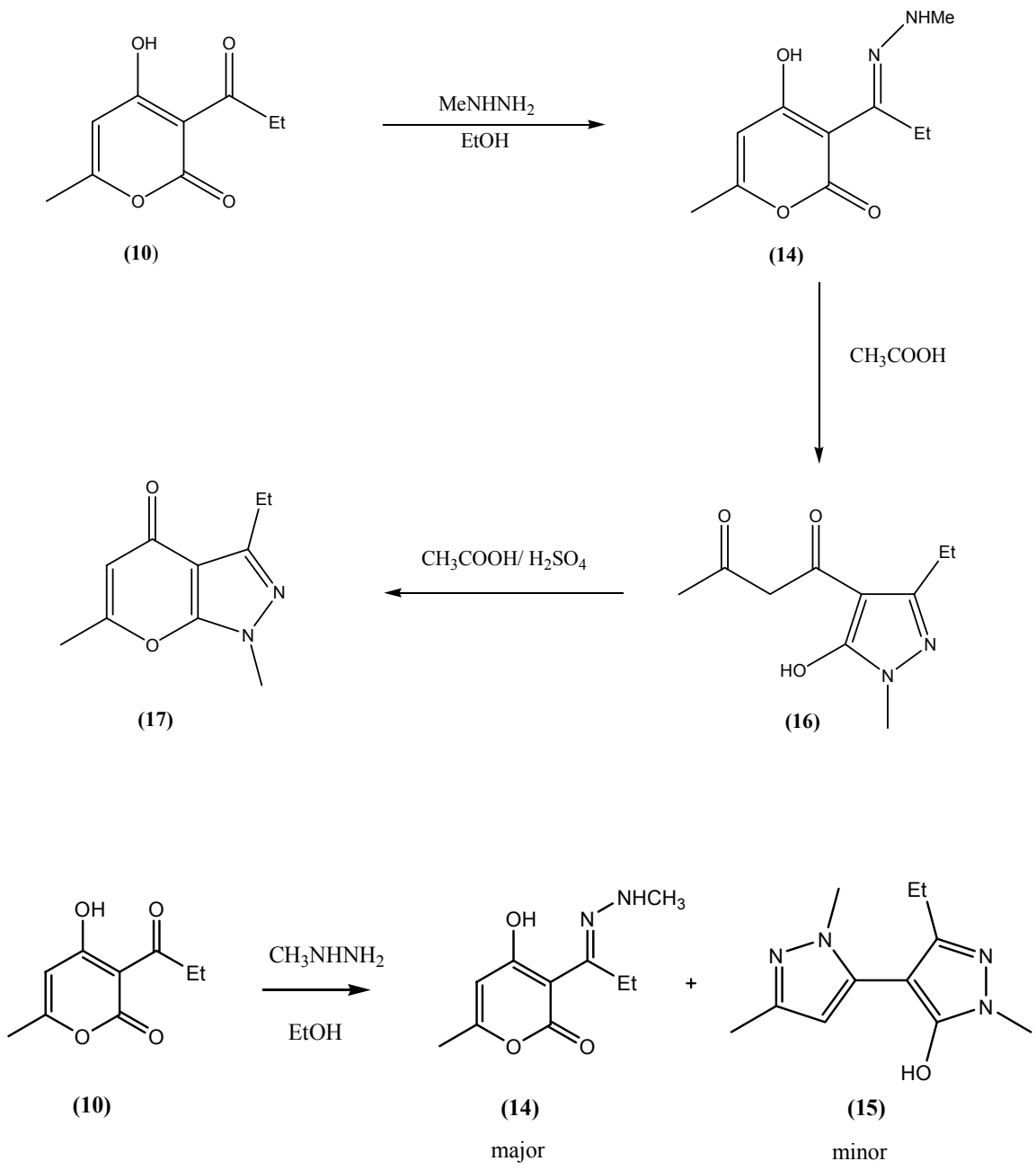
113.0, and 19.9 still appear in the positive direction which is consistent with their assignment to the three CH type carbons of phenyl ring, the CH type carbon of the pyrone ring, and the methyl carbon of the pyrone ring. The positive signal at δ 13.2 is due to the methyl carbon of the ethyl side chain of the pyrazole ring, while the signal at δ 22.4 appears in negative direction consistent with its assignment to the CH_2 type carbon of the ethyl side chain of the pyrazole ring.



(11) **(12)** **(13)**

Scheme 17: Synthesis of 3-ethyl-6-methyl-1-phenylpyrano[2,3-*c*]pyrazole-4(1*H*)-one **(13)**.

The conversion of **11** to **13** without isolation of **12** was also attempted. To accomplish this, N-phenylhydrazone **11** was refluxed in acetic acid for one hour. Concentrated sulfuric acid was then added dropwise and the mixture was refluxed for one additional hour to give **13** in a yield of 79 %. This approach led to the isolation of **13** in an overall yield of 61 % (Scheme 17) which is this substantially higher than the yield of 42 % which was obtained when intermediates 1**2** was isolated and purified.



Scheme 18: Synthesis of 4-hydroxy-6-methyl-3-(1-(2-methylhydrazono)propyl)-3,4-dihydro-2*H*-pyran-2-one **(14)**.

Ethyl derivative **10** was also shown to be a suitable starting material for the synthesis of the corresponding N-methylpyranopyrazole **17**. To accomplish this **10** was allowed to react with methylhydrazine in ethanol solution at room temperature for 2

hours. The new 4-hydroxy-6-methyl-3-(1-(2-methylhydrazono)propyl)-3,4-dihydro-2*H*-pyran-2-one **(14)** was observed to be the major product in a yield of 56%, mp 97-98^{o}C and also the new 5-hydroxy-3-ethyl-1-methyl-4-(1,3-dimethyl-pyrazol-5-yl)pyrazole **(15)** was observed as a minor product in a yield of 13%, mp 162-163^{o}C (Scheme 18).

(a)

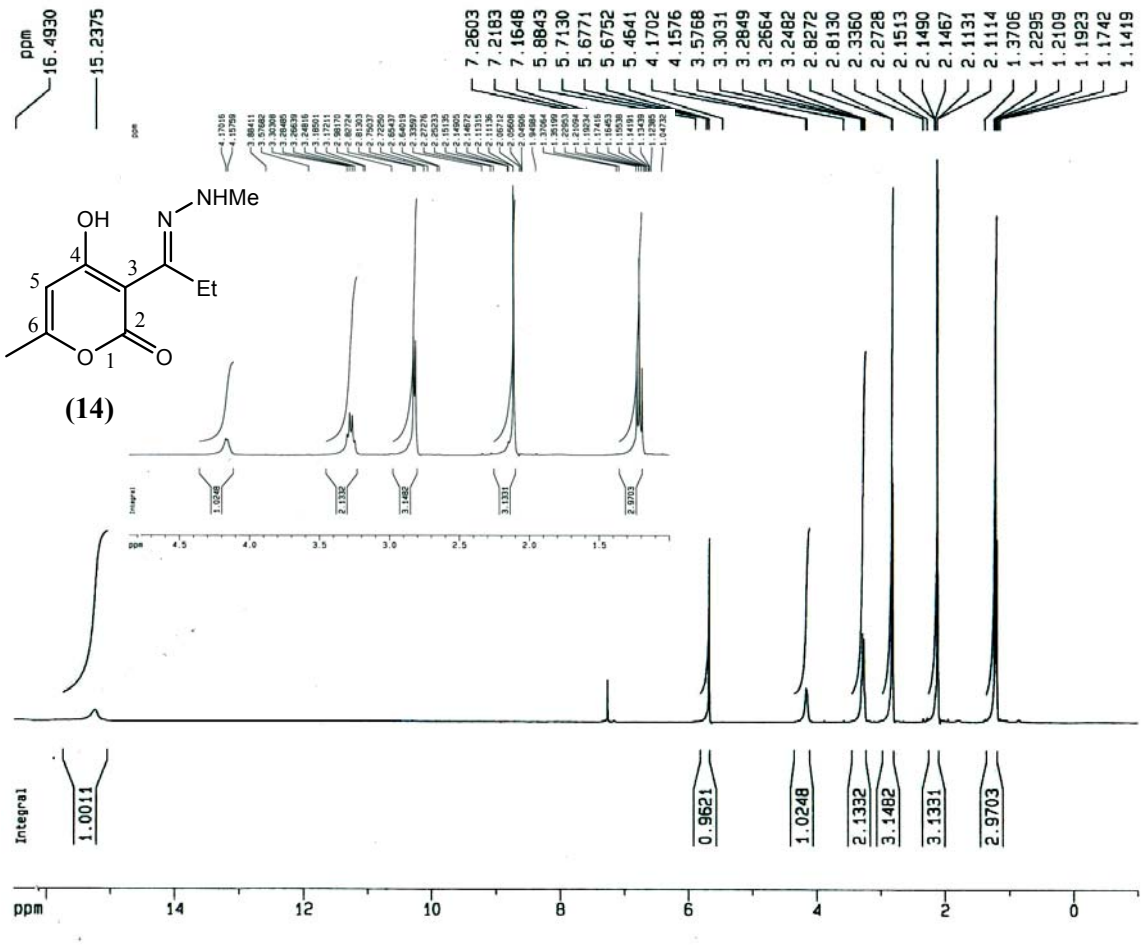
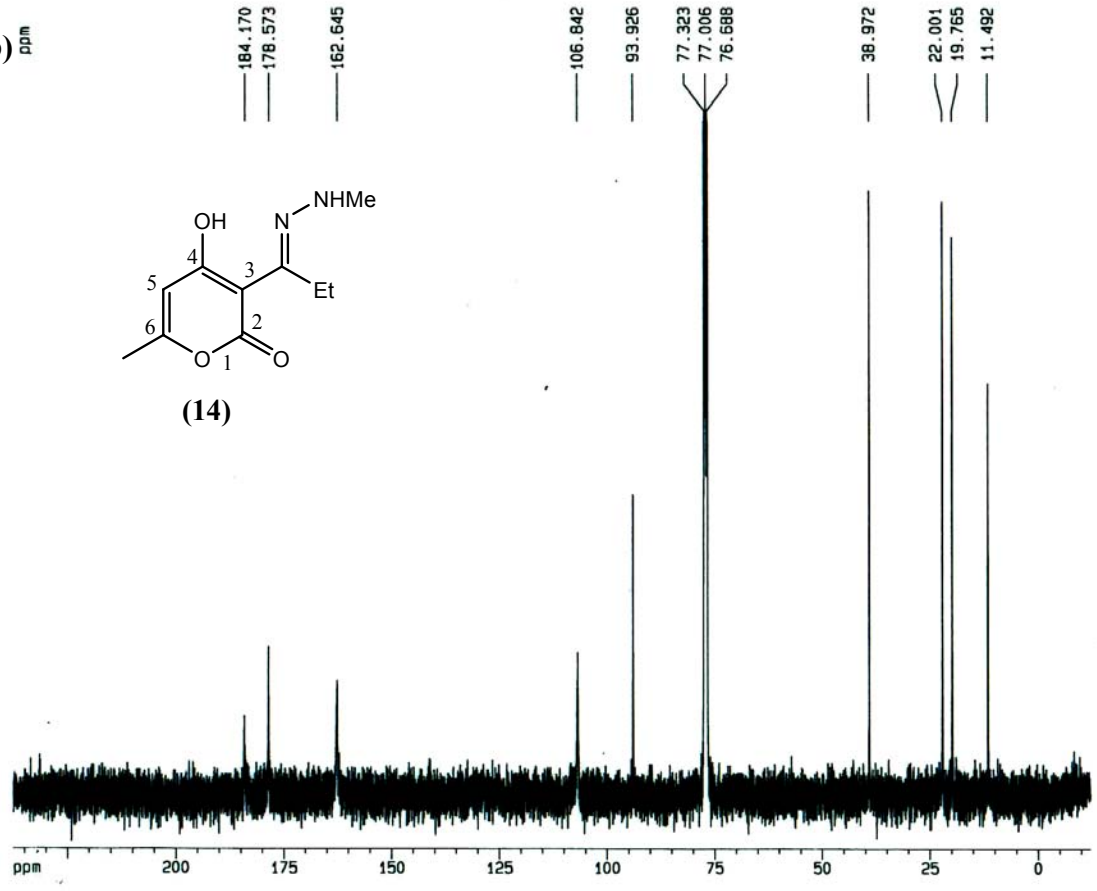


Figure 16(a) shows the ^{1}H-NMR spectrum of the structure of **14.** The key signal for this compound is the singlet at δ 5.68 (1H) due to the C-5 proton of the pyrone ring. The spectrum also shows a 2H quartet (J = 6.1 Hz) at δ 3.26 and a 3H triplet (J = 7.3

Hz) at δ 1.21 for the ethyl side chain. The spectrum also exhibit a 3H singlet at δ 2.11 due to the C-6 methyl group and a 3H doublet (J = 5.5 Hz) at δ 2.82 due to the N-methyl group which is coupling with the NH proton. The latter proton on the nitrogen atom appears as a broad signal at δ 4.03, while the proton on the C-4 hydroxyl group appears as a broad signal at δ 15.2. As expected, upon addition of D_2O the signals at δ 15.2 and 4.03 disappeared while the doublet at δ 2.82 collapsed to a singlet.

(b)

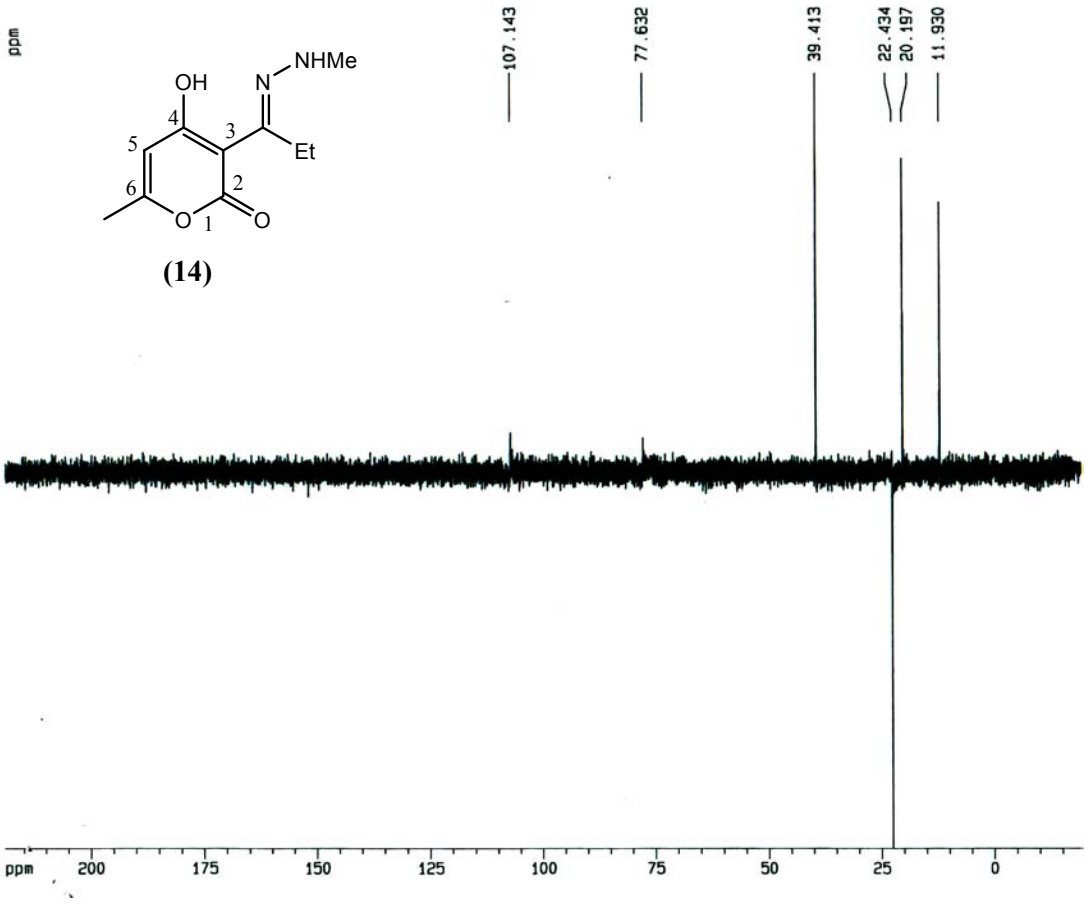


(14)

The ^{13}C-NMR spectrum (Figure 16(b)) is also consistent with the structure of **14**. The hydroxyl carbon in the lactone ring absorbs the furthest downfield at δ 184.2.

The signal at δ 178.6 was assigned to the hydrazone carbon. The signals due to the carbons at positions 2, 3, 5, and 6 of the pyrone ring are observed at δ 162.7, 93.9, 106.8 and 162.6, respectively. The signal at δ 38.9 appears for the N-methyl carbon, while the signal at δ 19.8 appears for the C-6 methyl carbon of the pyrone ring. Finally, the carbon signals at δ 22.0 and 11.5 appear for the ethyl side chain.

(c)

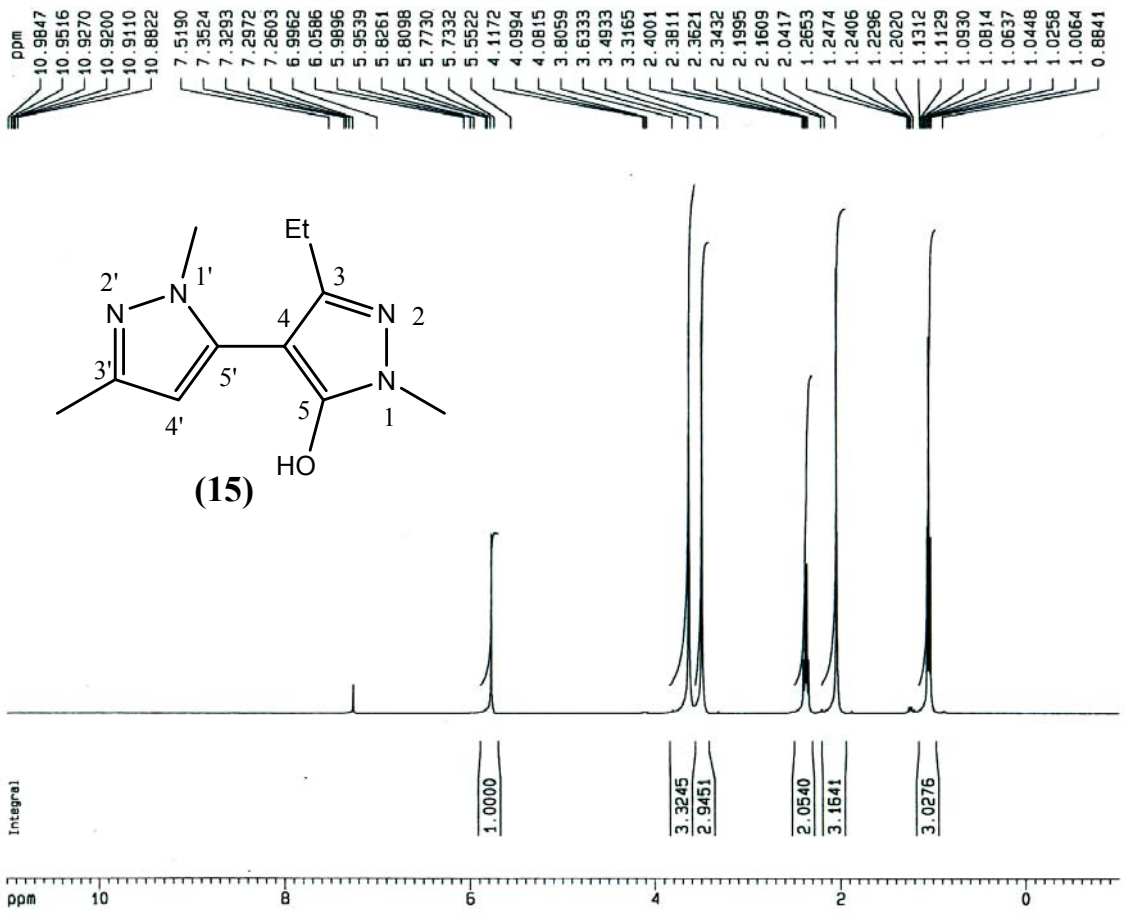


(14)

Figure 16: (a) ^{1}H-NMR of compound **14**; (b) ^{13}C-NMR of compound **14**; (c) ^{13}C-NMR DEPT 135 of compound **14**.

These assignments are consistent with the ^{13}C-DEPT 135 spectrum (Figure 16(c)). The five signals at δ 184.2, 178.6, 162.7, 162.6, and 93.93 disappeared which is consistent with their assignment to the four quaternary carbons of the pyrone ring and the hydrazone group. In addition, the signal at δ 106.8 still appears as a positive signal which is consistent with a CH type carbon of the pyrone ring. Also, the signals at δ 39.41, 20.19, and 11.93 are due to carbons of the methyl groups on the nitrogen atom, the pyrone ring, and the ethyl side chain, respectively. But the signal at δ 22.0 appears in the negative position as expected for the CH_2 type carbon of the ethyl side chain

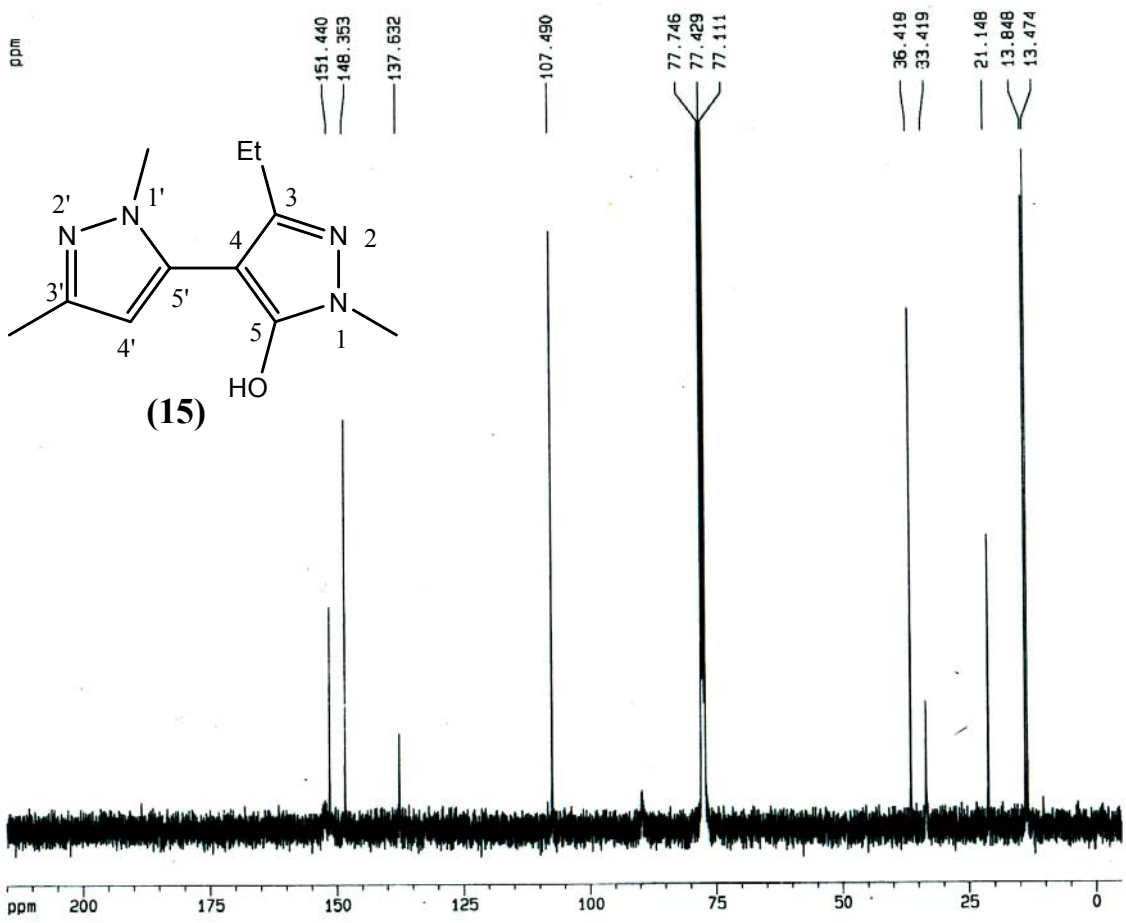
(a)



(15)

Figure 17(a) shows that the ^{1}H-NMR spectrum of the white crystalline minor product is consistent with the structure of **15**. The key proton at C-4' of the pyrazole ring appears as a 1H singlet at δ 5.75. The N- methyl protons of C-1 and C-1' appear as 3H singlets at δ 3.49 and 3.63, respectively. The methyl protons at C-3' appear as a 3H singlet at δ 2.04, while the protons of the ethyl side chain at C-3 appear as a 2H quartet (J = 7.6 Hz) signal at δ 2.36 and a 3H triplet (J = 7.8 Hz) signal at δ 1.02.

(b)

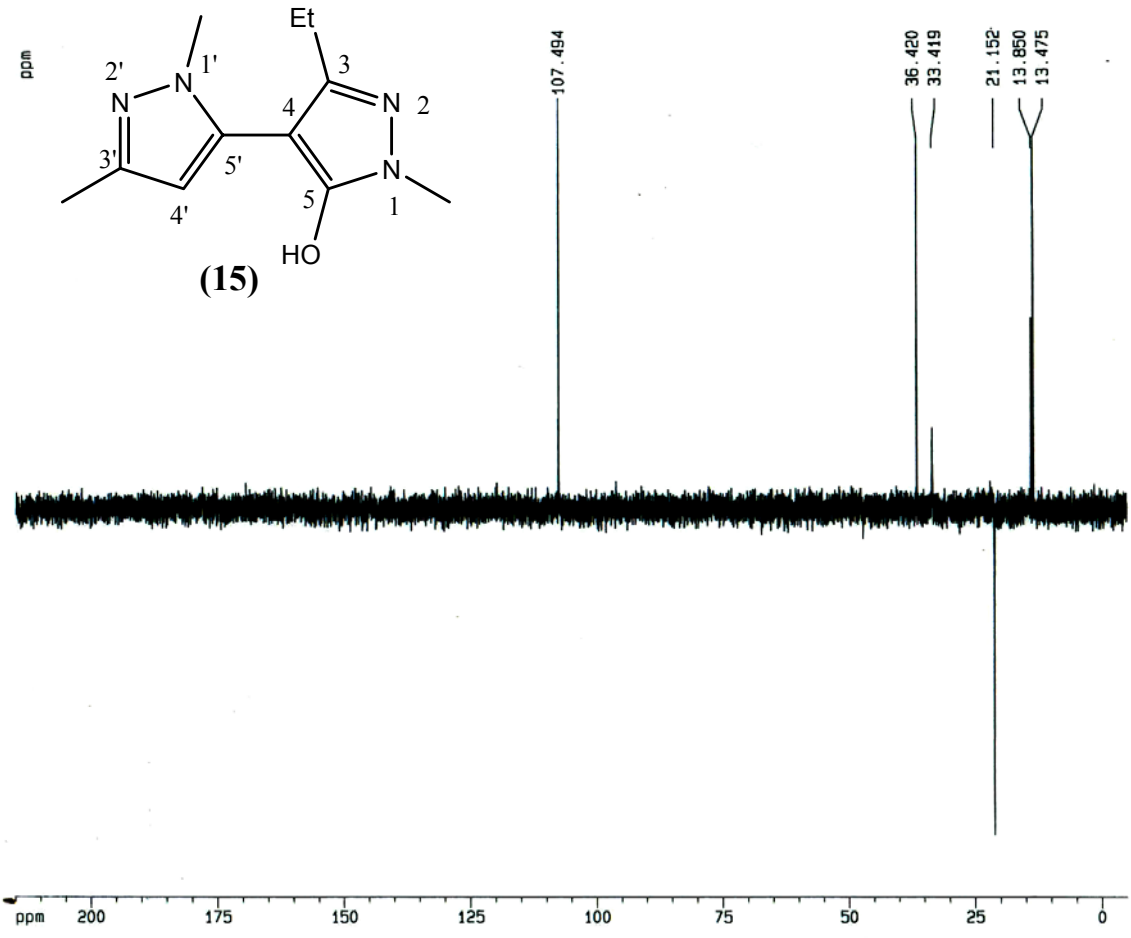


(15)

The ^{13}C-NMR spectrum (Figure 17(b)) is also consistent with the structure of **15** and is similar to the spectrum of bipyrazol **8** in which the carbon signals of the

hydroxyl pyrazole ring are observed with very low intensity. The hydroxyl carbon of the pyrazole ring absorbs furthest downfield and is observed as the very small signal at δ 151.9. The signal at 137.6 is due to the carbon at C-5 position. The signals at δ 151.4 and 148.4 were assigned to the carbons at C-3' and C-3 positions, respectively, while the carbons at C-4' and C-4 appear at δ 107.5 and 89.15, respectively. In addition, the signals at δ 36.42, 33.42, and 13.85 are due to carbons of the methyl groups on the nitrogen atom at C-1 and C-1' positions, and C-3' position of the pyrazole ring, respectively. Finally, the carbons of the ethyl side chain are observed the signals at δ 21.15 and 13.47.

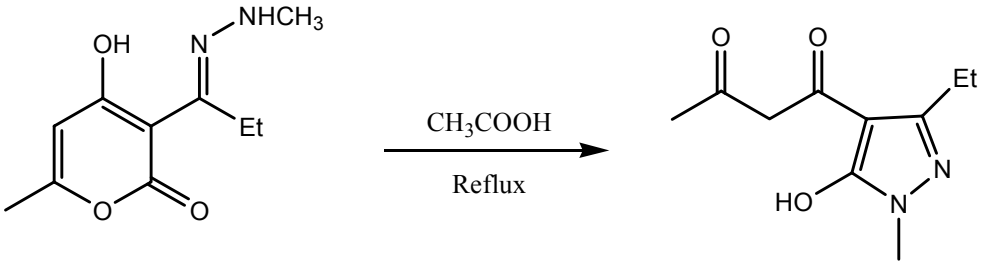
(c)



(15)

Figure 17: (a) ^{1}H-NMR of compound **15**; (b) ^{13}C-NMR of compound **15**; (c) ^{13}C-NMR DEPT 135 of compound **15**.

These assignments are consistent with the ^{13}C-DEPT 135 spectrum (Figure 17(c)). The five signals at δ 151.9, 151.4, 148.4, 137.6, and 89.1 disappeared which is consistent with their assignment to the five quaternary carbons of the bipyrazole **15**. The signal at δ 107.5 still appears in the positive direction which is consistent with the CH type carbon of the pyrazole ring, while the methyl signals at δ 36.4, 33.4, 13.8, and 13.5 are due to the carbons of the methyl groups on the nitrogen atom and side chain of the pyrazole ring. However, the signal at δ 21.2 is observed in the negative direction which is consistent with the CH_2 type carbon of the ethyl side chain.



(14) **(16)**

Scheme 19: Synthesis of 1-(3-ethyl-5-hydroxy-1-methyl-1*H*-pyrazol-4-yl)butane-1,3-dione **(16)**.

The intramolecular cyclization of the methylhydrazone **14** was accomplished by refluxing **14** in acetic acid for one hour. The new compound 1-(3-ethyl-5-hydroxy-1-methyl-1*H*-pyrazol-4-yl)butane-1,3-dione **(16)** was obtained in a yield of 70%, mp 123-124^{o}C (Scheme 20).

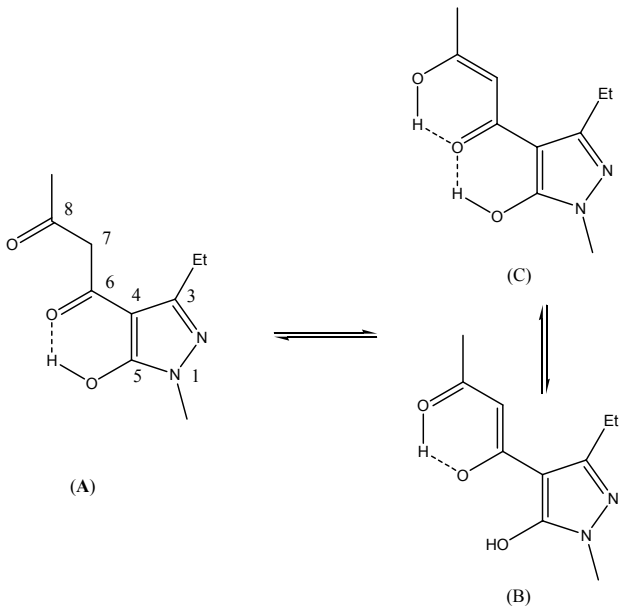
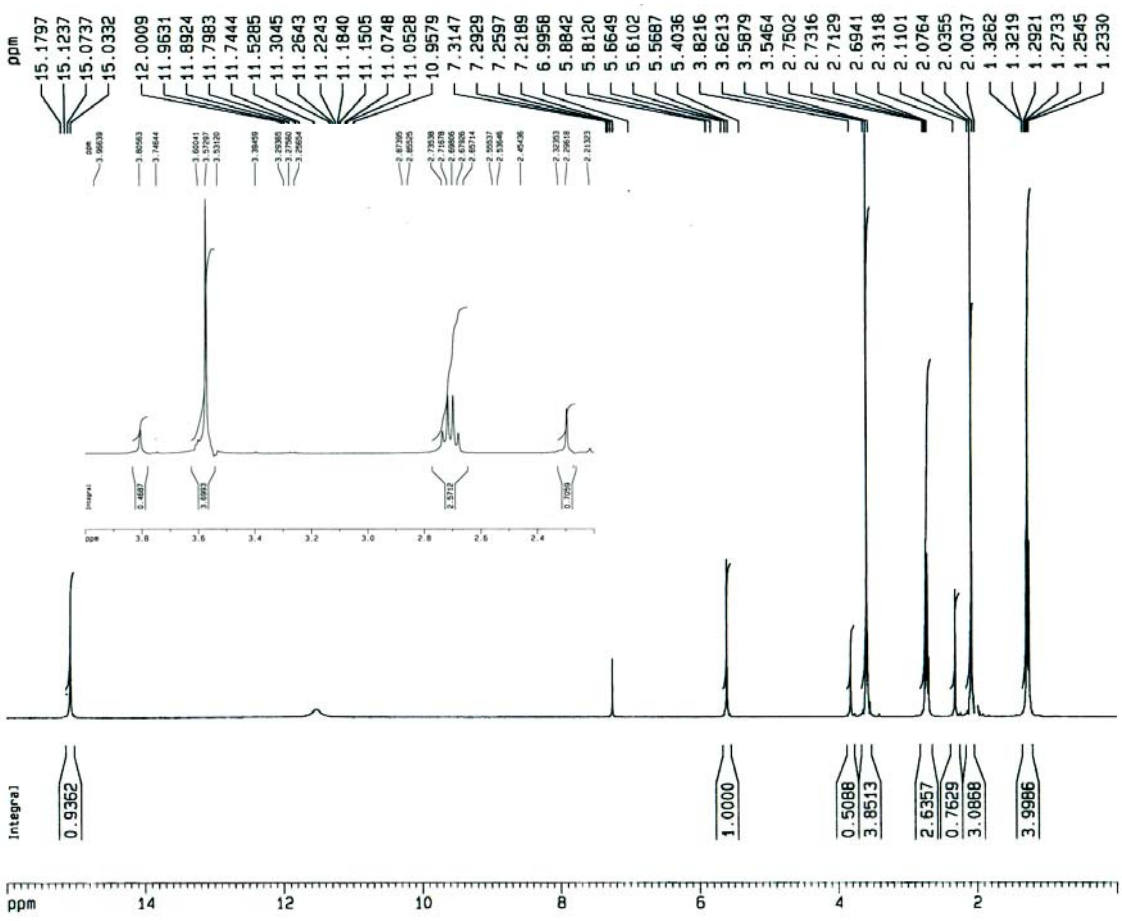


Figure 18: Tautomerization of compound **16**

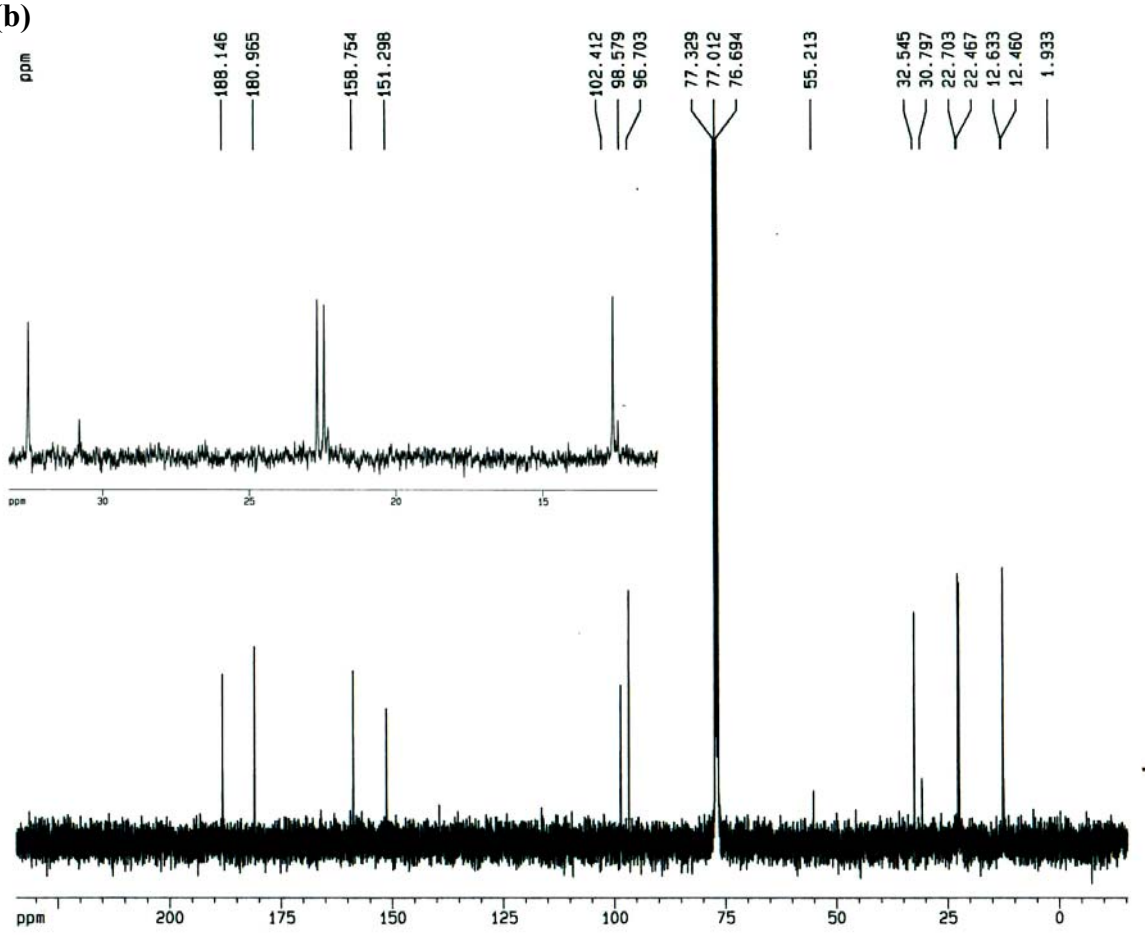
(a)



The ^{1}H NMR spectrum (Figure 19(a)) shows that the enol and keto forms are most easily detected by the signal at δ 5.57 for the vinyl proton in the enol structure and the signal at δ 3.80 for the methylene protons in the keto structure. Based on the integral rises of 1.00 and 0.509 respectively for these signals, and noting that they are due to 1H and 2H signals respectively, the enol to keto ratio is calculated to be 3.93 to 1.

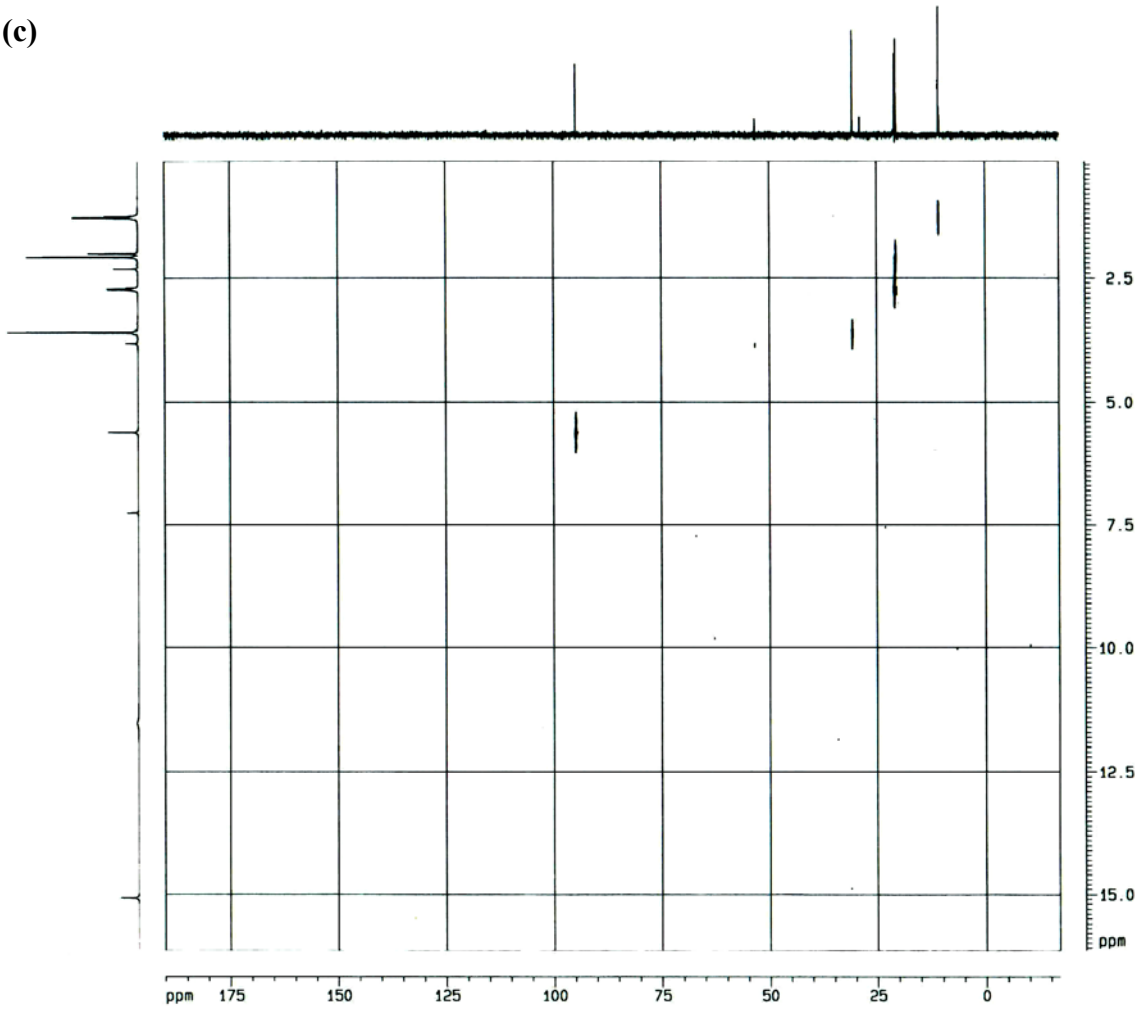
The sharp peak down field at δ 15.0 (D_2O exchangeable) is consistent with the intramolecularly H-bonded enolic proton in conformer B and C, while the very broad signal at 11.3 is more consistent with the more acidic, C-5 hydrogen bonded hydroxyl proton in tautomers A, B, and C. The 3H singlet protons at δ 2.31 were assigned to the C-8 methyl protons in the keto tautomer A, respectively, while the singlet protons at δ 2.08 (3H) were assigned to the C-8 methyl protons in the enol tautomer (B $\rightleftharpoons$ C), respectively. In addition, the 3H singlet at δ 3.57 is due to the N-methyl protons, while a 2H quartet (7.6 Hz) at δ 2.78 and a 3H triplet (7.3 Hz) at δ 1.32 appear for the protons in the ethyl side chain in tautomers A, B, and C.

(b)



The upfield portion of the ^{13}C-NMR spectrum (figure 19(b)) of compound **16** in $CDCl_3$ solution shows evidence of two sets of the methyl carbon atoms. The carbon signals at δ 22.70 and 12.63 were assigned to the ethyl side chain of the pyrazole ring of the major tautomer, while the carbon signals at δ 22.30 and 12.46 were assigned to minor tautomer. The C-8 methyl groups of the side chain of the major and minor tautomers absorb at δ 22.46 and 30.79, respectively. The signal at δ 32.54 was assigned to the carbons of the N-methyl groups of the tautomers A, B, and C.

(c)



The signal at δ 55.21 is assigned to the C-7 carbon of the keto tautomer A. As expected for this assignment, the ^{1}H-^{13}C correlation spectrum shown in Figure 19(c) reveals that this signal correlates with the absorption at δ 3.80 which was previously assigned to the CH_2 group of the keto tautomer A. The signals in the ^{13}C-NMR spectrum δ 188.1 and 180.9 were assigned to the C-6 and C-8 carbonyl carbons of the keto-enol side chain of tautomers B and C. As expected, the ^{1}H-^{13}C correlation spectrum shows that these signals do not correlate with any signals in the ^{1}H-NMR spectrum. The ^{13}C-NMR spectrum exhibits two sets of signals, which were shown to be

quaternary carbons by the ^{1}H-^{13}C correlation spectrum and were therefore assigned to the carbon atoms of the pyrazole rings in the enol and keto tautomers. Thus, signals at δ 158.8, 151.3, and 102.4 were assigned to the C-5, C-3, and C-4 carbon atoms of the major enol tautomers. Finally, the ^{13}C-NMR exhibits a signal at δ 98.58 which correlates with the signal at δ 5.57 in the ^{1}H-NMR spectrum and was therefore assigned to the C-7 vinyl carbon in the side chain of the major enol tautomer.

These assignments are also consistent with the NMR ^{13}C-DEPT 135 of compound **16** (Figure 19(d)).

(d)

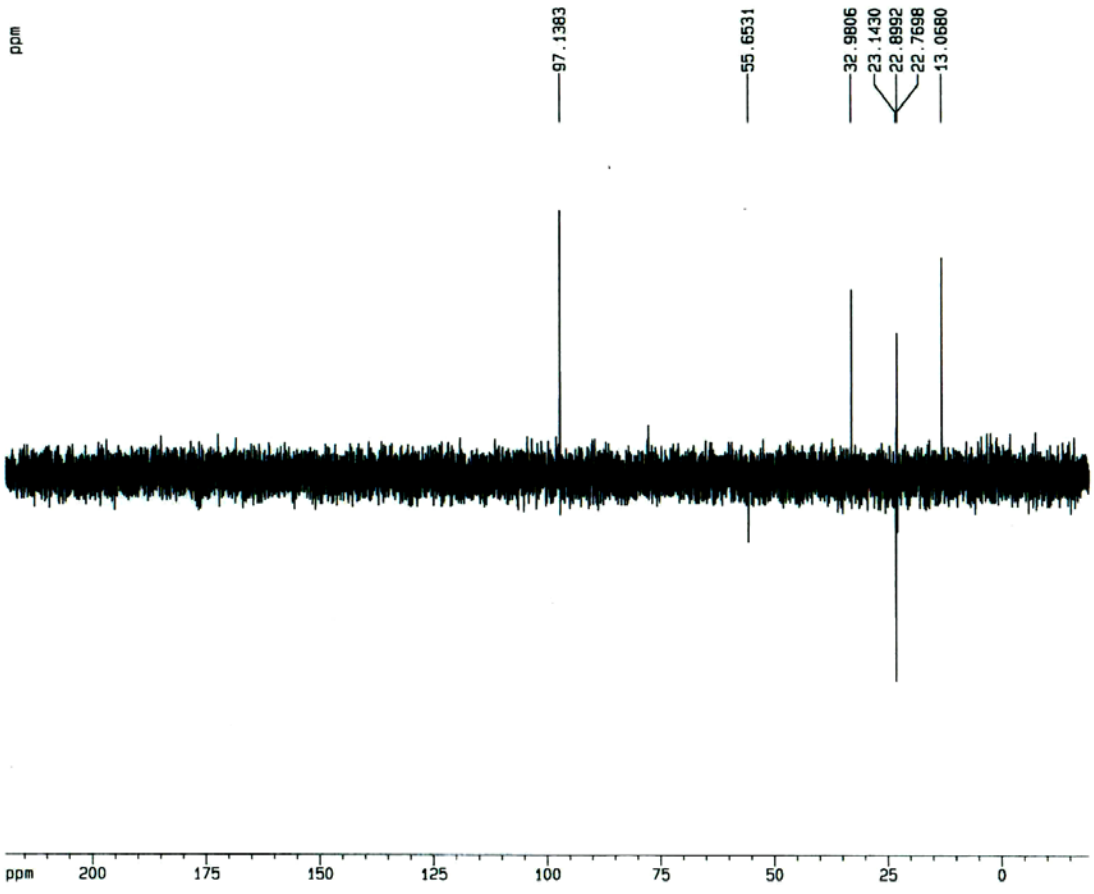
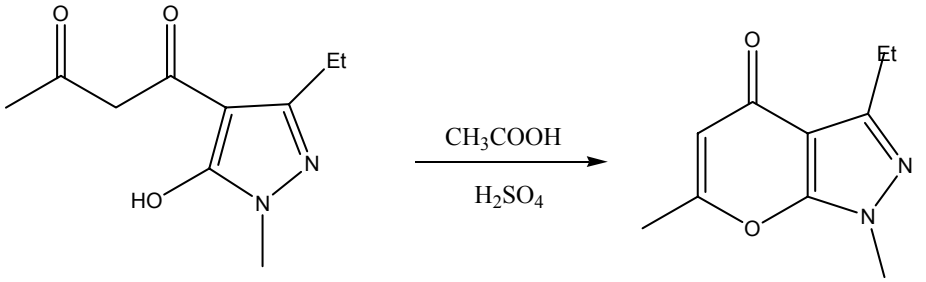


Figure 19: (a) ^{1}H-NMR of compound 16; (b) ^{13}C-NMR of compound 16; (c) C-H correlation of compound 16; (d) ^{13}C-NMR DEPT 135 of compound 16.

As expected the ^{13}C-NMR DEPT 135 (figure 19(d)) of compound **16** shows that the five signals at δ 188.1, 180.9, 158.8, 151.3, and 102.4 disappeared which is consistent with their assignment the quaternary signals of the major enol tautomers. These signals that disappeared due to the keto and enol carbons on the C-6 and 8 side chain and the quaternary carbons of the pyrazole ring at C-3, C-4, and C-5 positions. But, the signals at δ 97.14, 32.98, 22.89, and 13.07 appear in the positive direction which is consistent with their assignment to the CH type carbon of the CH vinyl side chain, the methyl carbon of the ethyl side chain for the major tautomer, and the two C-8 methyl types for the major and minor tautomers. On the other hand, the negative signal is observed at δ 55.65 which is due to the methylene carbon of the diketo side chain ring in keto tautomer. Also, the signal at δ 23.24 and 22.77 appears for the CH_2 type carbon of the ethyl chain ring in the major and minor tautomers, respectively.

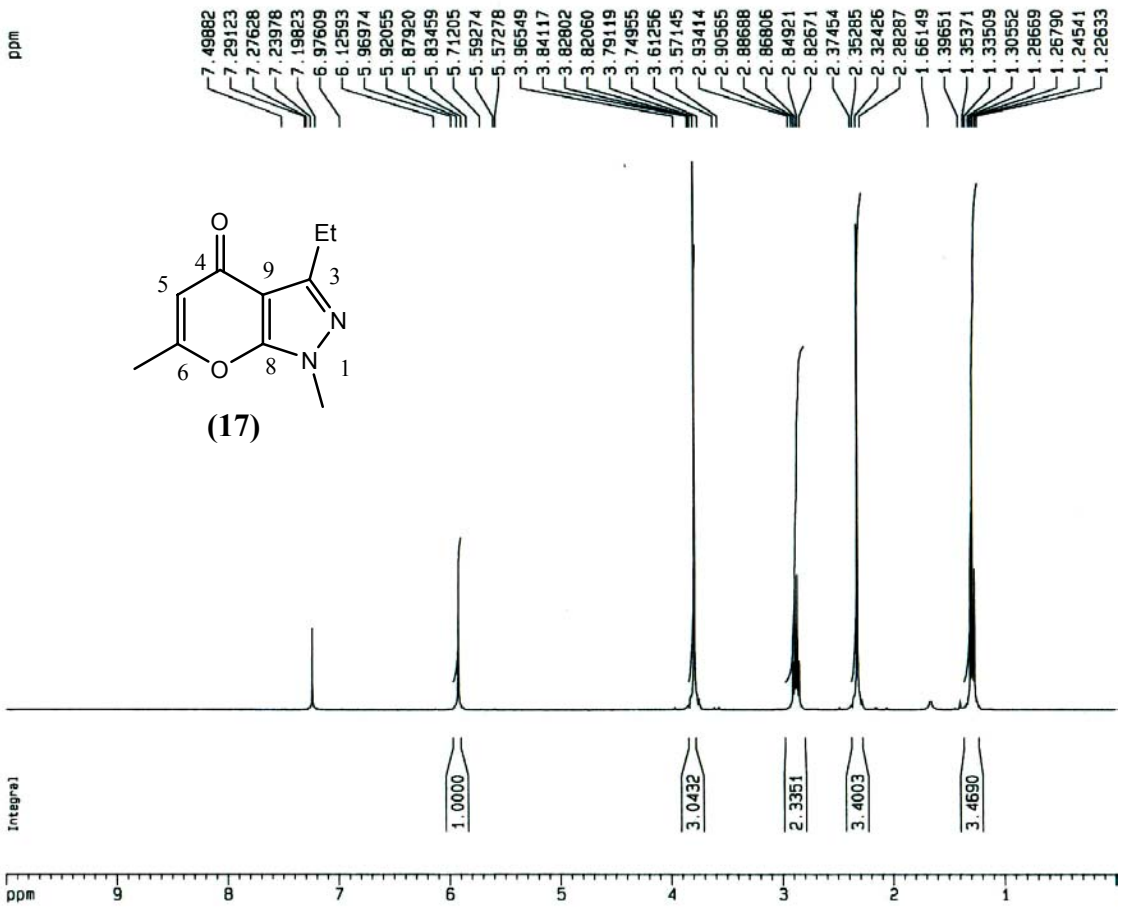


(16) **(17)**

Scheme 20: Synthesis of 3-ethyl-1,6-dimethylpyrano[2,3-*c*]pyrazole-4(1*H*)-one **(17)**.

The ring closure of **16** to the new compound 3-ethyl-1,6-dimethylpyrano[2,3-*c*]pyrazole-4(1*H*)-one **(17)** was achieved by refluxing **16** in acetic acid in the presence of sulfuric acid as catalyst for one hour to obtain **17** in a yield of 79%, mp 99-100^{o}C (Scheme 20).

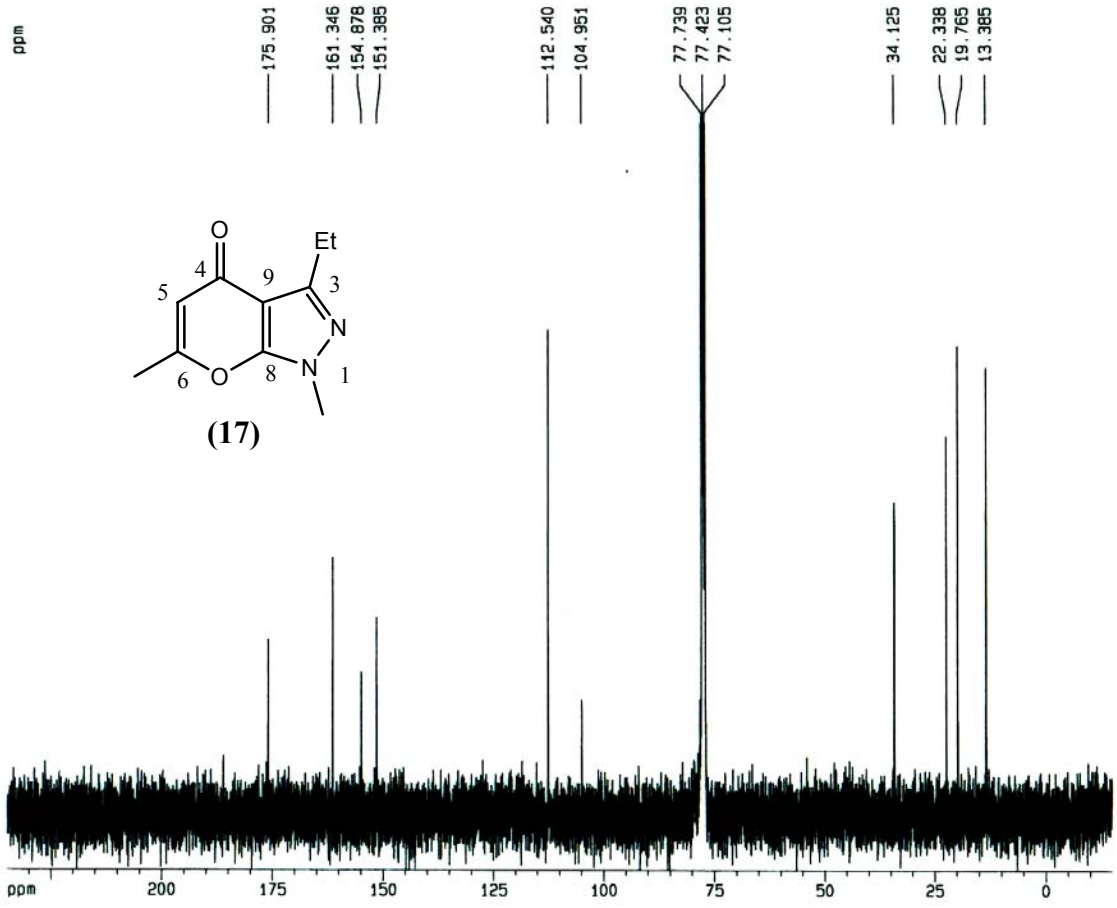
(a)



(17)

Figure 20(a) shows that the ^{1}H-NMR spectrum of the colorless crystals is consistent with the structure of **17**. A key signal due to the C-5 proton of the pyrone ring is observed as a 1H singlet at δ 5.92, while the N-methyl and C-6 protons give rise to 3H singlets at δ 3.79 and 2.32, respectively. In addition, the 2H quartet (J = 7.6 Hz) at δ 2.91 and 3H triplet (J = 7.8 Hz) at δ 1.29 are consistent with the ethyl side chain of the pyrazole ring.

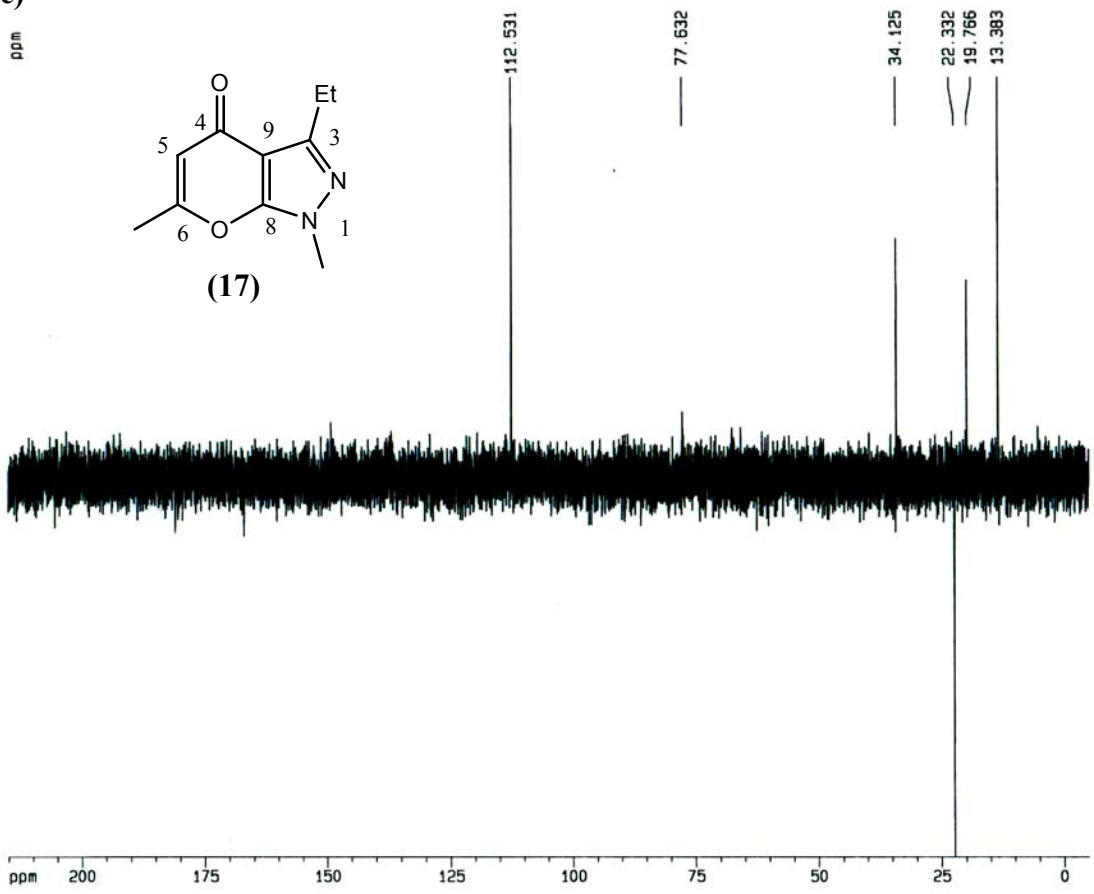
(b)



(17)

The ^{13}C-NMR spectrum (Figure 20(b)) is also consistent with the structure **17**. The carbonyl carbon of the pyrone ring absorbs the furthest downfield at δ 175.9. The signals at δ 154.9 and δ 104.9 were assigned to the bridgehead carbons at positions 8 and 9, respectively. The pyrone ring carbons in positions 5 and 6 appear at δ 112.5 and 161.3, respectively. The imine carbon of the pyrazole ring was assigned to the signal at δ 151.4. The methyl carbon of the pyrone ring is observed at δ 19.76, while the downfield signal at δ 34.12 is due to N-methyl carbon. The signals at δ 22.34 and 13.36 were assigned to the carbon atoms of the ethyl side chain of the pyrazole ring.

(c)

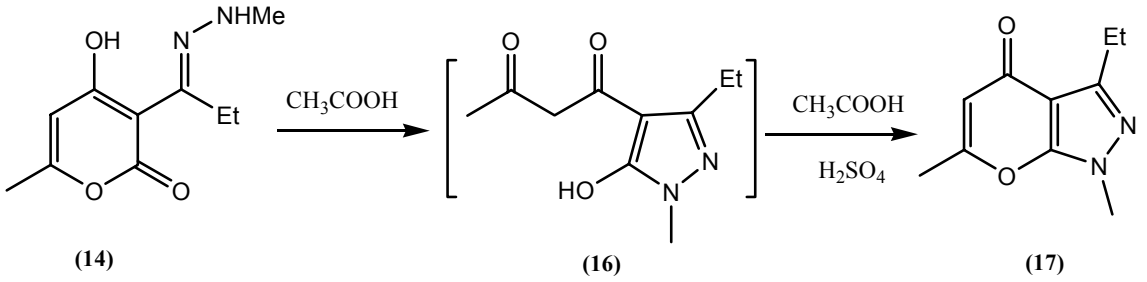


(17)

Figure 20: (a) ^{1}H NMR of compound **17**; (b) ^{13}C NMR of compound **17**; (c) ^{13}C NMR DEPT 135 of compound **17**.

These assignments are consistent with the ^{13}C-DEPT 135 spectrum (Figure 20(c)). The five signals at δ 175.9, 161.3, 154.9, 152.6 and 104.9 disappeared which is consistent with their assignment to the five quaternary carbons. Thus, two of these quaternary carbons are at C-4 and 6 positions of the pyrone ring, one of the C-3 carbon of the pyrazole ring, and two carbons at C-8 and 9 at the fused ring. In addition, the signals at δ 112.5, 34.12, 19.76, and 13.38 still appear in the positive direction which is consistent with their assignment to the CH type carbon at C-5 of the pyrone ring and

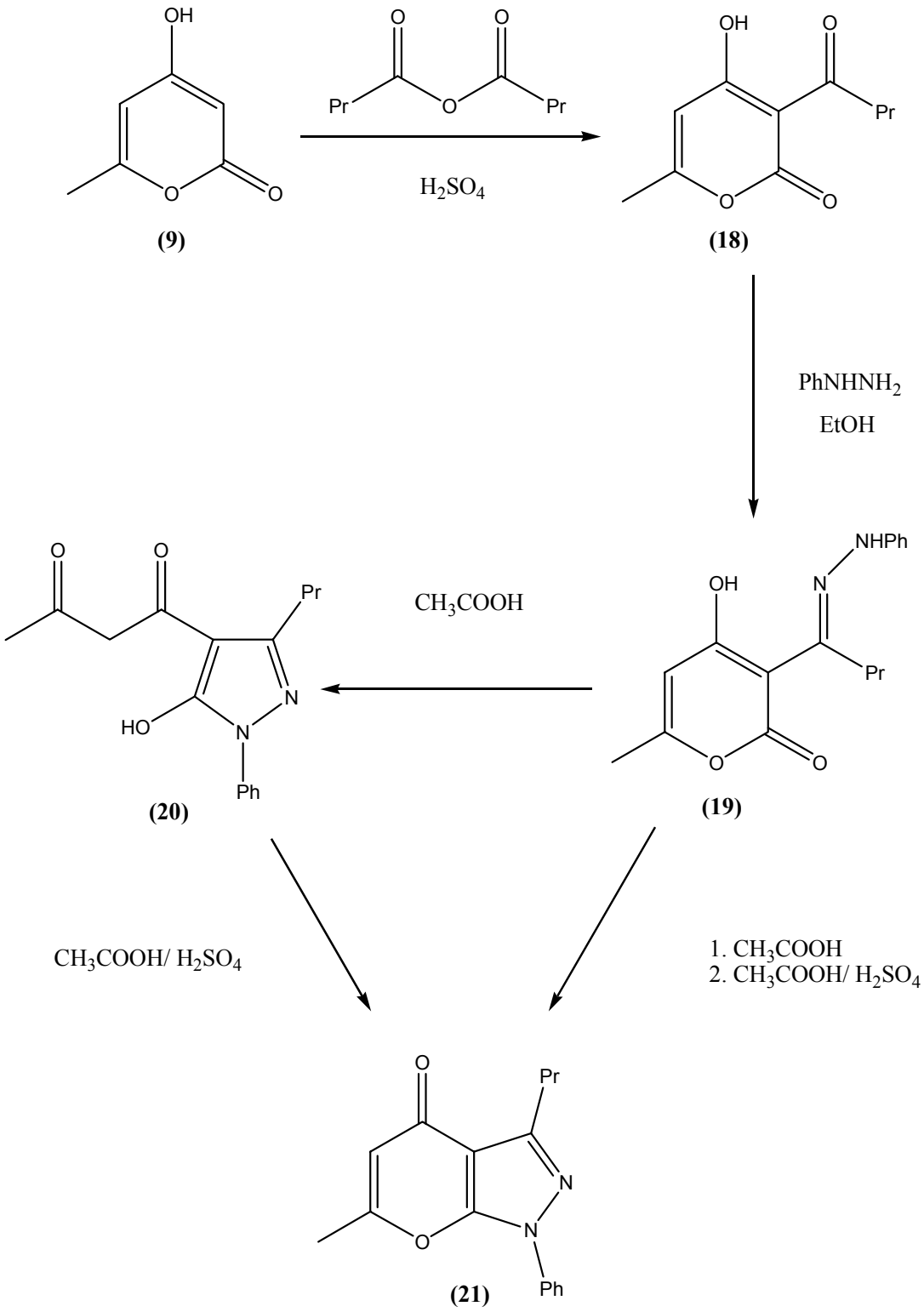
the three types of the methyl carbons at the N-methyl, the ethyl side chain, and C-6 position. However, the signal at δ 22.33 appears in negative direction due to its assignment to the CH_2 type carbon of the ethyl side chain of the pyrazole ring.

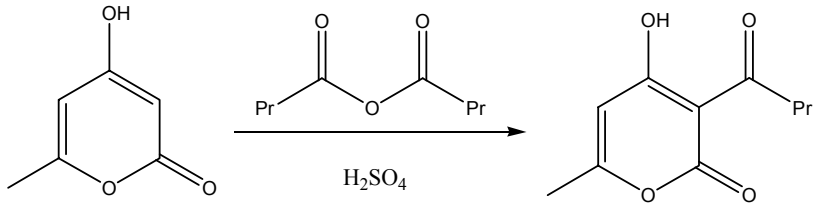


(14) **(16)** **(17)**

Scheme 21: Synthesis of 3-ethyl-1,6-dimethylpyrano[2,3-*c*]pyrazole-4(1*H*)-one **(17)**.

N-methylhydrazone **14** could also be converted to pyranopyrazole **17** without isolation and purifying **16**. To accomplish this, **14** was first refluxed in acetic acid for one hour. Concentrated sulfuric acid was then added and the mixture refluxed for one additional hour. This provided **17** in a yield of 66% (Scheme 21).


OH
O
O
Pr
O
Pr
H2SO4
(9)
(18)
PhNHNH2
EtOH
NHPh
N
CH3COOH
HO
Ph
(20)
(19)
CH3COOH/ H2SO4
1. CH3COOH
2. CH3COOH/ H2SO4
(21)



(9) **(18)**

Scheme 22: Synthesis of 3-butyryl-4-hydroxy-6-methyl-2*H*-pyran-2-one **(18)**.

Following the literature procedure of Marcus, E. and colleague,[7] the dehydroacetic acid derivative 3-butyryl-4-hydroxy-6-methyl-2*H*-pyran-2-one **(18)** was also prepared by C-acylation of 4-hydroxy-6-methyl-2-pyrone **(9)** with butyric anhydride in the presence of a catalytic amount of sulfuric acid to give **18** in a yield of 57 %, mp 57-58^{o}C (Lit.[7] mp 57-59^{o}C) (Scheme 22).

(a)

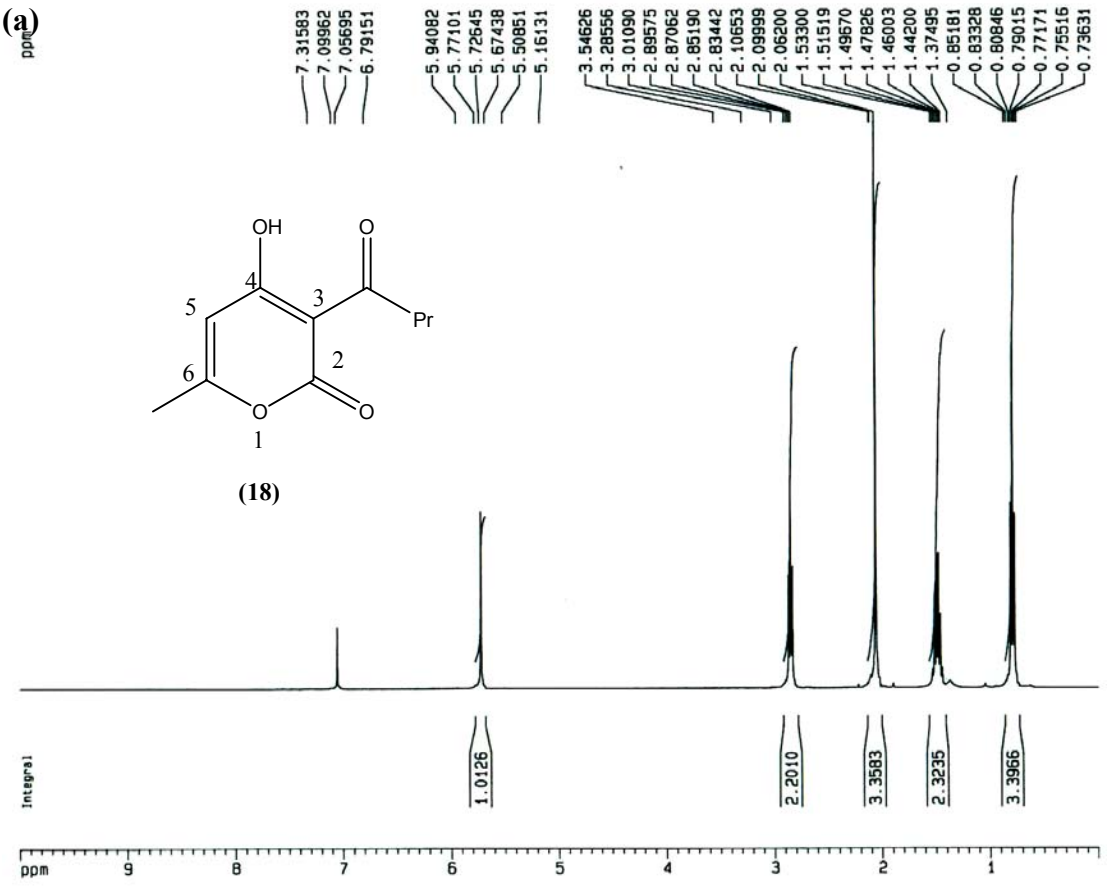
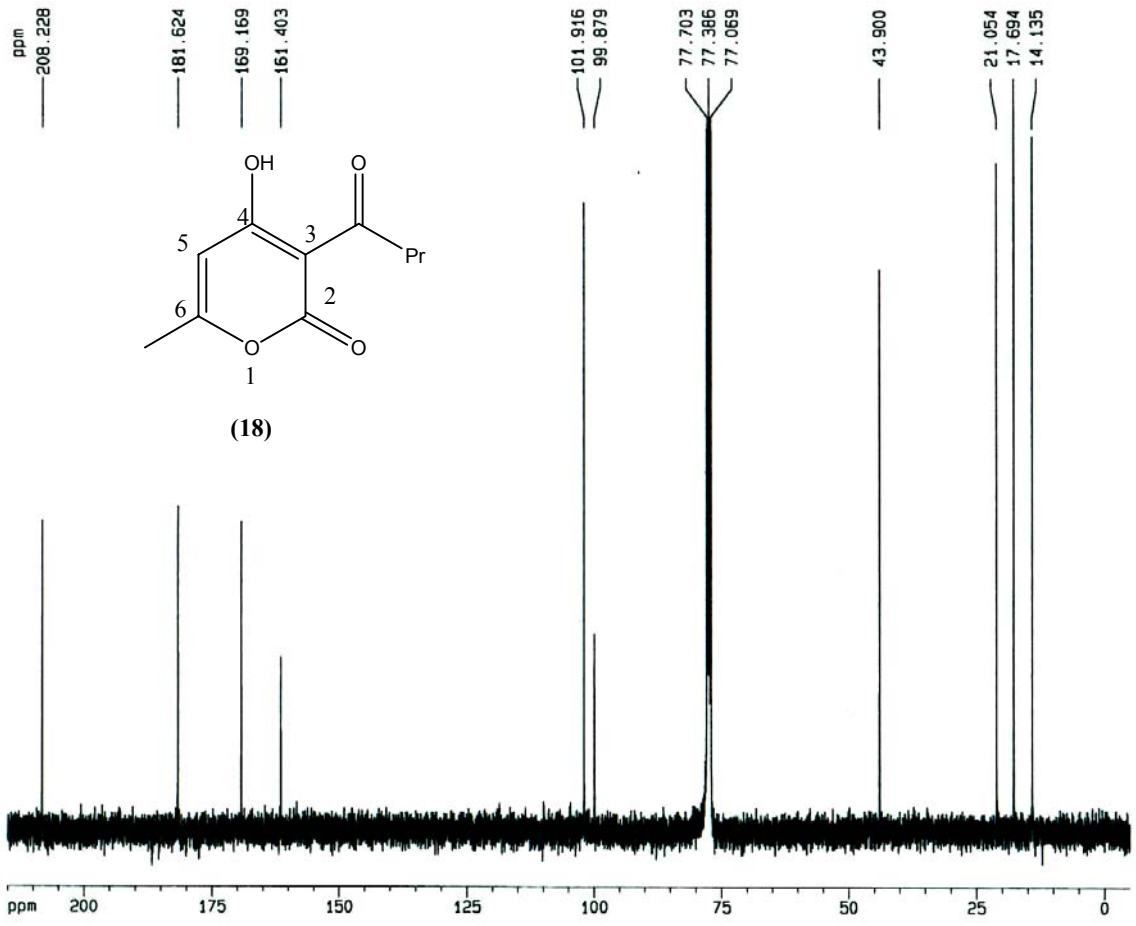


Figure 21(a) shows that the ^{1}H-NMR spectrum of the white crystalline product is consistent with the structure of **18.** The key proton at C-5 of the pyrone ring of compound **18** appears as a 1H singlet at δ 5.91, while the C-6 methyl protons of the pyrone ring appear as a 3H singlet at δ 2.25. In addition, the n-propyl group of the butanoyl side chain appears as a 2H triplet (J = 6.8 Hz) at δ 3.04, a 2H sextet (J = 7.3 Hz) at δ 1.66, and a 3H triplet (J = 7.3 Hz) at δ 0.974 for the protons α, β, and γ, respectively, from the carbonyl group.

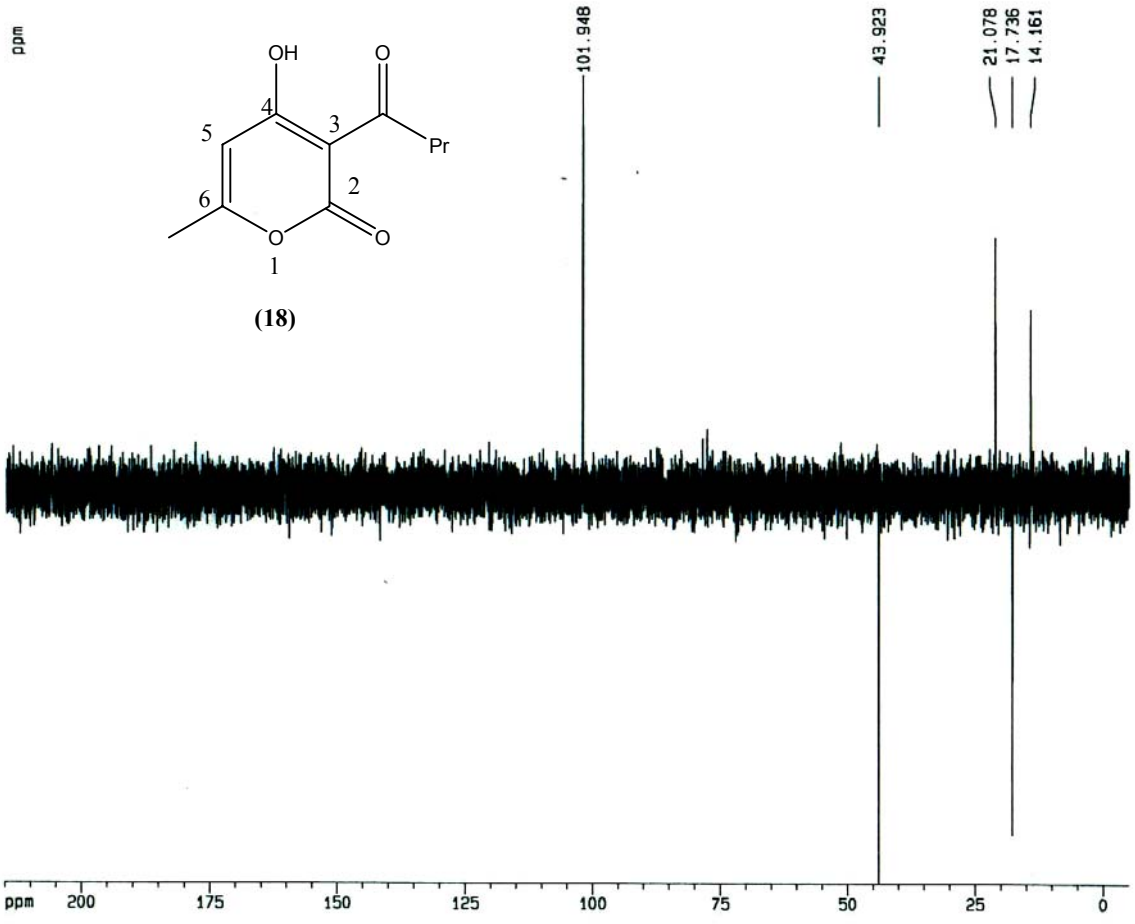
(b)



(18)

The ^{13}C-NMR spectrum (Figure 21(b)) is also compatible with the structure of **18**. The carbonyl carbon of the acyl side chain absorbs the furthest downfield at δ 208.2. The carbons at positions 2, 3, 4, 5, and 6 of the pyrone ring absorb at δ 169.2, 99.88, 181.6, 101.9 and 161.4, respectively. In addition, the two methyl carbons of the pyrone ring and the acyl side chain are observed at δ 21.0 and 14.1, respectively. The two CH_2 type carbons of the acyl side chain give rise to signals at δ 43.9 and 17.7.

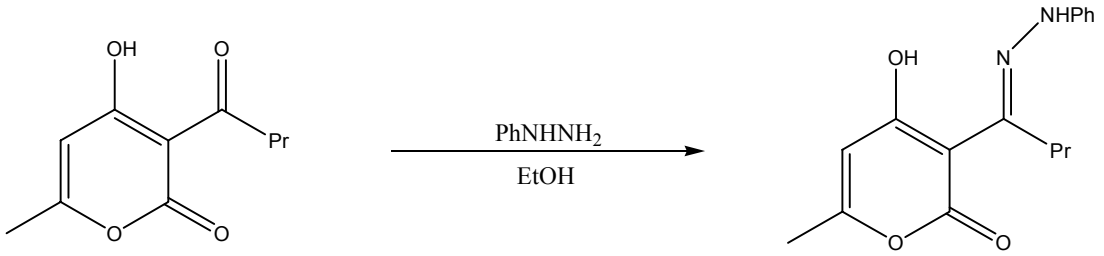
(c)



(18)

Figure 21: (a) ^{1}H NMR of compound **18**; (b) ^{13}C NMR of compound **18** and (c) ^{13}C NMR DEPT 135 of compound **18**.

These assignments are consistent with the ^{13}C-DEPT 135 spectrum (Figure 21(c)). The five signals at δ 208.2, 181.6, 169.2, 161.4 and 99.88 disappeared which is consistent with their assignment to the four quaternary carbons of the pyrone ring and the quaternary carbon of the hydrazone group. In addition, the signals at δ 101.9, 21.1 and 14.1 still appear in positive direction which is consistent with their assignment to a CH type carbon of the pyrone ring, the methyl carbons of the pyrone ring and the acyl side chain. However, the signals at δ 43.9 and 17.7 appear in negative direction due to two CH_2 type carbons of the acyl side chain.



(18) **(19)**

Scheme 23: Synthesis of 4-hydroxy-6-methyl-3-(1-(2-phenylhydrazono)butyryl)-2*H*-pyran-2-one **(19)**.

Treatment of dehydroacetic acid derivative **18** with phenylhydrazone for a few minutes at 80^{o}C led to the formation of the new compound 4-hydroxy-6-methyl-3-(1-(2-phenylhydrazono)butyryl)-2*H*-pyran-2-one **(19)** in a yield of 93%, mp 72-74^{o}C (Scheme 23).

(a)

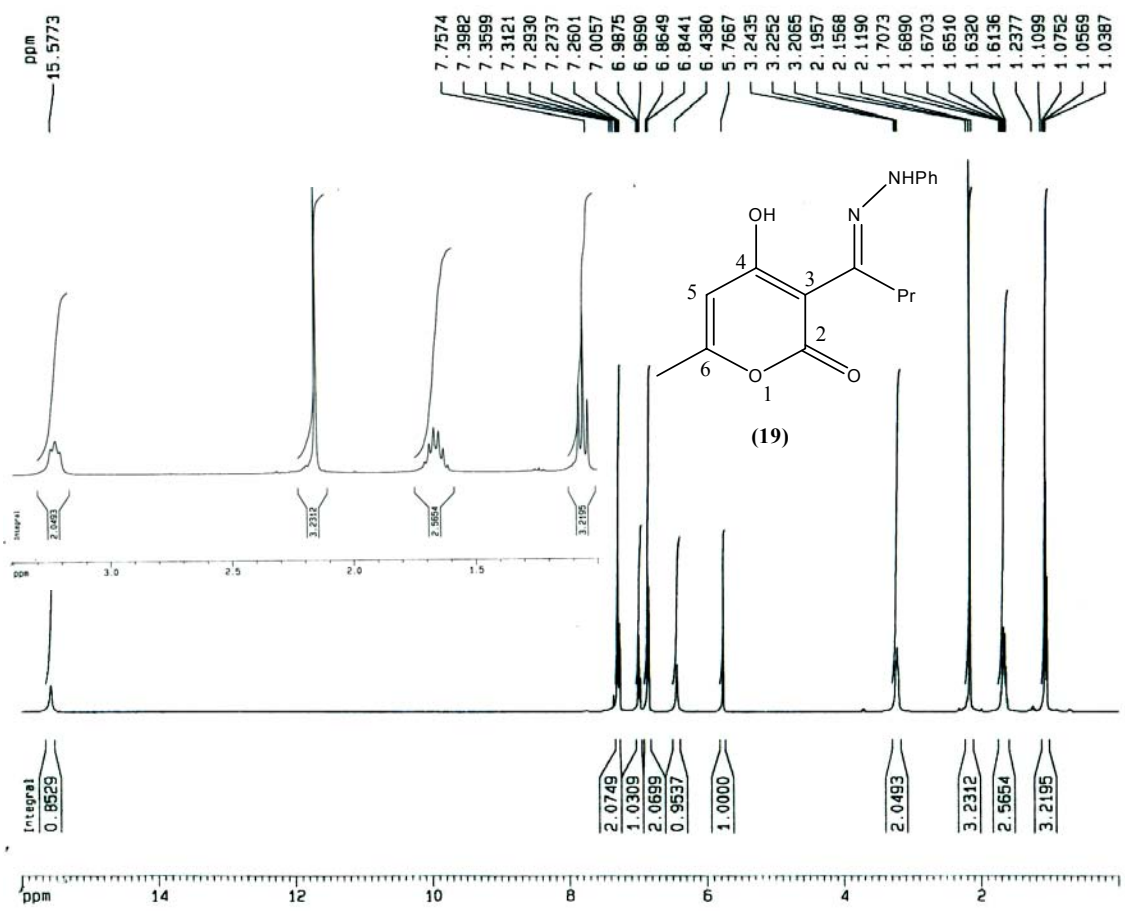
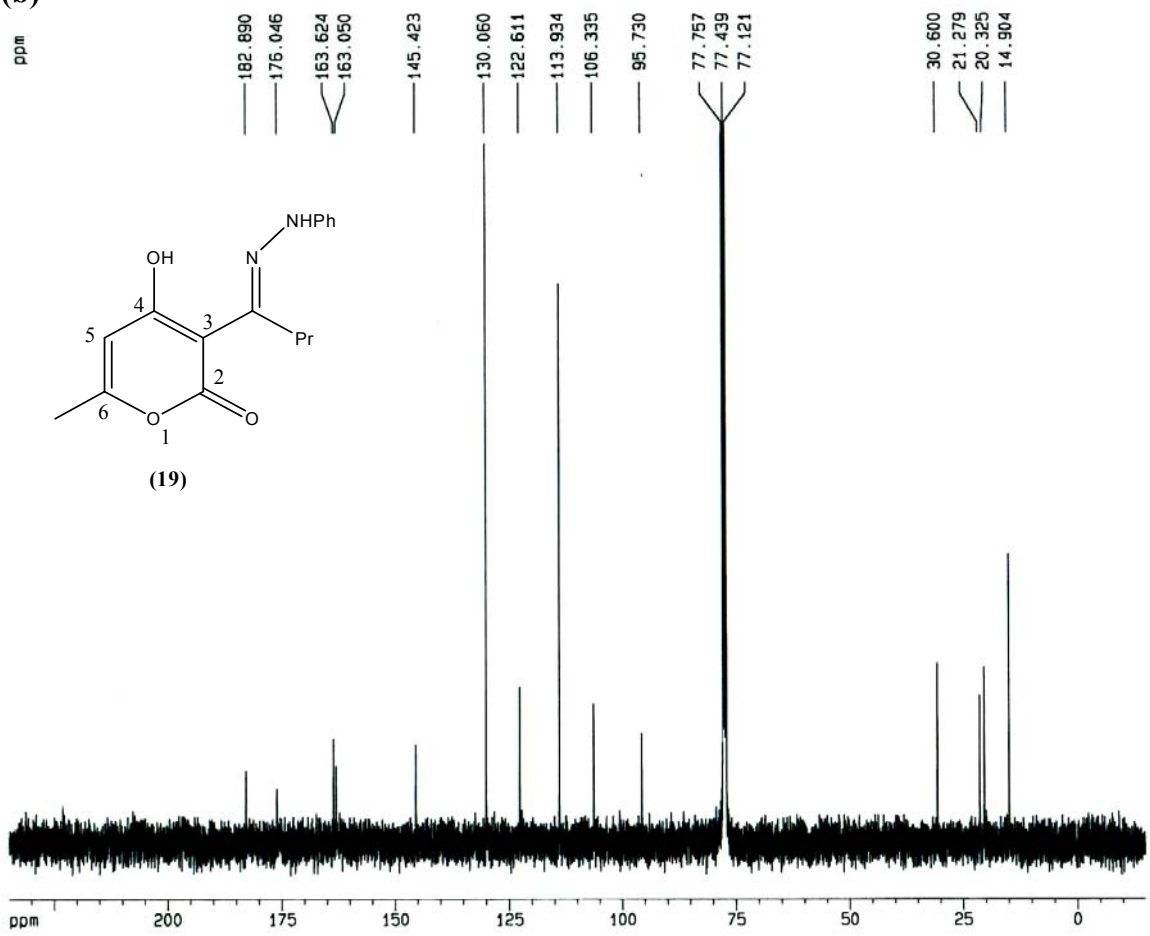


Figure 22(a) shows that the ^{1}H-NMR spectrum of the yellow crystalline product corresponds with the structure of **19**. In addition to a 3H singlet at δ 2.14 due to the C-6 methyl group, the spectrum also shows a key 1H singlet at δ 5.75 due to the C-5 proton of the pyrone ring. The 2H triplet (J = 7.6 Hz) at δ 3.20, the 2H sextet (J = 8.1 Hz) at δ 1.65, and the 3H triplet (J = 7.1 Hz) at δ 1.04 are consistent with the n-propyl group of the hydrazone side chain. Furthermore, the two triplets at δ 7.27 (2H; J = 7.6 Hz) and 6.96 (1H; J = 7.1 Hz) and a doublet at δ 6.84 (2H; J = 8.6 Hz) are due to absorptions of the phenyl ring protons at meta, para, and ortho positions, respectively. The D_2O

exchangeable signals at δ 15.6 and 6.42 were assigned to the protons of the hydroxyl group and amine group, respectively.

(b)



(19)

The ^{13}C-NMR spectrum (Figure 22(b)) is also consistent with the structure of **19**. The hydroxyl carbon in the lactone ring absorbs the furthest downfield at δ 182.9. The signal at δ 176.0 was assigned to the hydrazone carbon. The carbon atoms at positions 2, 3, 5, and 6 of the pyrone ring exhibit the signals at δ 163.6, 95.73, 106.3, and 163.1, respectively. In addition, the quarternary carbon of the phenyl group and the carbon at the para position absorb at δ 145.4 and 122.6, respectively, while the carbon

atoms at ortho and meta positions appear as two singlets at δ 113.9 and 130.1, respectively. The signal at δ 20.3 is due to the methyl carbon of pyrone ring, while the signals at δ 30.6, 21.3, and 14.9 are expected for the propyl side chain of the hydrazone position.

(c)

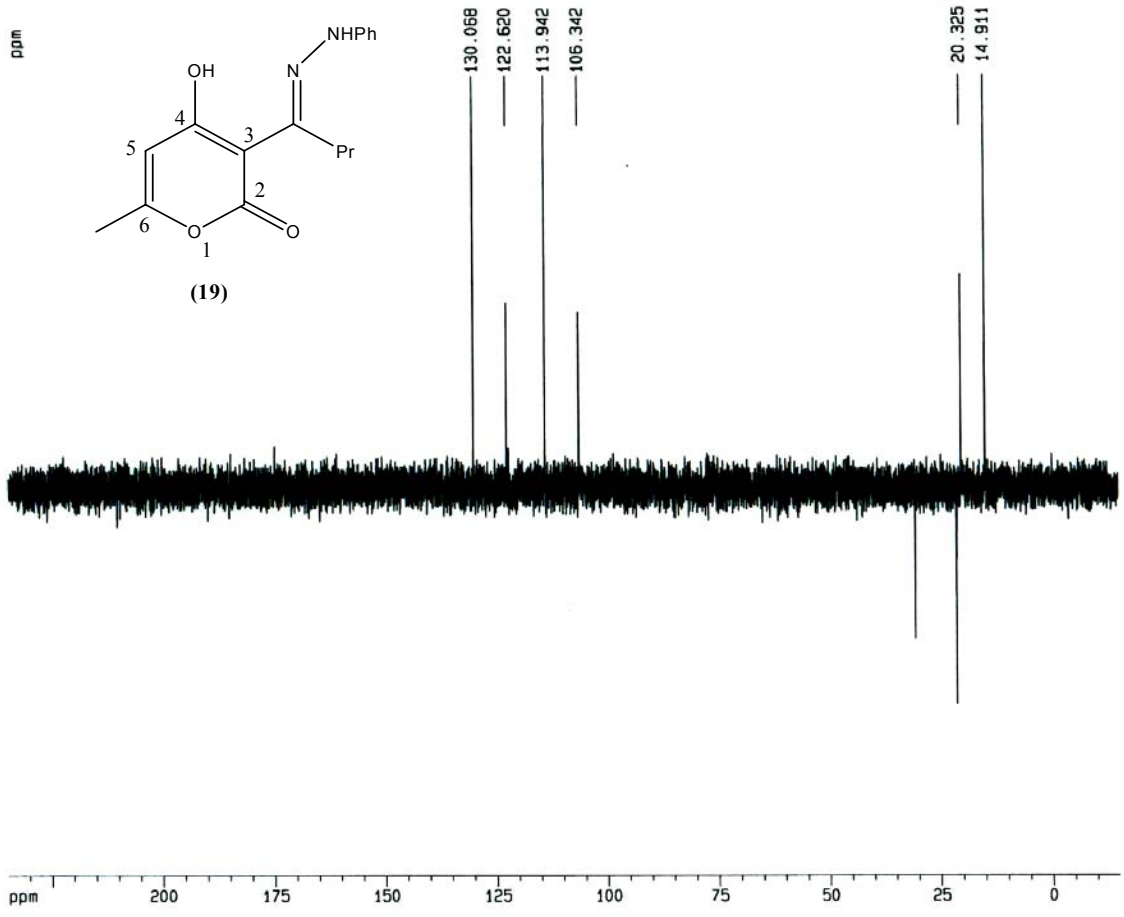
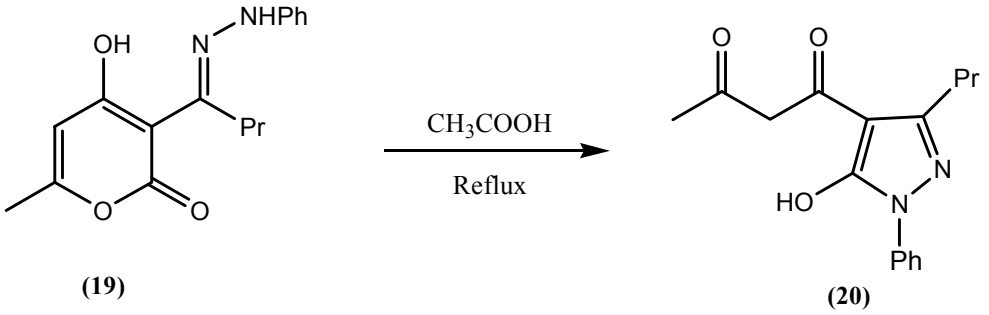


Figure 22: (a) ^{1}H-NMR of compound **19**; (b) ^{13}C-NMR of compound **19**; (c) ^{13}C-NMR DEPT 135 of compound **19.**

These assignments are also consistent with the ^{13}C-DEPT 135 spectrum (Figure 22(c)). The six signals at δ 182.9, 176.0, 163.6, 163.1, 145.4, and 95.73 disappeared which is consistent with their assignment to the six quaternary carbons of the phenyl ring, the pyrone ring, and the hydrazone group. But the signals at δ 130.1, 122.6, 113.9, 106.3, 20.32 and 14.91 still appear in the positive direction which is consistent with their assignment to the CH type carbons of the phenyl ring, the CH type carbon of the pyrone ring, the methyl carbon of the pyrone ring, and the methyl carbon of the propyl side chain. However, the signals at δ 30.6 and 22.4 appear in negative direction which is consistent with their assignment to the CH_2 type carbons of the propyl side chain.



(19) **(20)**

Scheme 24: Synthesis of 1-(5-hydroxy-3-propyl-1-phenyl-1*H*-pyrazol-4-yl)butane-1,3-dione **(20)**.

The intramolecular cyclization of the N-phenylhydrazone **19** was accomplished by refluxing **19** in acetic acid for one hour. The new 1-(5-hydroxy-3-propyl-1-phenyl-1*H*-pyrazol-4-yl)butane-1,3-dione **(20)** was obtained in a yield of 74%, mp 93-95^{o}C (Scheme 24).

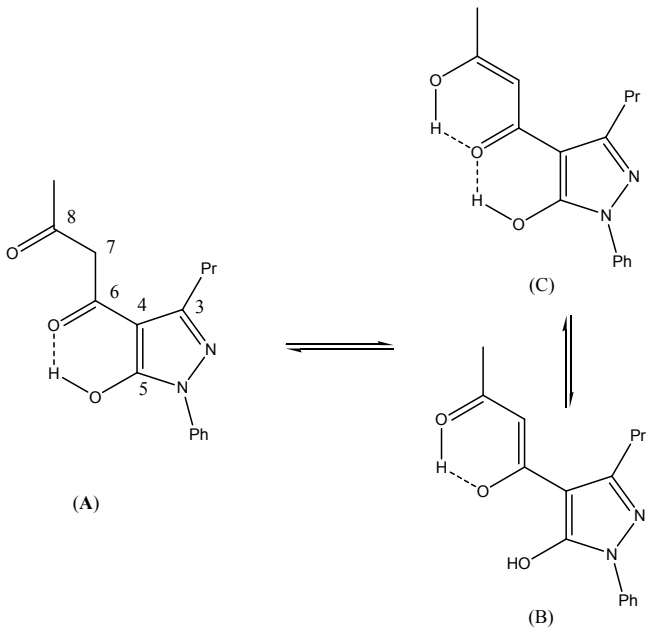
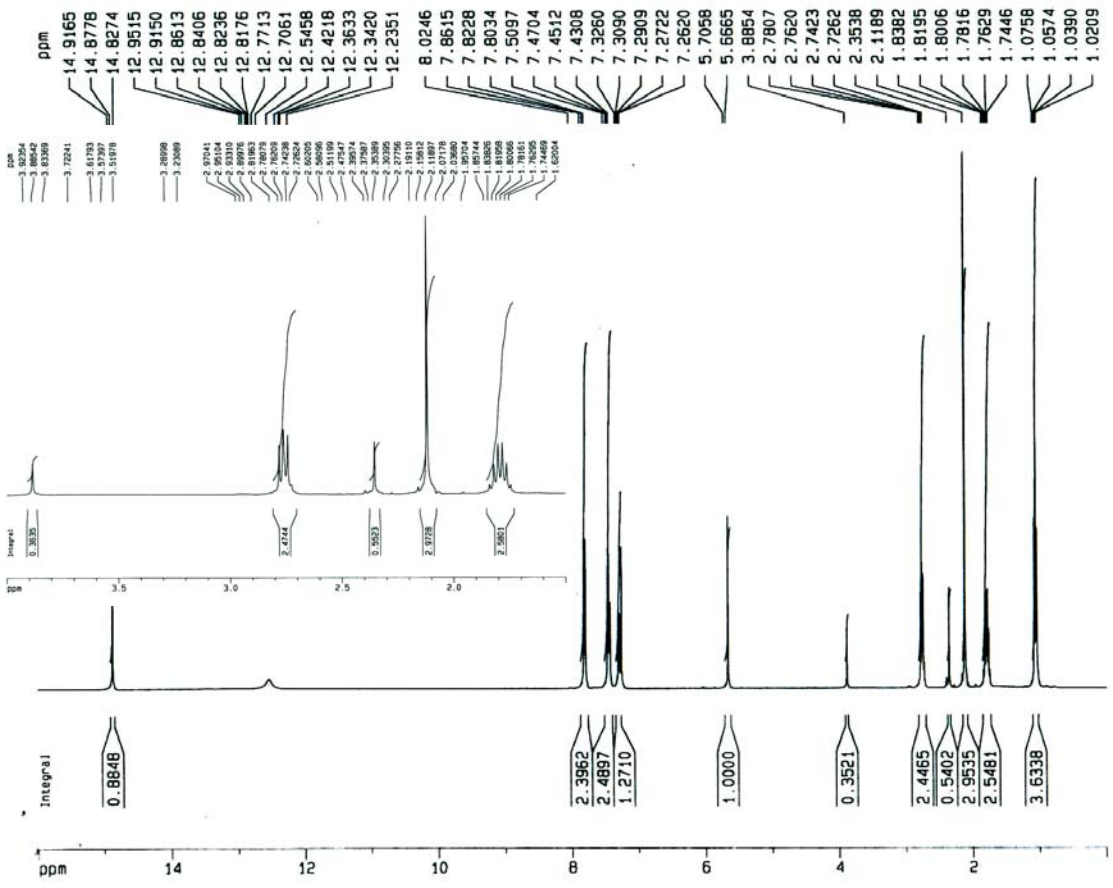


Figure 23: Tautomerization of compound **20**

(a)

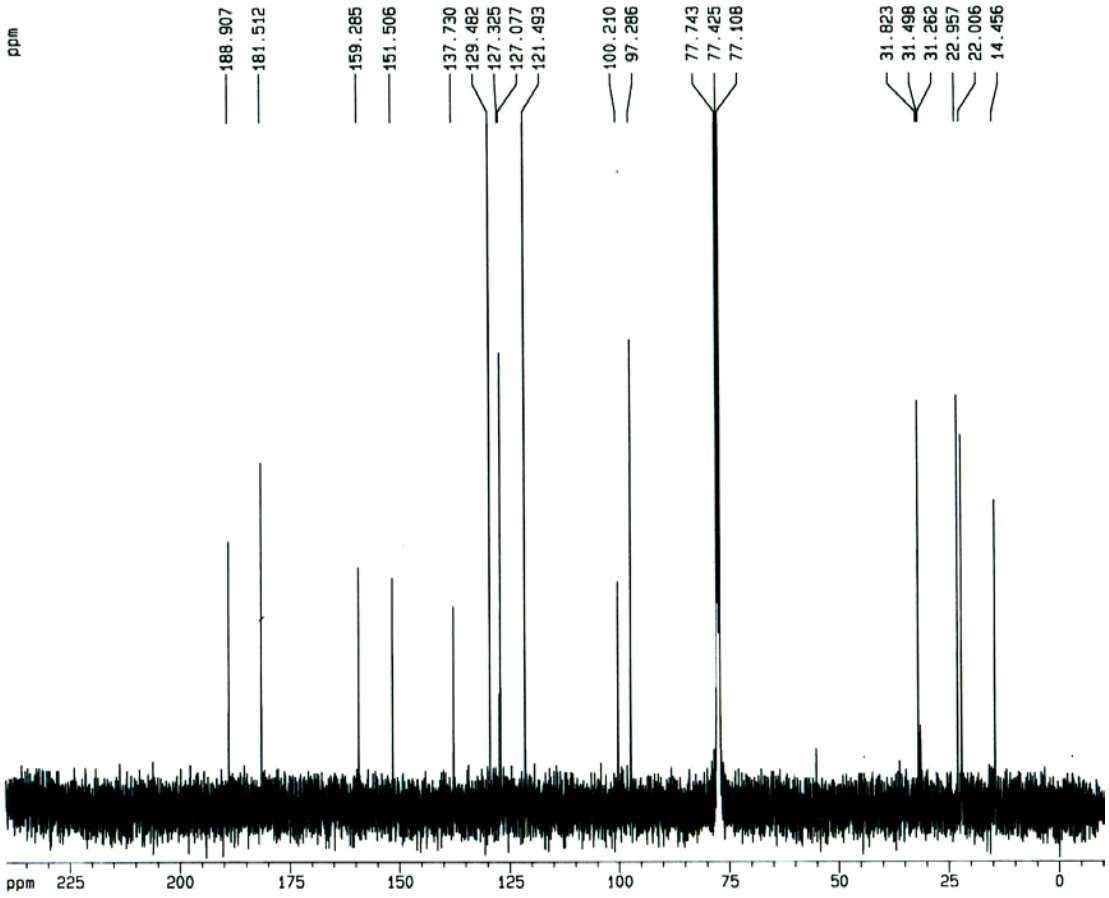


The ^{1}H-NMR in Figure 24(a) shows that compound **20** in $CDCl_3$ exists as an equilibrium mixture of keto form A and an enol form which is the average of B and C. The enol form (B $\rightleftharpoons$ C) can be detected by the singlets at δ 5.64 and 2.09 due to the C-7 vinyl and C-8 methyl group, while the singlets at δ 3.86 and 2.33 result from the C-7 methylene and C-8 methyl protons of the keto tautomer A. Based on the integral rises of 1.00 and 0.352 respectively for the vinyl and methylene proton signals, the enol to keto ratio was calculated to be 5.68 to 1.

The signals at δ 14.9 and 12.5 are due to protons bonded to oxygens. The sharp enolic signal at δ 14.9 is consistent with the strongly chelated hydroxyl proton on the side chain of the enol tautomer (B $\rightleftharpoons$ C), while the broad signal at δ 12.5 is consistent with the more acidic proton at the C-5 hydroxyl group.

In addition, the ^{1}H-NMR also shows a 2H doublet (J = 7.8 Hz) at δ 7.79, a 2H triplet at δ 7.43 (J = 7.8 Hz), and a 1H multiplet at δ 7.27 characteristic of protons in the ortho, meta, and para positions respectively of the phenyl ring. As expected, the spectrum also exhibits a 2H triplet (7.8 Hz) at δ 2.74, a 2H sextet (7.6 Hz) at δ 1.78, and a 3H triplet (7.3 Hz) at δ 1.04 for the propyl side chain at C-3 of the pyrazole ring.

(b)



The ^{13}C-NMR spectrum (figure 24(b)) in $CDCl_3$ solution of compound **20** gives rise to two resonances for all the carbon atoms corresponding to the major enol and minor keto tautomers. It is known that a hydrogen-bonded carbonyl carbon resonates at lower field than a corresponding free carbonyl carbon and that an enolic carbon atom resonates at higher field than a corresponding keto carbon atom, according to literature reported[3] The C-6 resonance of the enol form (B $\rightleftharpoons$ C) would be at a lower field than the C-8 carbon atom. From the chemical shift values, respectively at δ 188.9 and 181.5, it can be reasonably concluded the enol tautomer contributes mainly to the tautomeric

population in $CDCl_3$ solution. The characteristic ^{13}C-NMR spectrum of the enol tautomer at δ 188.9, 181.5, 97.29 and 22.96 is consistent with C-6, C-8, C-7, and methyl C-8 on the side chain of the pyrazole ring, respectively. The carbons of the pyrazole ring at δ 159.3, 151.5, and 100.2 were assigned to C-5, C-3 and C-4, respectively. The phenyl ring carbons at positions 1 and 4 absorb at δ 137.7 and 127.1, while the ortho and meta carbons of the phenyl ring appear as two singlets at δ 121.5 and 129.5, respectively. Thus, the three carbons of the propyl side chain of the pyrazole ring appear at δ 31.82, 22.00, and 14.5. In the other hand, the A tautomer could not be completely assigned in ^{13}C-NMR because of the low intense signals in minor A tautomer. However, from the ^{13}C-NMR exhibit some key signals of A tautomer, the signals at δ 55.18 and 31.26 could be assigned to the C-7 methylene carbon and the methyl C-8 on the side chain, respectively.

These assignments are also consistent with the ^{13}C-NMR DEPT 135 of compound **20** (Figure 24(c)).

(c)

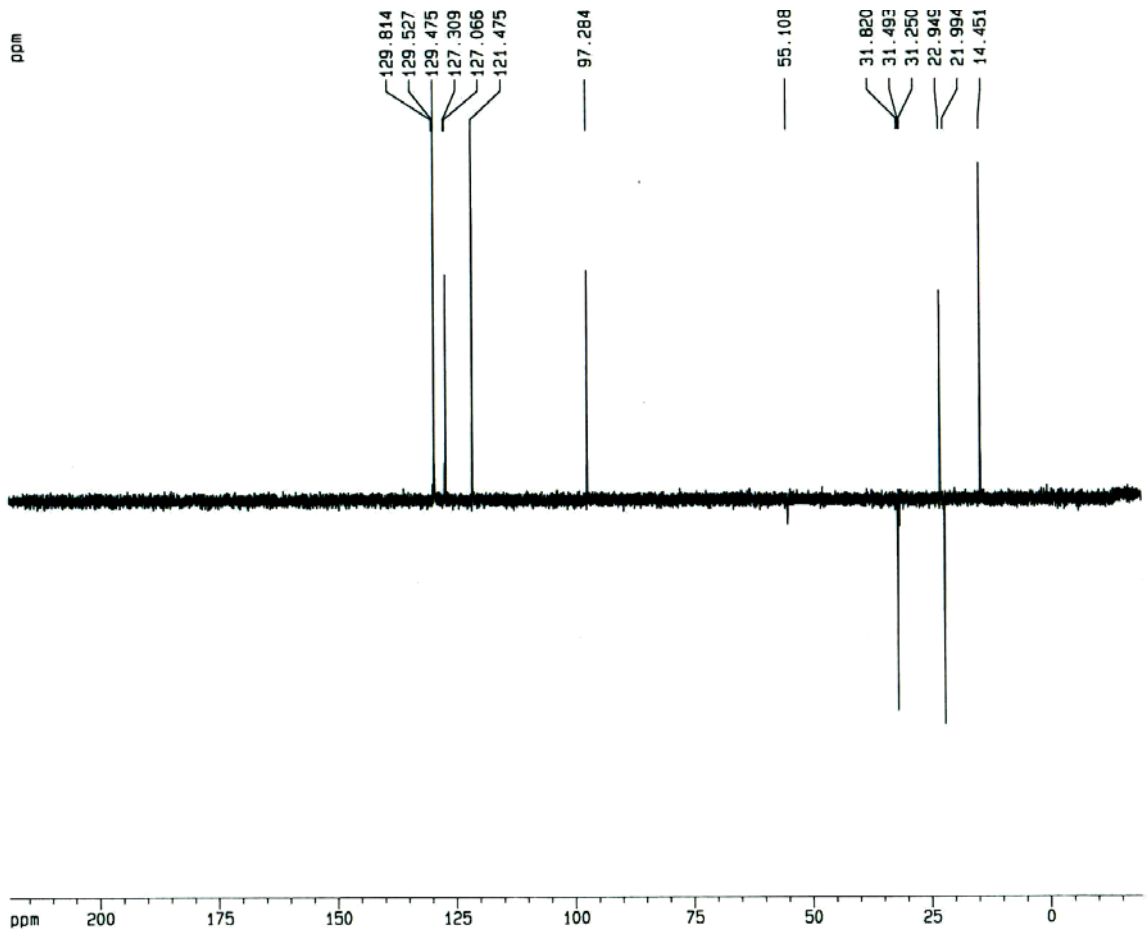
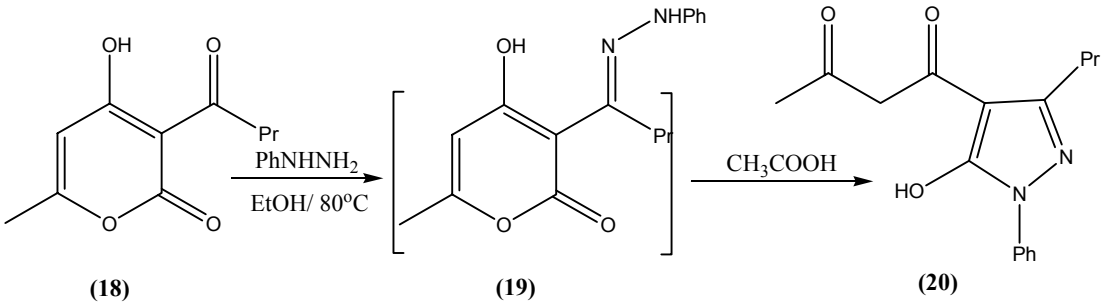


Figure 24: (a) ^{1}H-NMR of compound **20**; (b) ^{13}C-NMR of compound **20**; (c) ^{13}C-NMR DEPT 135 of compound **20**.

As expected the ^{13}C-NMR DEPT 135 (figure 24(c)) of compound **20** shows that the seven signals at δ 188.9, 181.5, 159.3, 151.5, 137.7, and 100.2 disappeared which is consistent with their assignment to the quaternary carbons of the major enol tautomers. These signals that disappeared are due to the keto and enol carbons on the C-6 and 8 side chain of the pyrazole ring, the quaternary carbon of the phenyl ring, and the carbons at C-3, C-4, and C-5 positions of the pyrazole ring. However, the signals at δ

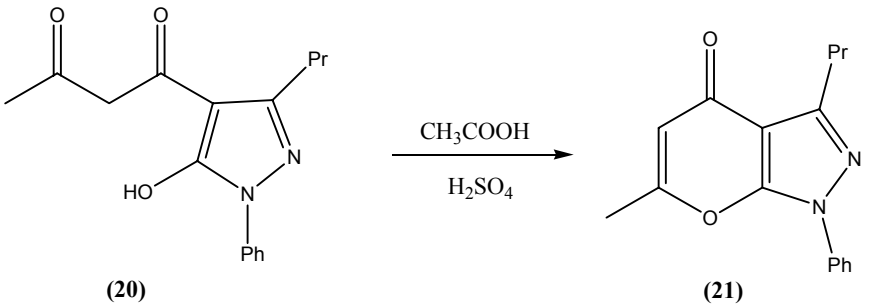
129.8, 127.3, 121.5, 97.28, 22.95, and 14.45 appear in the positive direction which is consistent with their assignment to the CH type carbons at ortho, meta, and para positions of the phenyl ring, the CH vinyl side chain, and the two methyl types at C-8 and propyl side chain. On the other hand, the negative signal is observed at δ 55.11, which is due to the methylene carbon of the diketo side chain ring in keto tautomer. Also, the signals at δ 31.82 and 21.99 appear for the CH_2 type carbons of the propyl side chain.



(18) **(19)** **(20)**

Scheme 25: Synthesis of 1-(5-Hydroxy-3-propyl-1-phenyl-1*H*-pyrazol-4-yl)butane-1,3-dione **(20)**.

1-(5-Hydroxy-3-propyl-1-phenyl-1*H*-pyrazol-4-yl)butane-1,3-dione **(20)** could also be prepared without isolation and purification of N-phenylhydrazone **19**. Thus, an ethanol solution of **18** was first treated at 80°C with phenylhydrazine. After a few minutes the solvent was evaporated and the crude N-phenylhydrazone **19** was allowed to reflux in acetic acid for 1 hour to give **20** in a yield of 64% (Scheme 25).



(20) **(21)**

Scheme 26: Synthesis of 6-methyl-1-phenyl-3-propylpyrano[2,3-*c*]pyrazole-4(1*H*)-one **(21)**.

The ring closure of **20** to the new compound 6-methyl-1-phenyl-3-propylpyrano[2,3-*c*]pyrazole-4(1*H*)-one **(21)** was achieved by refluxing **20** in acetic acid in the presence of sulfuric acid as catalyst for one hour to obtain **21** in a yield of 74%, mp 105-106^{o}C (Scheme 26).

(a)

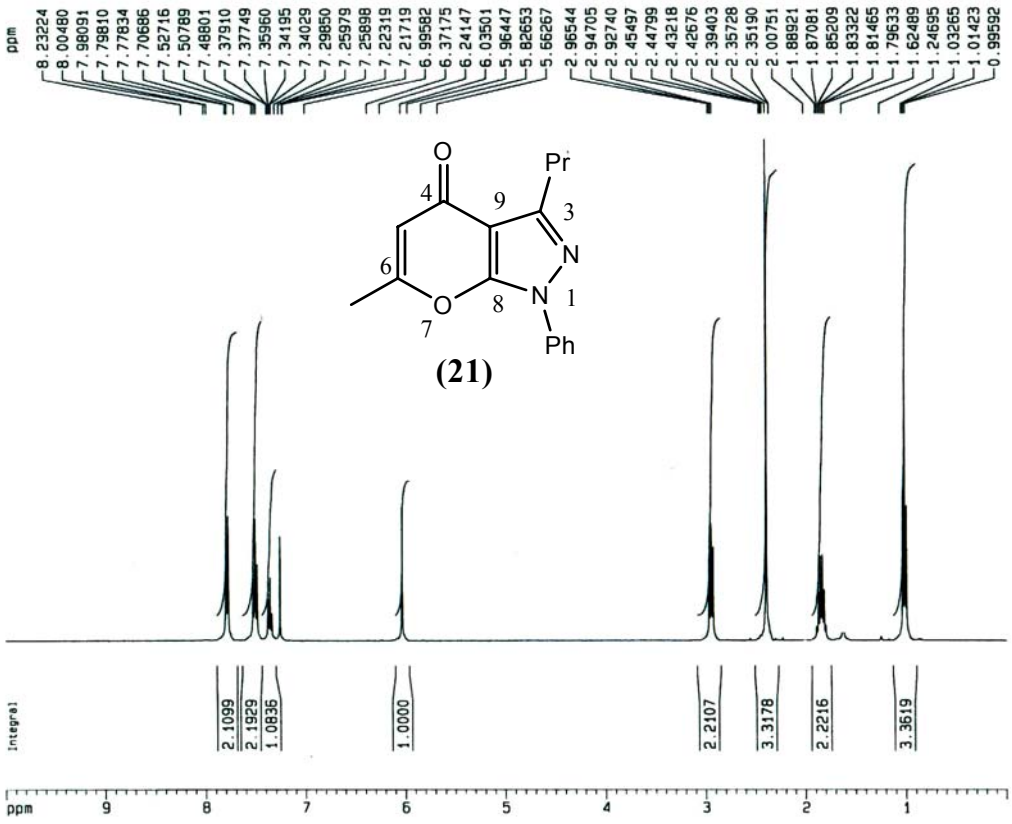
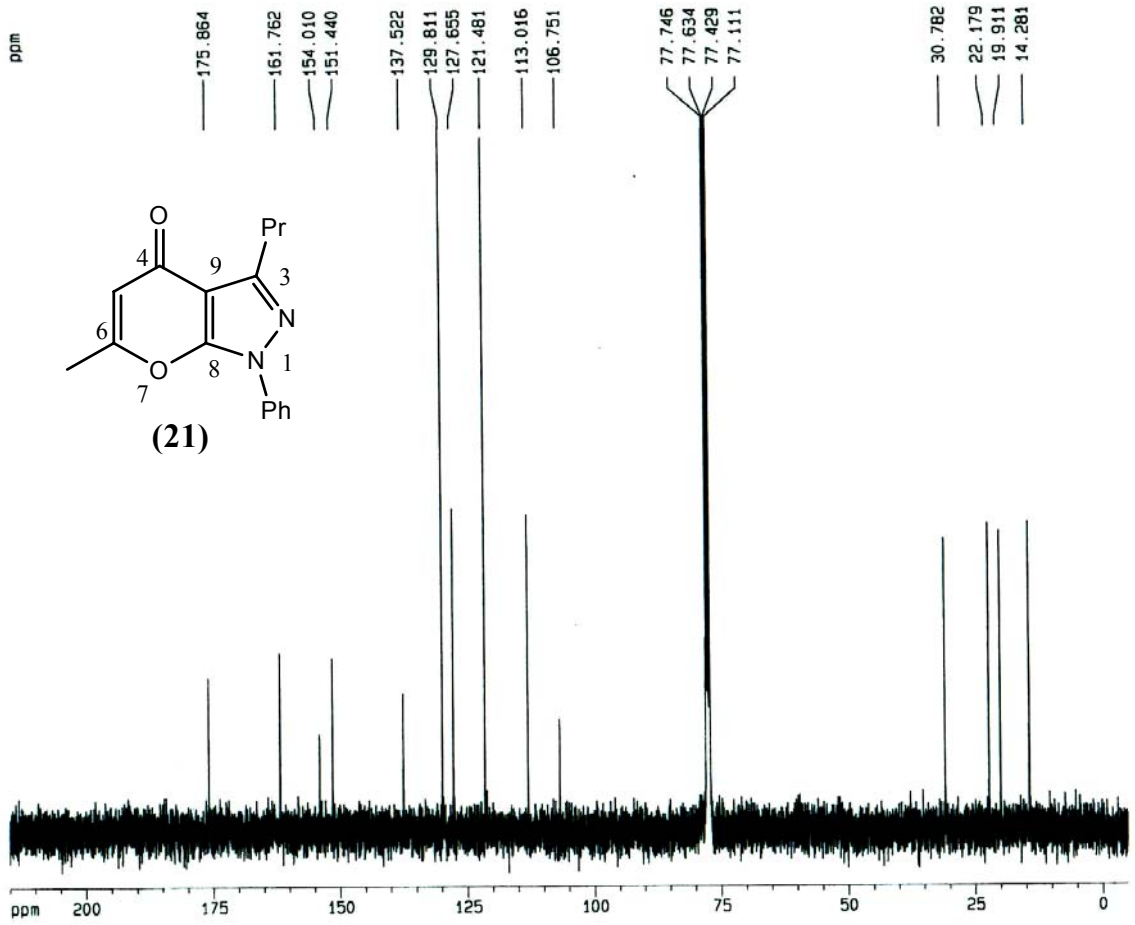


Figure 25(a) shows that the ^{1}H-NMR spectrum of the colorless crystalline product is consistent with the structure **21**. A key signal due to the proton of the pyrone ring appears as a 1H singlet at δ 6.02, while the 3H singlet at δ 2.38 is consistent with the methyl group at C-6 of the pyrone ring. The 2H triplet (J = 7.6 Hz) at δ 2.93, the 2H sextet (J = 7.8 Hz) at δ 1.82, and the 3H triplet (J = 7.3 Hz) at δ 0.99 are consistent with the n-propyl side chain in the pyrazole ring. In addition, the 2H doublet (J = 7.6 Hz) at δ 7.78, the 2H triplet (J = 8.1 Hz) at δ 7.49, and the 1H triplet (J = 6.8 Hz) at δ 7.34 are due to the protons of the phenyl ring at ortho, meta, and para positions, respectively.

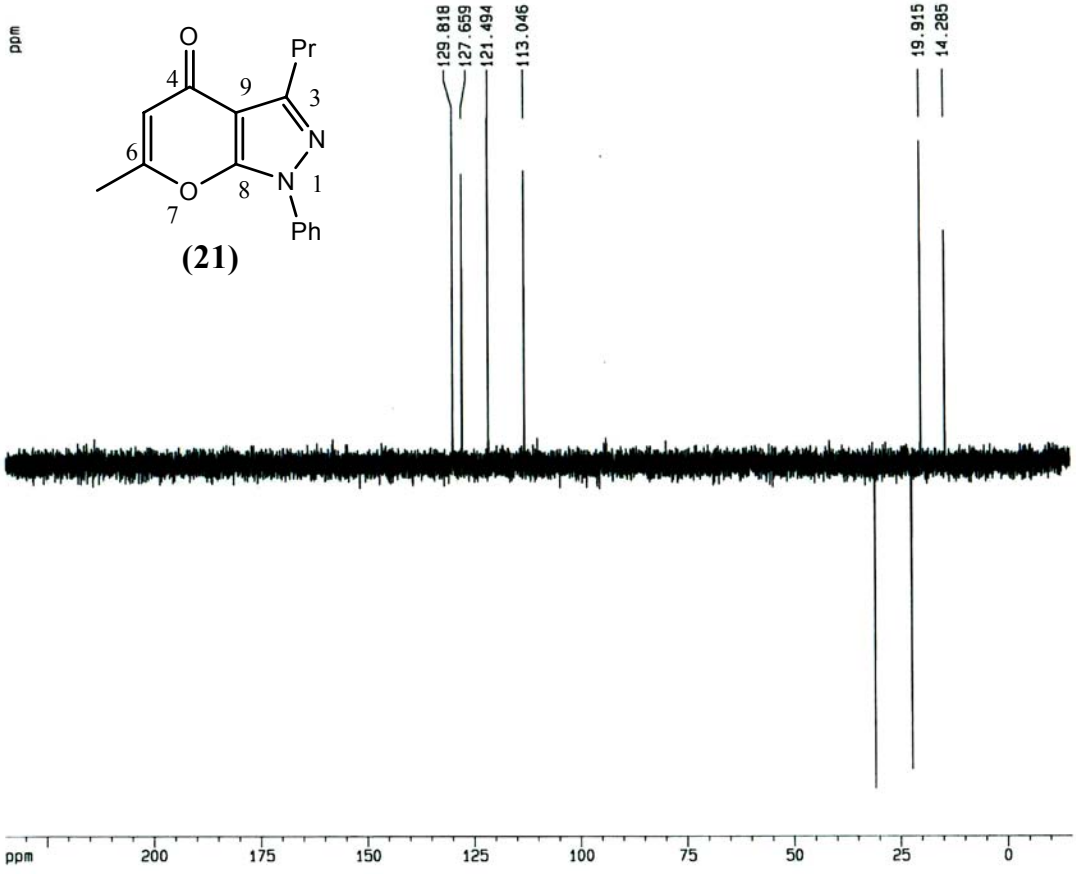
(b)



(21)

The ^{13}C-NMR spectrum (Figure 25(b)) is also consistent with the structure for **21**. The carbonyl carbon in the pyrone ring absorbs the furthest downfield at δ 175.9. The carbon atoms at positions 5, 6, 8, and 9 of the pyrone ring appear as the signals at δ 113.0, 161.8, 154.0, and 106.8, respectively. The signal at δ 151.4 is due to the carbon at C-3 of the pyrazole ring. In addition, the signal at δ 19.91 is due to the carbon of the methyl group at C-6 of the pyrone ring, while the signals at δ 30.78, 22.17, and 14.28 are due to the propyl side chain of the pyrazole ring. Finally, the signals at δ 137.5, 129.8, 127.7, and 121.5 are consistent with the quaternary, meta, para, and ortho carbons of the phenyl ring, respectively.

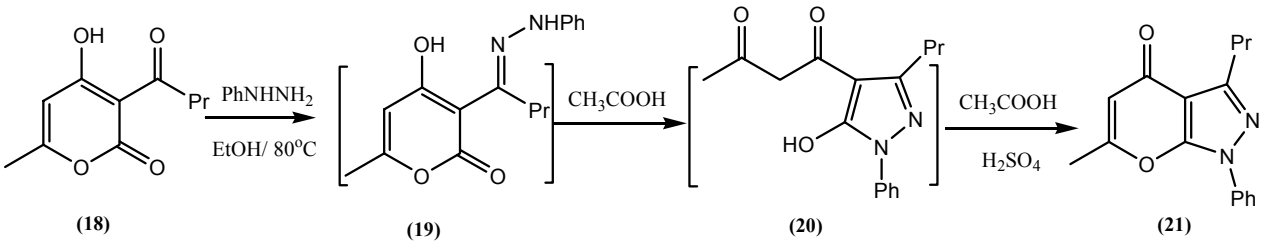
(c)



(21)

Figure 25: (a) ^{1}H-NMR of compound **21**; (b) ^{13}C-NMR of compound **21**; (c) ^{13}C-NMR DEPT 135 of compound **21**.

These assignments are consistent with the ^{13}C-DEPT 135 spectrum (Figure 25(c)). The six signals at δ 175.9, 161.8, 154.0, 151.4, 137.5, and 106.8 disappeared which is consistent with their assignment to quaternary carbon atoms. In addition, the signals at δ 129.8, 127.7, 121.5, 113.0, 19.91, and 14.28 appear in the positive direction which is consistent with their assignment to the CH type carbons of the phenyl and pyrone rings, and for the methyl carbons of the pyrone ring and the propyl side chain. The signals at δ 30.78 and 22.18 appear in the negative direction which is consistent with their assignment to the two CH_2 type carbons of the propyl side chain of the pyrazole ring.

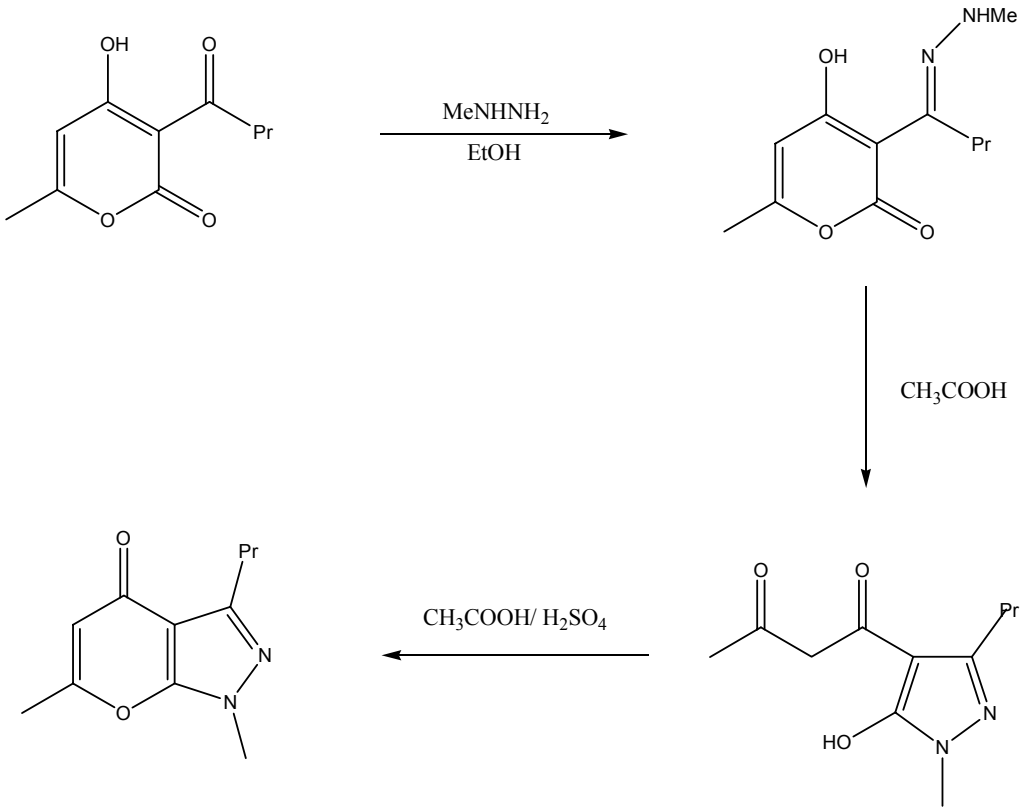


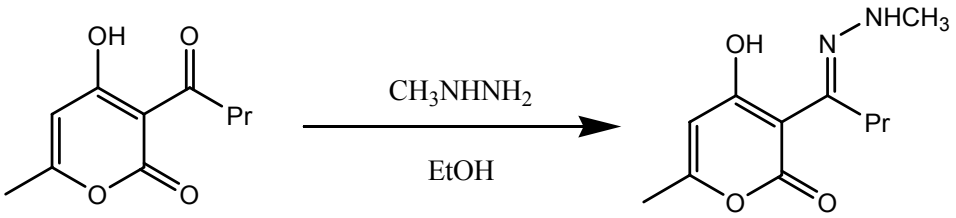
(18) **(19)** **(20)** **(21)**

Scheme 27: Synthesis of 6-methyl-1-phenyl-3-propylpyrano[2,3-*c*]pyrazole-4(1*H*)-one **(21)**.

The synthesis of 6-methyl-1-phenyl-3-propylpyrano[2,3-*c*]pyrazole-4(1*H*)-one **(21)** can also be accomplished without isolation of the either **18** and **19**. In this

experiment an ethanol solution of **18** was treated with phenylhydrazine at 80°C. After several minutes the solvent was evaporated and the crude N-phenylhyrazone **19** was allowed to reflux in acetic acid for one hour. Concentrated sulfuric acid was then added and the mixture was allowed to reflux for one additional hour. This procedure provided **21** in a yield of 60%.





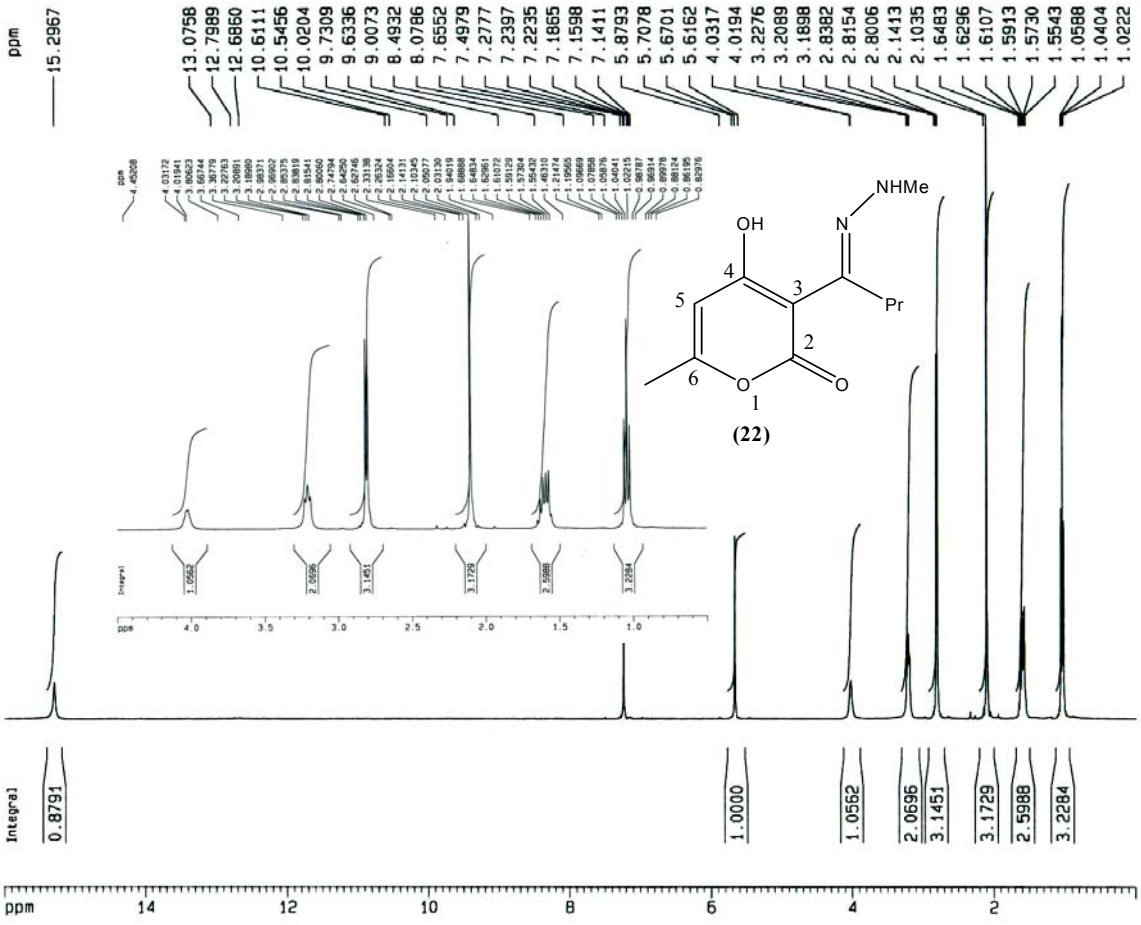
(18) **(22)**

Scheme 28: Synthesis of 4-hydroxy-6-methyl-3-(1-(2-methylhydrazono)butyryl)-3,4-dihydro-2*H*-pyran-2-one **(22)**.

Dehydroacetic acid derivative **18** was also found to be a suitable precursor of the N-methyl analog of pyranopyrazole **21**. When an ethanol solution of **18** was treated with methylhydrazine at room temperature for 2 hours, the new 4-hydroxy-6-methyl-3-(1-(2-methylhydrazono)butyryl)-3,4-dihydro-2*H*-pyran-2-one **(22)** was obtained in a yield of 45%, mp 70-71^{o}C (Scheme 28).

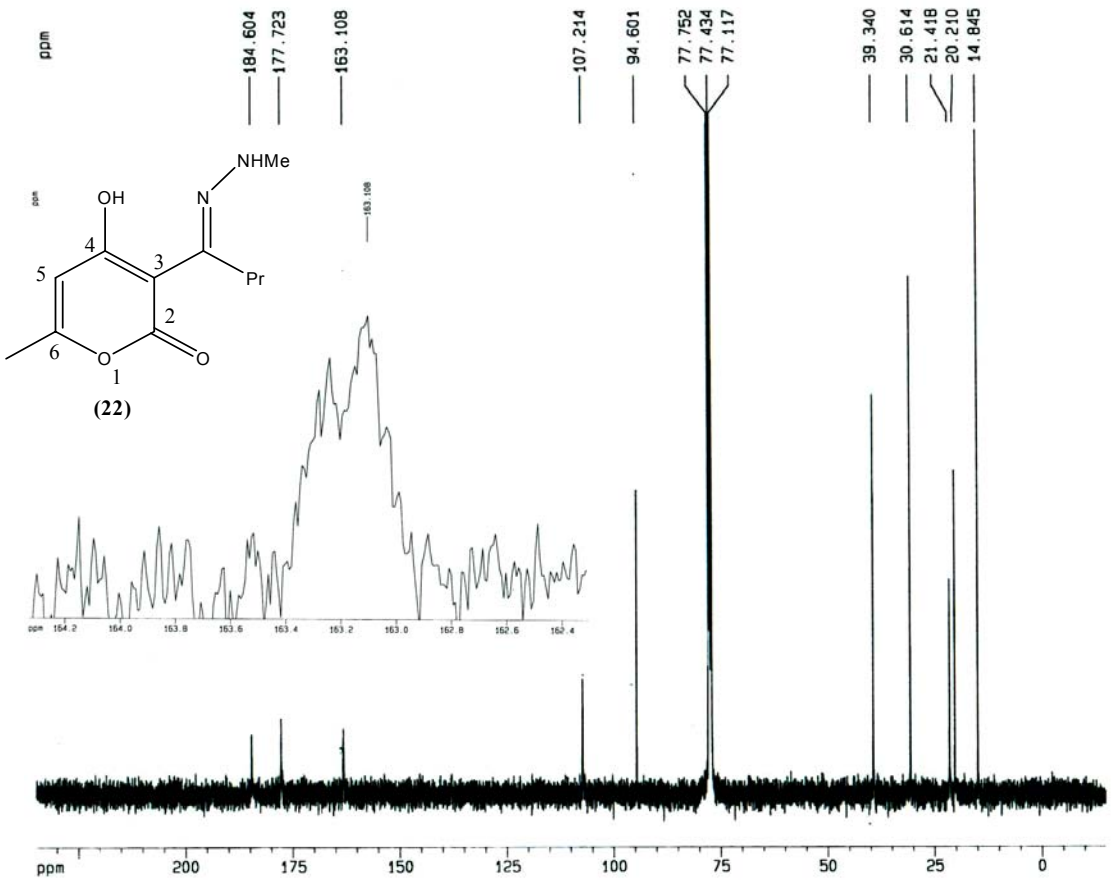
Figure 26(a) shows the ^{1}H-NMR spectrum of the structure of **22.** The key signal for this compound is the 1H singlet observed at δ 5.67 for the proton of the pyrone ring, while the methyl group of the pyrone ring appears as a 3H singlet at δ 2.10. In addition, a 2H triplet (J = 7.6 Hz) at δ 3.21, a 2H sextet (J = 7.8 Hz) at δ 1.57 and a 3H triplet (J = 7.3 Hz) at δ 1.04 are consistent with the propyl side chain of the hydrazone group. The 1H singlet at δ 15.3 is due to hydroxyl proton of the pyrone ring, while the amino proton

(a)



at δ 4.02 appears as a broad 1H quartet (J = 5.1 Hz) coupling with the N-methyl protons of the hydrazone group, which appears at δ 2.80 as a 3H doublet (J = 5.8 Hz). As expected, upon addition of D_2O the signals at δ 15.3 and 4.02 disappeared while the doublet at δ 2.80 collapsed to a singlet.

(b)



(22)

The ^{13}C-NMR spectrum (Figure 26(b)) is also consistent with the structure of **22**. The hydroxyl carbon in the lactone ring absorbs the furthest downfield at δ 184.6. The signal at δ 177.7 was assigned to the hydrazone carbon. The signals due to the carbons at positions 2, 3, 5, and 6 of the pyrone ring are observed at δ 163.2, 94.60, 107.2, and 163.1, respectively. The signal at δ 39.34 appears for the N-methyl carbon, while the signal at δ 20.21 appears for the C-6 methyl carbon of the pyrone ring. Finally, the carbon signals at δ 30.62, 21.42, and 14.85 appear for the propyl side chain.

(c)

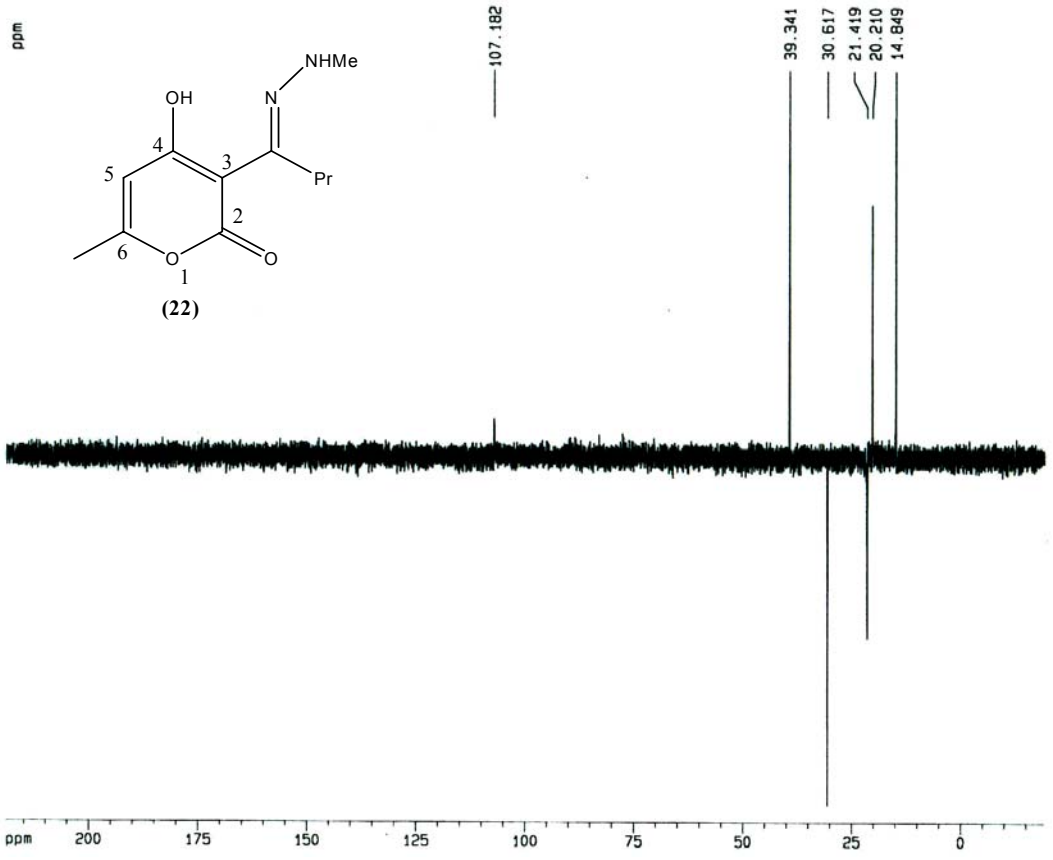
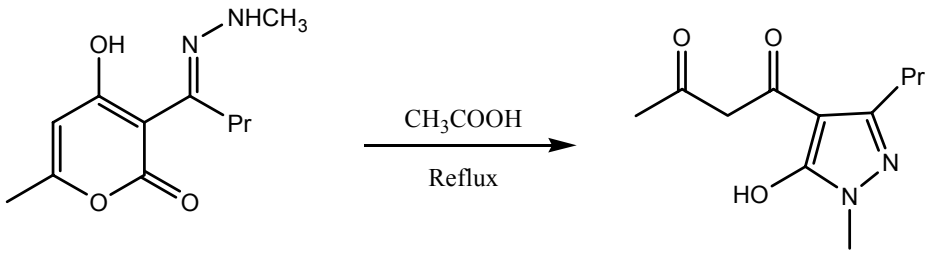


Figure 26: (a) ^{1}H-NMR of compound **22**; (b) ^{13}C-NMR of compound **22**; (c) ^{13}C-NMR DEPT 135 of compound **22**.

These assignments are consistent with the ^{13}C-DEPT 135 spectrum (Figure 26(c)). The five signals at δ 184.6, 177.72, 163.2, 163.1, and 107.2 disappeared which is consistent with their assignment to the four quaternary carbons of the pyrone ring and the carbon of the hydrazone group. In addition, the signal at δ 107.2 still appears as a positive signal which is consistent with a CH type carbon of the pyrone ring. Also, the signals at δ 39.34, 20.21, and 14.85 are due to carbons of the methyl groups on the nitrogen atom, the pyrone ring, and the propyl side chain, respectively. But the signals

at δ 30.62 and 21.42 appear in the negative direction which is consistent with the CH_2 type carbons of the propyl side chain.



(22) **(23)**

Scheme 29: Synthesis of 1-(5-hydroxy-1-methyl-3-propyl-1*H*-pyrazol-4-yl)butane-1,3-dione **(23)**.

The intramolecular cyclization of the N-methylhydrazone **22** in acid condition to new 1-(5-hydroxy-1-methyl-3-propyl-1*H*-pyrazol-4-yl)butane-1,3-dione **(23)** was accomplished by refluxing **22** in acetic acid for one hour. **23** was obtained in a yield of 61%, mp 96-97^{o}C (Scheme 29).

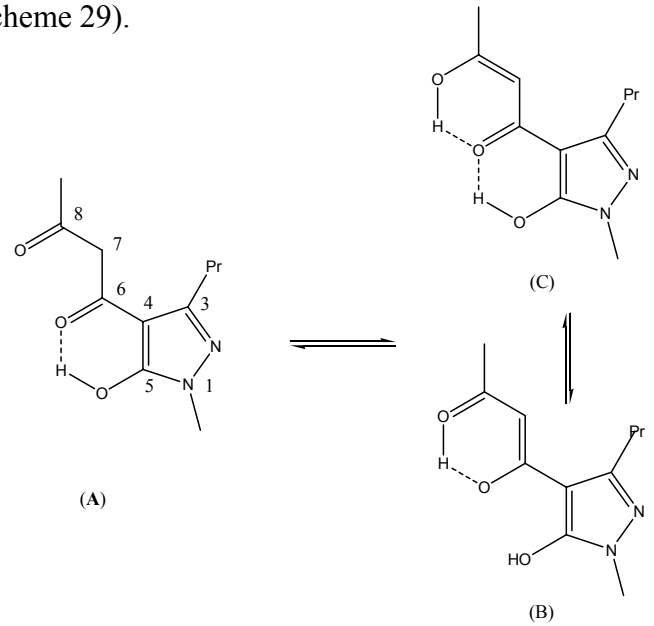
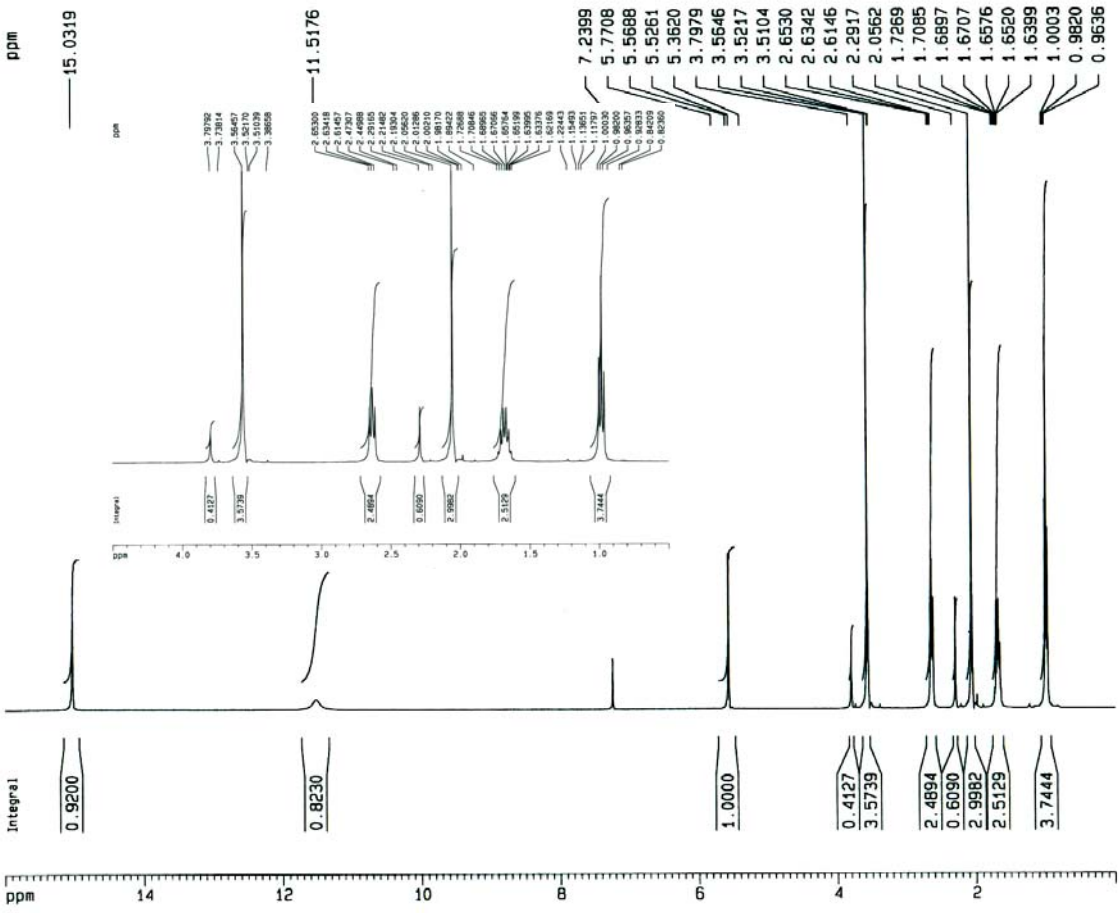


Figure 27: Tautomerization of compound **23**.

(a)

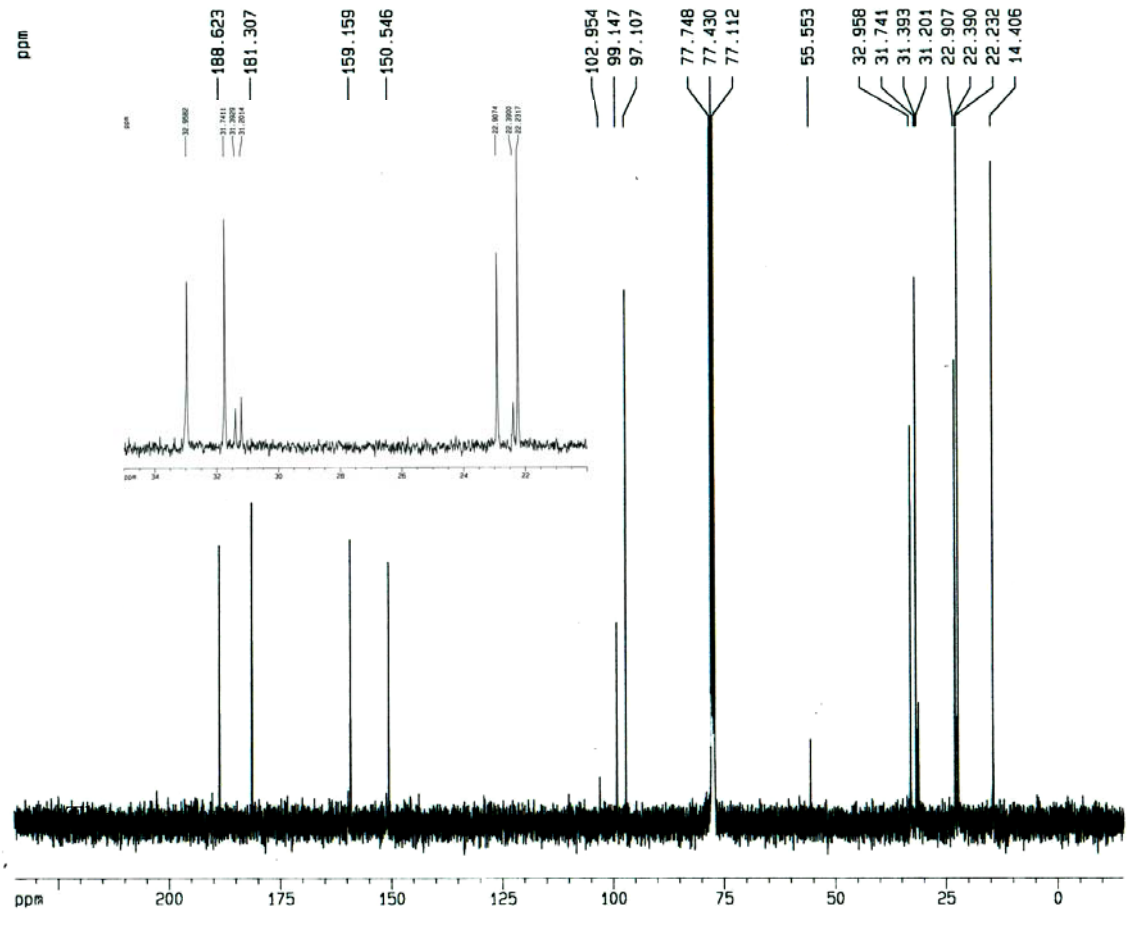


The ^{1}H-NMR spectrum (Figure 28(a)) shows that the enol and keto forms are most easily detected by the signal at δ 5.57 for the vinyl proton in the enol structure and the signal at δ 3.80 for the methylene protons in the keto structure. Based on the integral rises of 1.00 and 0.413 respectively for these signals, and noting that they are due to 1H and 2H signals respectively, the enol to keto ratio is calculated to be 4.84 to 1.

The sharp peak down field at δ 15.0 (D_2O exchangeable) is consistent with the intramolecularly H-bonded enolic proton in conformer B and C, while the very broad

signal at 11.5 is more consistent with the more acidic C-5 hydrogen bonded hydroxyl proton in tautomers A, B, and C. The 3H singlet signal at δ 2.29 were assigned to the C-8 methyl protons in the keto tautomer A, respectively, while the singlet at δ 2.06 (3H) was assigned to the C-8 methyl protons in the enol tautomer (B ⇌ C), respectively. In addition, the 3H singlet signal at δ 3.56 is due to the N-methyl protons, while a 2H triplet (J = 7.8 Hz) at δ 2.63, a 2H sextet (J = 7.5 Hz) at δ 1.67, and a 3H triplet (J = 7.6 Hz) at δ 0.982 appear for the protons in the propyl side chain in tautomers A, B, and C.

(b)



The ^{13}C-NMR spectrum (figure 28(b)) of compound **23** in $CDCl_3$ solution gives rise to two resonances for all the carbon atoms corresponding to the major enol and minor keto tautomers. It is known that a hydrogen-bonded carbonyl carbon resonates at lower field than a corresponding free carbonyl carbon and that an enolic carbon atom resonates at higher field than a corresponding keto carbon atom, according to literature reported.[3] The C-6 resonance of the enol form (B $\rightleftharpoons$ C) would be at a lower field than the C-8 carbon atom. From the chemical shift values, respectively at δ 188.6 and 181.3, it can be reasonably concluded the enol tautomer contributes mainly to the tautomeric population in $CDCl_3$ solution. The characteristic ^{13}C-NMR spectrum of the enol tautomer at δ 188.6, 181.3, 97.11, and 22.91 is consistent with the carbons at C-6, C-8, C-7, and the methyl C-8 on the side chain of the pyrazole ring, respectively. The carbons of the pyrazole ring at δ 159.2, 150.5, and 99.15 were assigned to C-5, C-3, and C-4, respectively. The N-methyl carbon appears at δ 32.96, while the three carbons of the propyl side chain appear at δ 31.74, 22.23, and 14.41. In the other hand, the A tautomer could not be completely assigned in ^{13}C-NMR because of the low intensity of the signals due to the minor A tautomer. However, the ^{13}C NMR spectrum exhibits some key signals for tautomer A, the signals at δ 55.55 and 31.20 can be assigned to the C-7 methylene carbon and the methyl C-8 on the side chain, respectively, while the signals at δ 31.39 and 22.39 are due to the methylene carbons of the propyl side chain.

These assignments are also consistent with the ^{13}C-NMR DEPT 135 of compound **23** (Figure 28(c)).

(c)

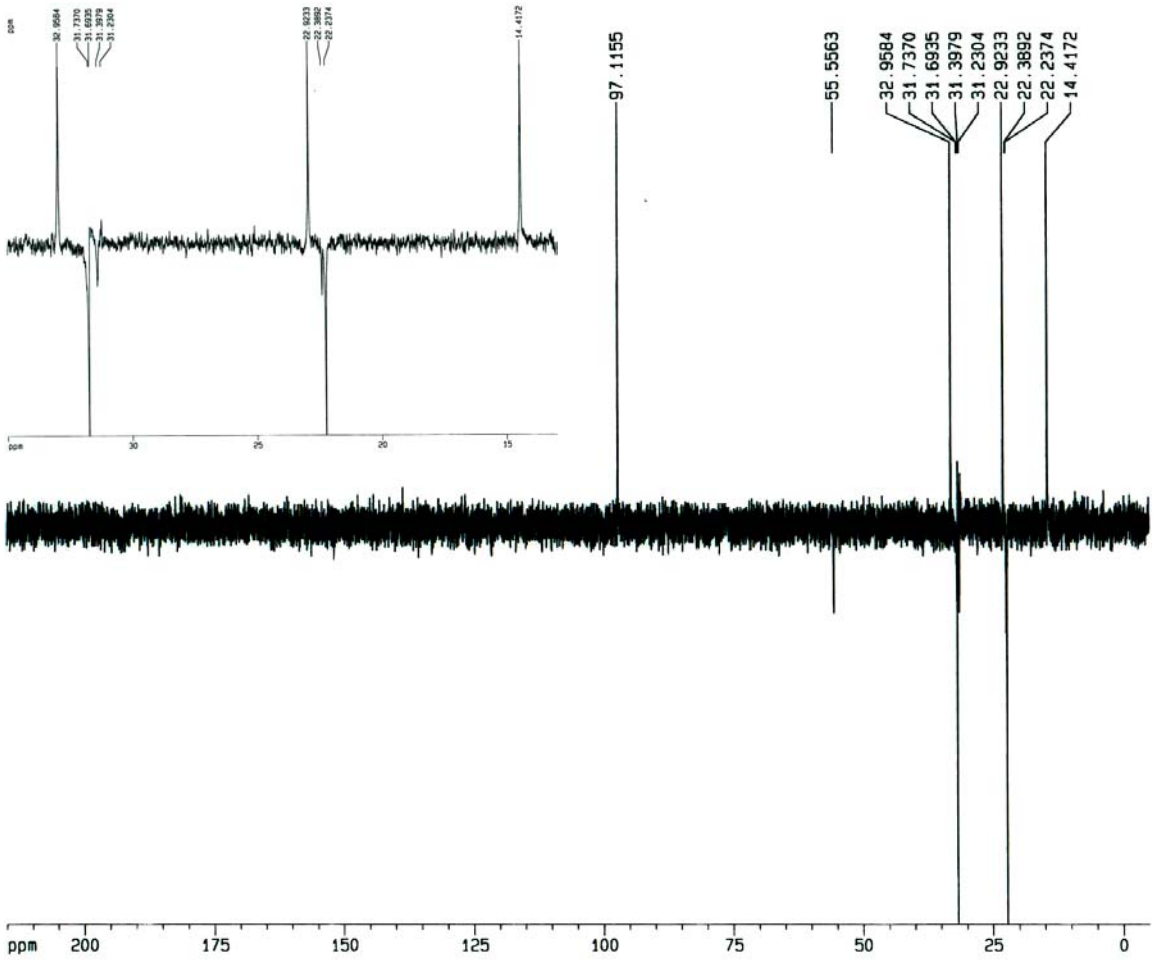
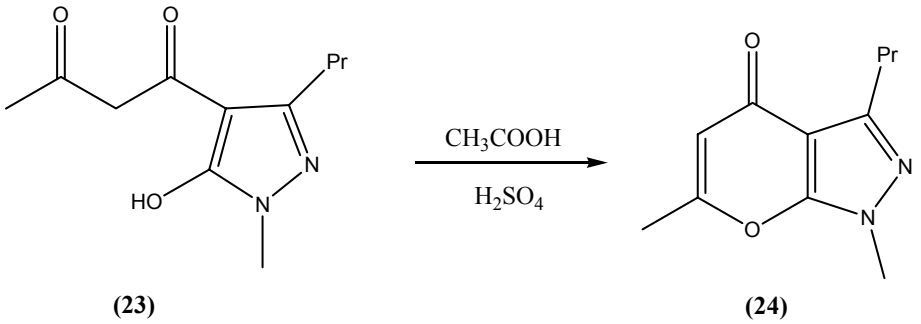


Figure 28: (a) ^{1}H-NMR of compound **23**; (b) ^{13}C-NMR of compound **23**; (c) ^{13}C-NMR DEPT 135 of compound **23**.

As expected the ^{13}C-NMR DEPT 135 (figure 28(c)) of compound **23** shows that the five signals at δ 188.6, 181.3, 159.2, 150.5, and 99.15 disappeared which is consistent with the quaternary signals of the major tautomer. These disappearing signals are due to the C-6 and 8 side chain and the quaternary carbons of the pyrazole ring at C-3, C-4, and C-5 positions. The signals at δ 97.12, 32.96, 22.92, and 14.41

appear in the positive direction which is consistent with their assignment to the CH vinyl side chain, the methyl carbon of the propyl side chain, and the C-8 methyl of the major tautomer. The signal at δ 31.23 is due to the C-8 methyl of the minor tautomer. In the other hand, the negative signals at 31.74 and 22.24 are due to the CH_2 type carbons of the propyl chain ring of the major tautomer. For the minor tautomer, the negative signal at δ 55.55 is due to the methylene carbon on side chain ring, while the signal at δ 31.39 and 22.39 appears for the CH_2 type carbons of the propyl side chain of the pyrazole ring.



(23) **(24)**

Scheme 30: Synthesis of 1,6-dimethyl-3-propylpyrano[2,3-*c*]pyrazole-4(1*H*)-one **(24)**.

The ring closure of **23** to the new compound 1,6-dimethyl-3-propylpyrano[2,3-*c*]pyrazole-4(1*H*)-one **(24)** was achieved by refluxing **23** in acetic acid in the presence of sulfuric acid as a catalyst for one hour to obtain **24** in a yield of 74%, mp 61-62^{o}C (Scheme 30).

(a)

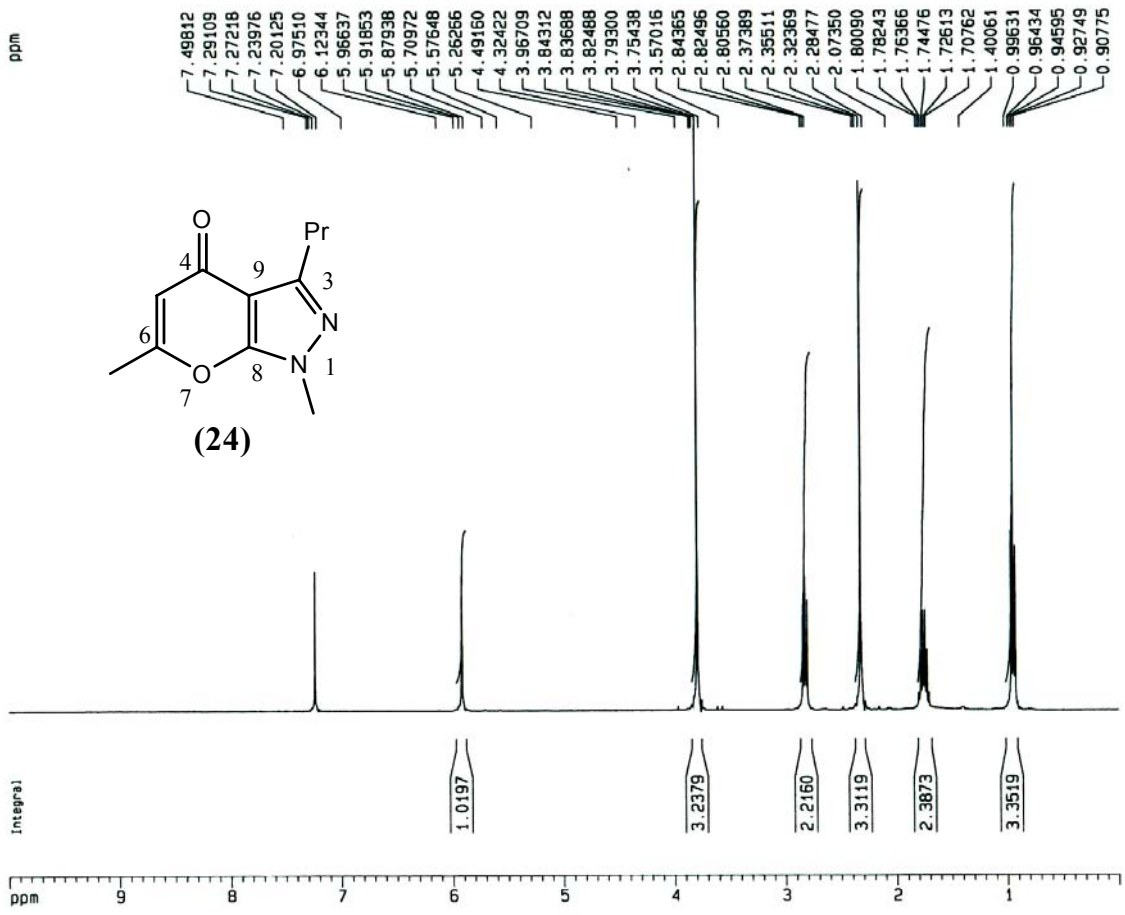
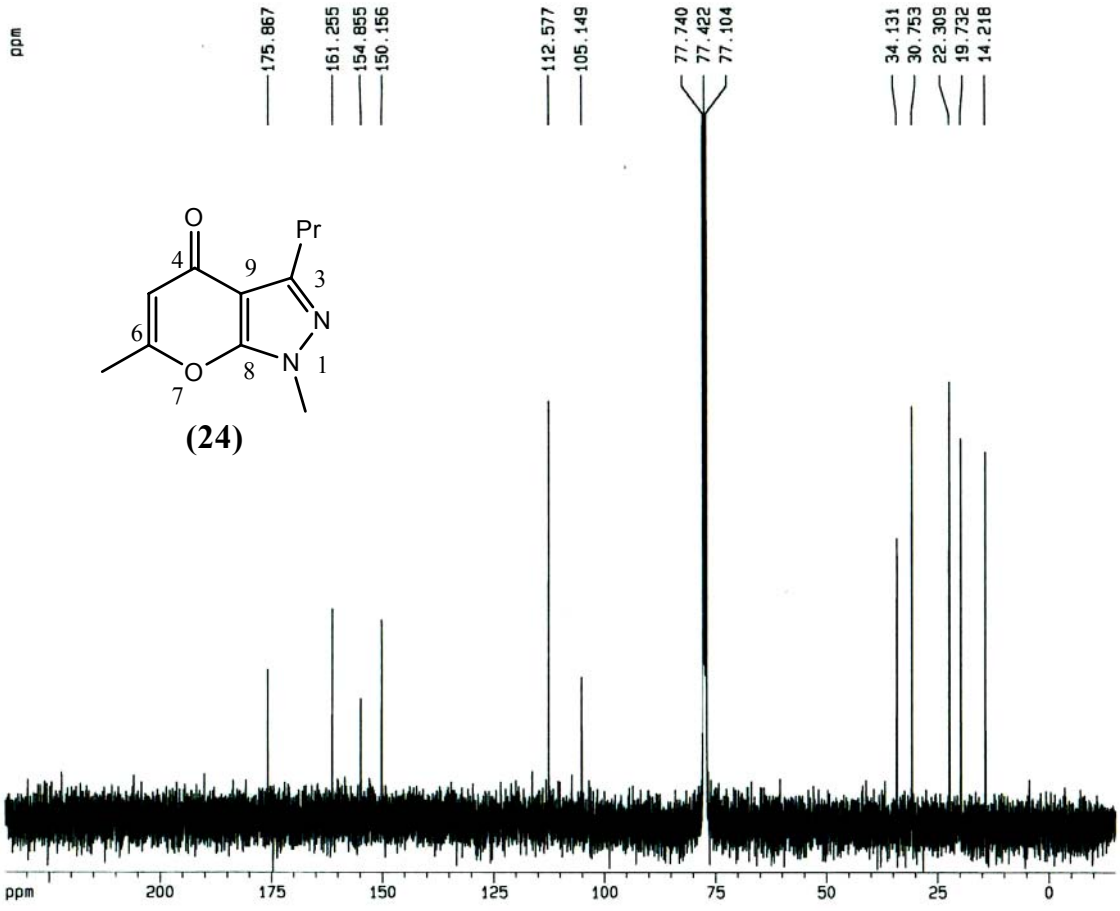


Figure 29(a) shows that the ^{1}H-NMR spectrum of the colorless crystalline product is consistent with the structure of **24.** The key signal due to the C-5 proton of the pyrone ring is observed at δ 5.92 (1H), while the two 3H singlets at δ 2.32 and 3.79 are consistent with the methyl groups at C-6 and N-1, respectively. In addition, the 2H triplet at δ 2.83 (J = 7.6 Hz), the 2H sextet (J = 7.6 Hz) at δ 1.76, and the 3H triplet (J = 7.3 Hz) at 0.946 are consistent with the n-propyl group in the structure.

(b)



(24)

The ^{13}C-NMR spectrum (Figure 29(b)) is also consistent with the structure of **24**. The carbonyl carbon in the pyrone ring absorbs the furthest downfield at δ 175.9. In addition, the signals due to C-3, C-6, C-8, and C-9 quaternary carbons are observed at δ 150.2, 161.3, 154.9, and 105.1, respectively. The signal at δ 112.2 is due to the CH carbon at C-5, while the signals at δ 34.13 and 19.73 are due to the C-6 and N-1 methyl groups, respectively. Furthermore, the signals at δ 30.76, 22.32, and 14.23 are due to the propyl side chain.

(c)

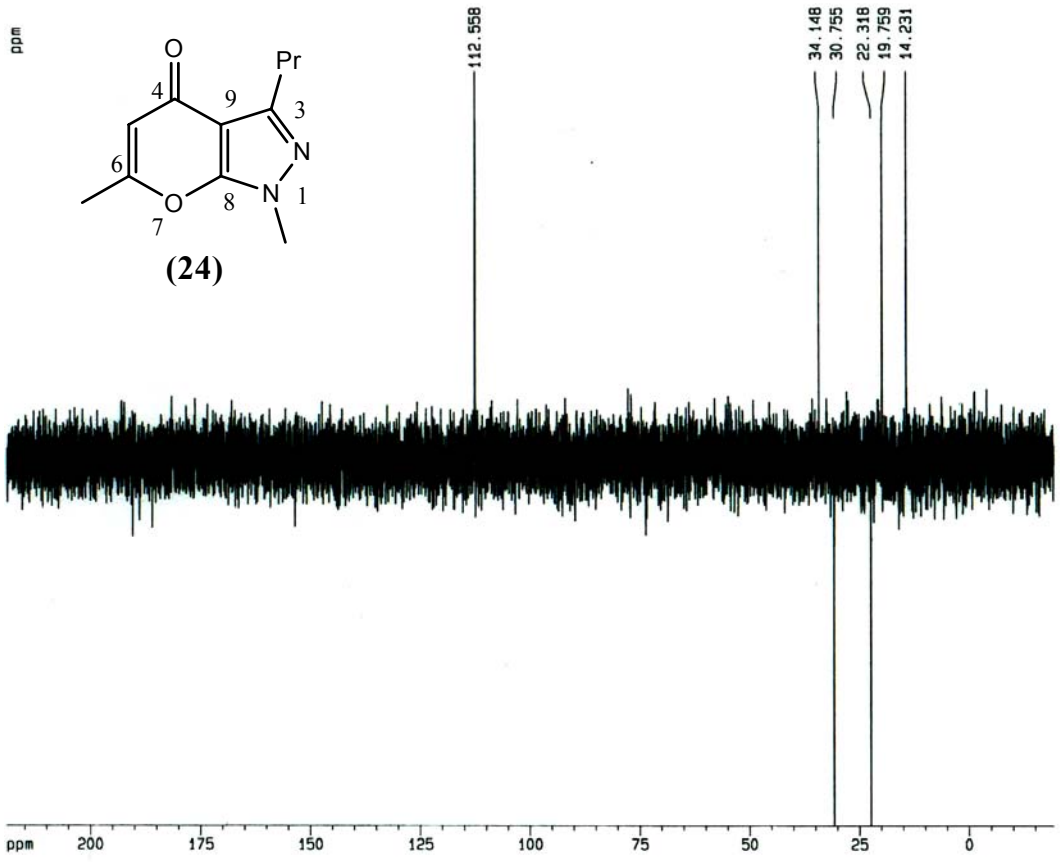
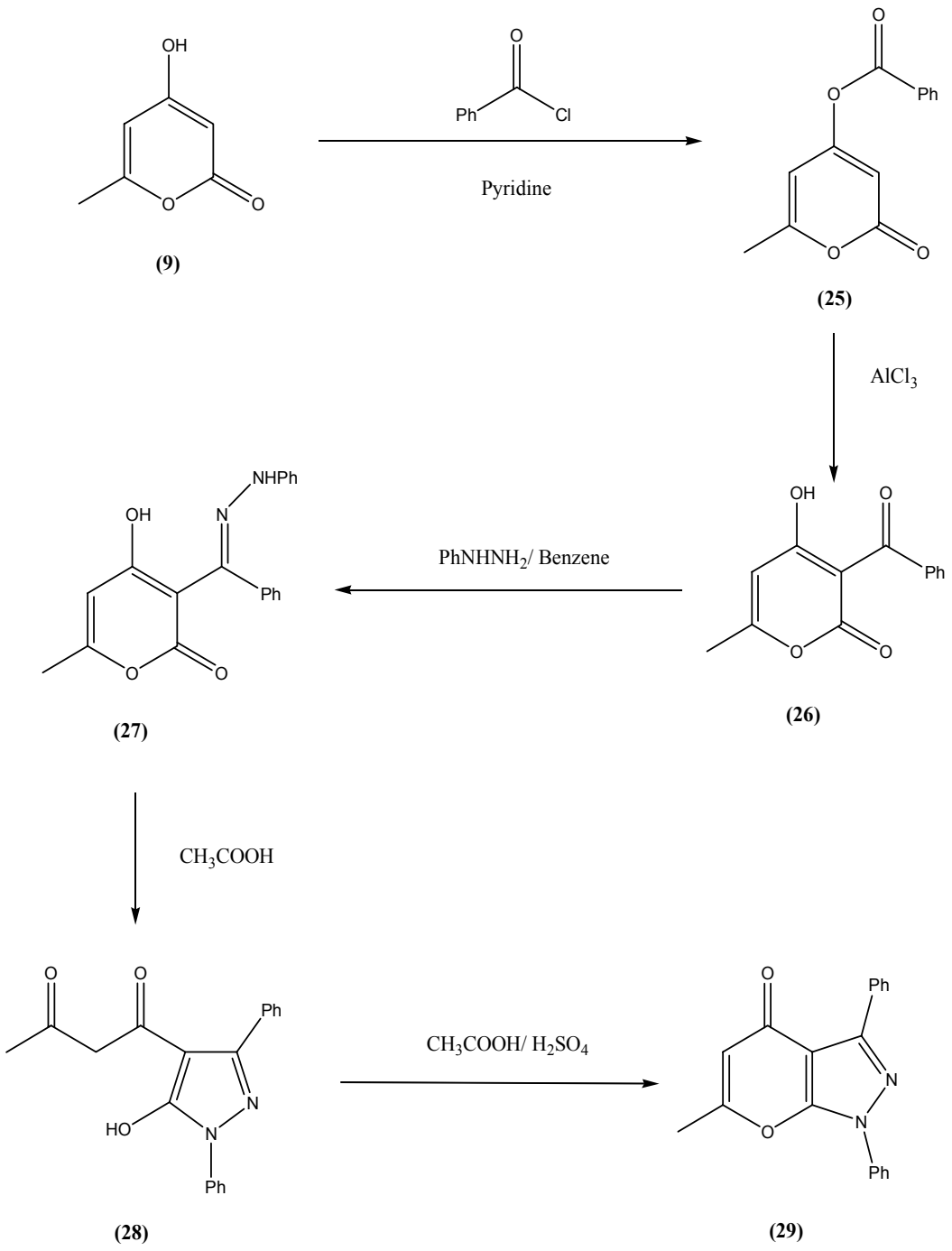


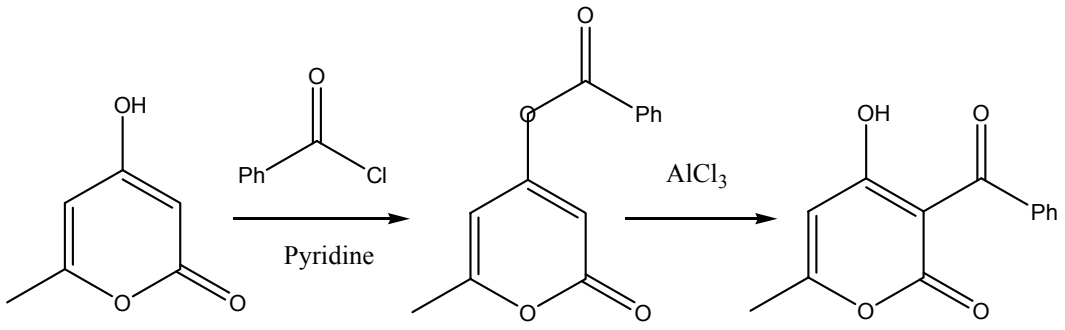
Figure 29: (a) ^{1}H NMR of compound **24**; (b) ^{13}C NMR of compound **24**; (c) ^{13}C NMR DEPT 135 of compound **24**.

These assignments are consistent with the ^{13}C-DEPT 135 spectrum (Figure 29(c)). The five signals at δ 175.9, 161.3, 154.9, 150.2, and 105.1 are not observed in the DEPT 135 spectrum, which is consistent with their assignment to the quaternary carbons of the structure. In addition, the positive signal at δ 112.6 appears for the CH type carbon at C-5, while the three positive signals at δ 34.15, 19.76, and 14.23 are due

to the methyl groups of structure. On the other hand, the methylene carbons of the propyl side chain are consistent with the negative signals at δ 30.75 and 22.32.



In order to synthesize the dehydroacetic derivative **26** with a phenyl group in the acyl side chain, the two step sequence shown in Scheme 31 was followed.



(9) **(25)** **(26)**

Scheme 31: Synthesis of 6-methyl-2-oxo-2H-pyran-4-yl benzoate **(25)**.

According to the literature procedure of Marcus, E. and colleague,[7] the 6-methyl-2-oxo-2H-pyran-4-yl benzoate **(25)** was prepared by O-acylation of 4-hydroxy-6-methyl-2-pyrone **(9)** under basic condition to give **25** in 69 % yield, mp 85-86 ^{o}C (Lit.[7] mp 87-89 ^{o}C) (Scheme 31).

(a)

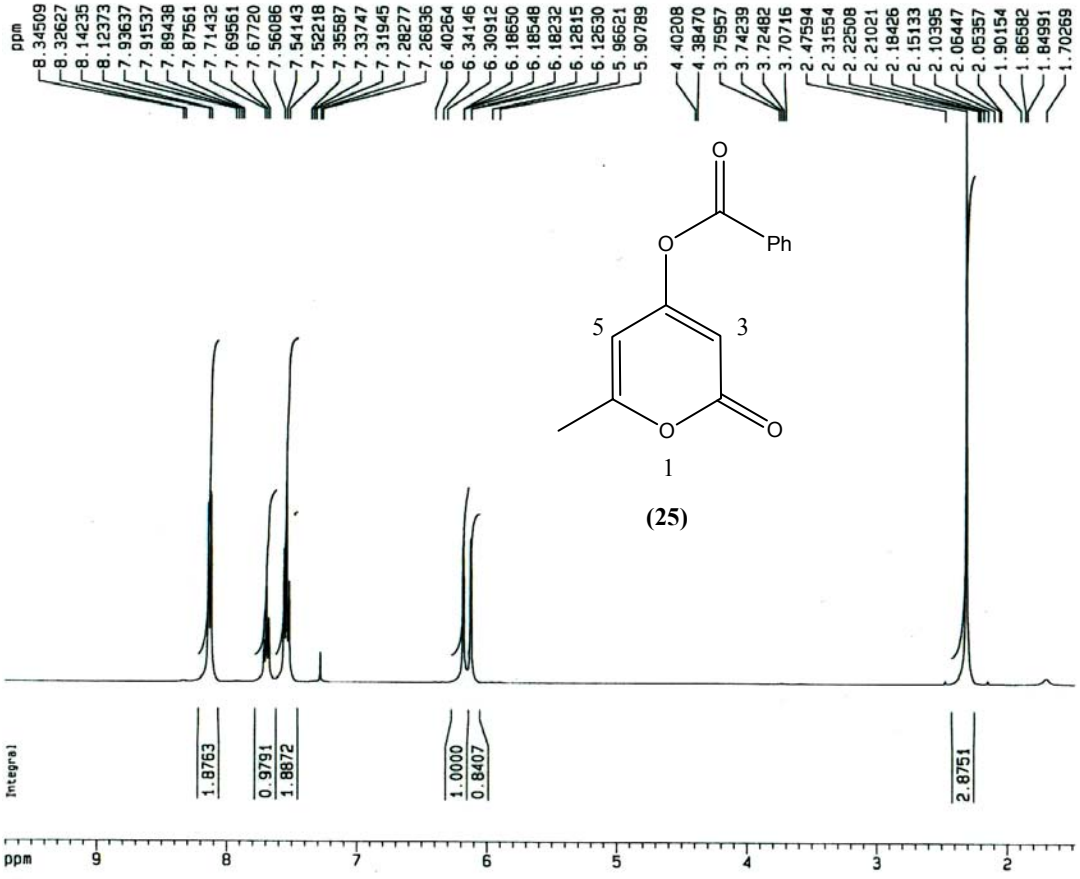
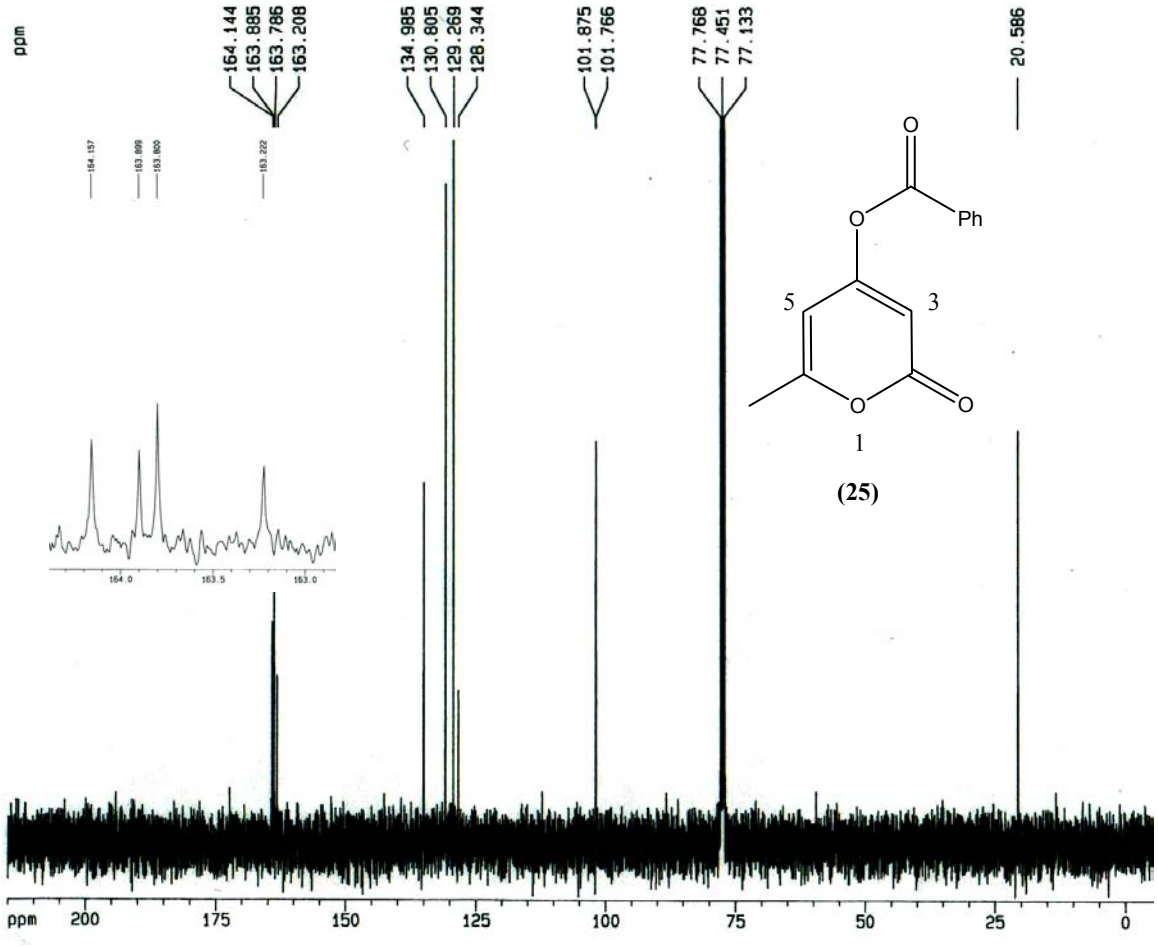


Figure 30(a) shows that the ^{1}H-NMR spectrum of the colorless crystals is consistent with the structure of **25.** The 1H singlets observed at δ 6.11 (1H) and δ 6.17 (1H) were assigned to the protons at C-3 and C-5 of the pyrone ring, respectively, while the 3H singlet at δ 2.30 is consistent with the methyl group at position 6. In addition, the two triplets at δ 7.32 (2H; J = 8.1 Hz) and 7.52 (1H; J = 8.1 Hz), and one doublet at δ 8.12 (2H; J = 7.6 Hz) are due to the protons at the meta, para, and ortho positions of the phenyl ring, respectively.

(b)



(25)

The ^{13}C-NMR spectrum (Figure 30(b)) is also consistent with the structure **25**. The carbon at C-4 of the pyrone ring absorbs the furthest downfield at δ 164.2, while the signals due to the carbons at C-2 and C-6 appear at δ 163.9 and 163.8 respectively. The carbonyl signal at δ 163.2 was assigned to the benzoyl carbon. The two CH carbons of the pyrone ring are observed at δ 101.8 and 101.9 due to C-3 and C-5, respectively. The phenyl ring carbons at position 1 and the para position absorb at δ 128.3 and 134.9 respectively, while the ortho and meta carbons of the phenyl ring appear as two singlets at δ 130.8 and 129.3. In addition, the signal due to the methyl

carbon is observed at δ 20.60. These assignments are consistent with the ^{13}C-DEPT 135 spectrum (Figure 30(c)).

(c)

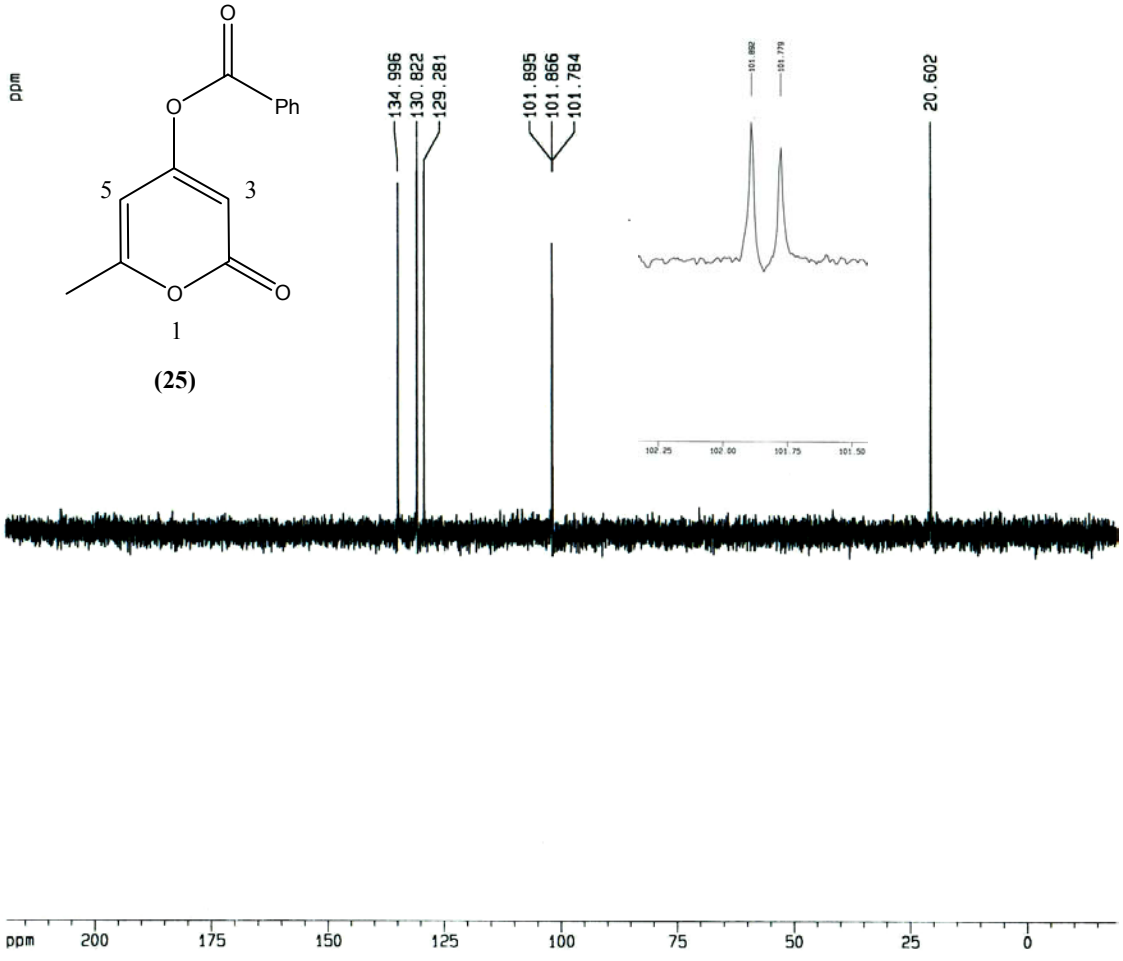
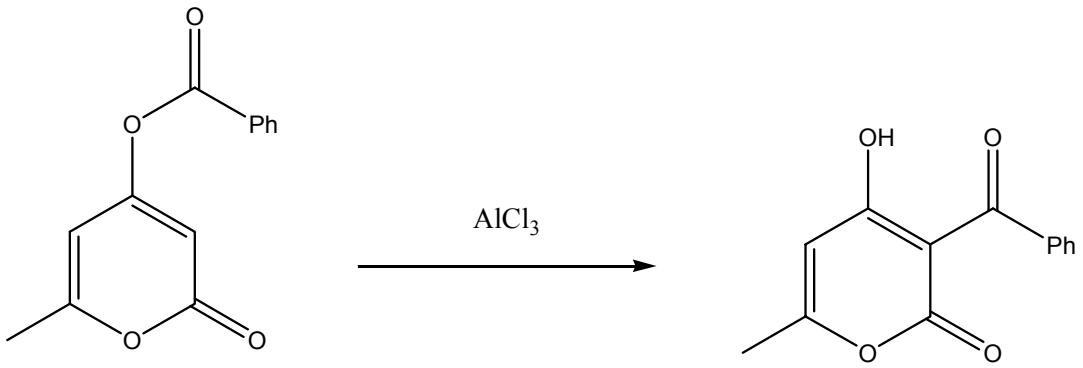


Figure 30: (a) ^{1}H NMR of compound **25**; (b) ^{13}C NMR of compound **25** and (c) ^{13}C NMR DEPT 135 of compound **25**.

The five signals at δ 164.2, 163.9, 163.8, 163.2, and 128.3 disappear which is consistent with their assignment to the five quaternary carbons in the structure.

However, all the signals at δ 134.9, 130.8, 129.3, 101.9, 101.8 and 20.60 appear in the positive direction which is consistent with their assignment to the three CH type carbons of the phenyl ring, two CH type carbons of the pyrone ring, and the methyl carbon of the pyrone ring.



(25) **(26)**

Scheme 32: Synthesis of 3-benzoyl-4-hydroxy-6-methyl-2*H*-pyran-2-one **(26)**.

As reported by Marcus and colleagues,[7] **25** was observed to undergo an $AlCl_3$ catalyzed Fries rearrangement to give 3-benzoyl-4-hydroxy-6-methyl-2*H*-pyran-2-one **(26)** in 61% yield, mp 105-107^{o}C (Lit.[7] mp 108-110^{o}C) (Scheme 32).

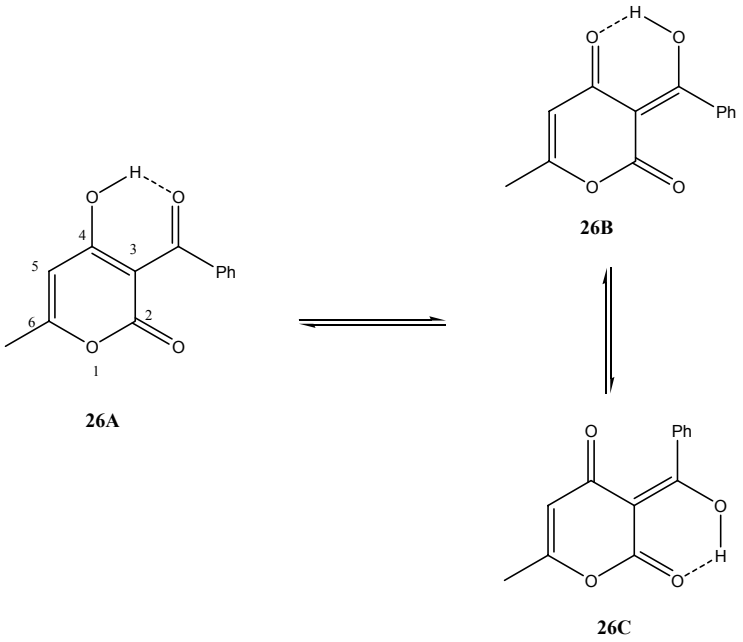
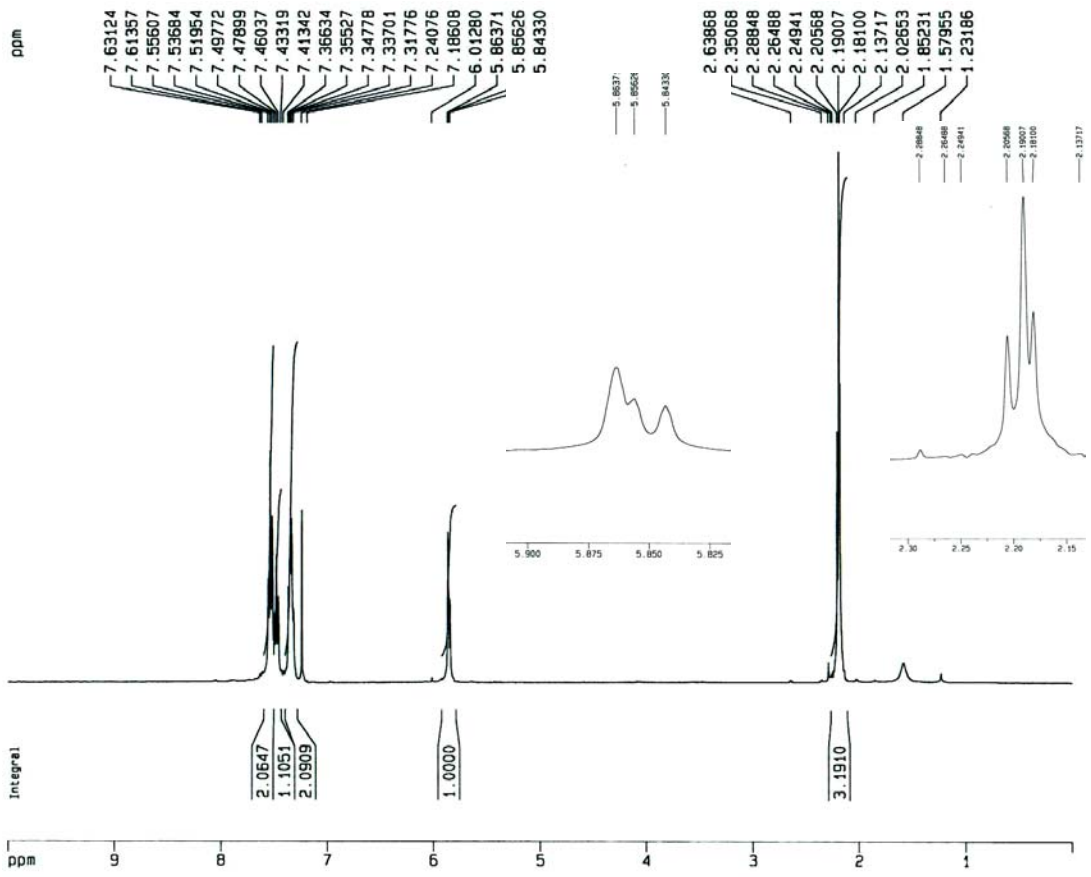


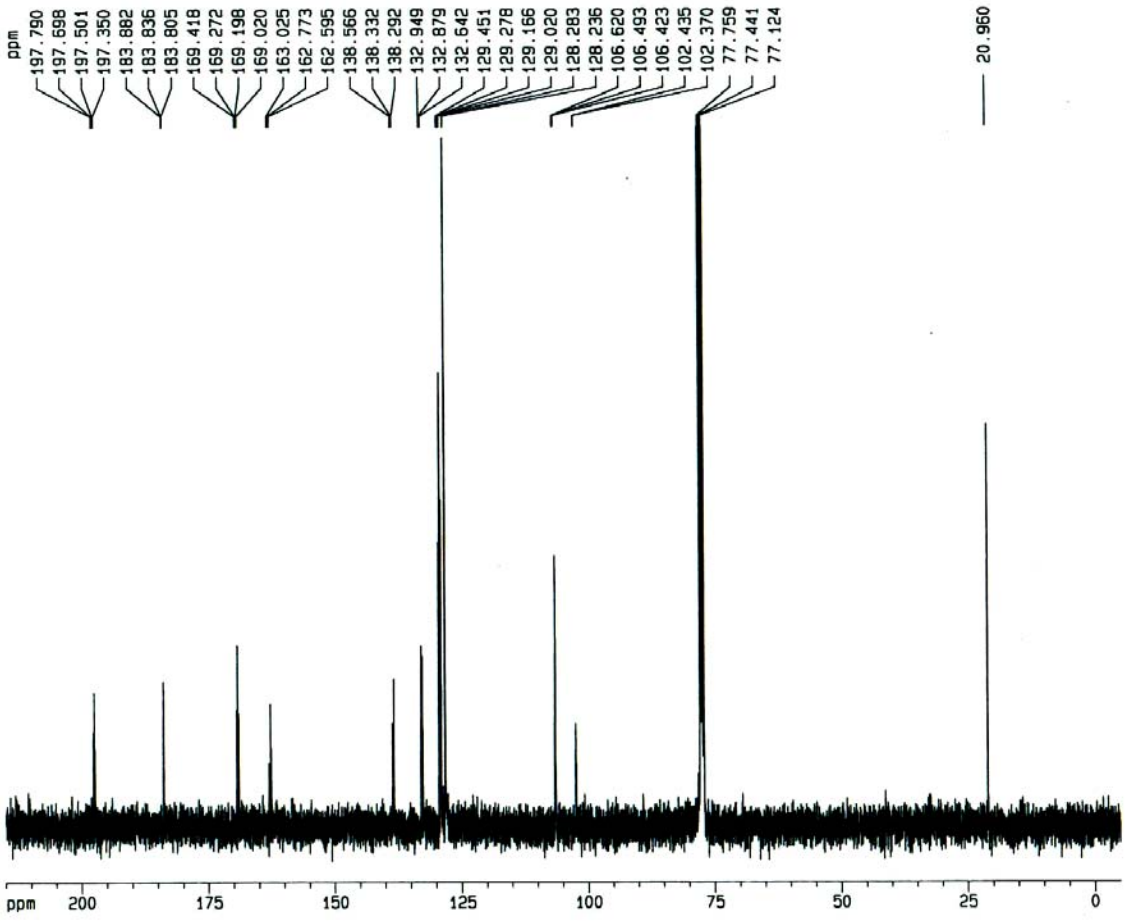
Figure 31: Tautomerization of compound **26**

(a)



The ^{1}H-NMR spectrum of **26** shown in Figure 32(a) suggests that in $CDCl_3$ solution **26** exists as a mixture of tautomers **26A**, **26B**, and **26C** in Figure 31. Thus, instead of the C-5 proton and the C-6 methyl group appearing as clear 1H singlets at δ 5.84-5.86 and 3H singlets at δ 2.18-2.20, respectively, the scale expansions shows that each signal can be resolved into three peaks. In addition, the spectrum shows a typical absorption pattern for the phenyl protons between δ 7.63-7.32.

(b)



The ^{13}C-NMR spectrum is also consistent with the gross features of structure **26**. Thus, the carbonyl carbon of the benzoyl side chain was assigned to the peak

furthest downfield at δ 197.6. The signals due to C-2, C-3, C-4, C-5, and C-6 carbons of the pyrone ring appear at δ 169.2, 102.4, 183.8, 106.5, and 162.8, respectively, while the signal due to the carbon of the methyl group is observed at δ 20.96. The signals due to C-1, ortho, meta, and para carbons of the phenyl ring appear at δ 138.3, 129.1, 128.2, and 132.8, respectively. These assignments are consistent with the DEPT-135 spectrum which confirms that all of these signals are due to quaternary carbon except the signals at δ 106.5, assigned to the non-quaternary C-5 carbon, and δ 20.96, assigned to the carbon of the methyl group. Finally, the signals due to C-1, ortho, meta, and para carbons of the phenyl ring appear at δ 138.3, 129.1, 128.2, and 132.8, respectively. Examination of the spectrum shows that almost all of these signals consist of multiple peaks due to the presence in solution of the tautomers.

(c)

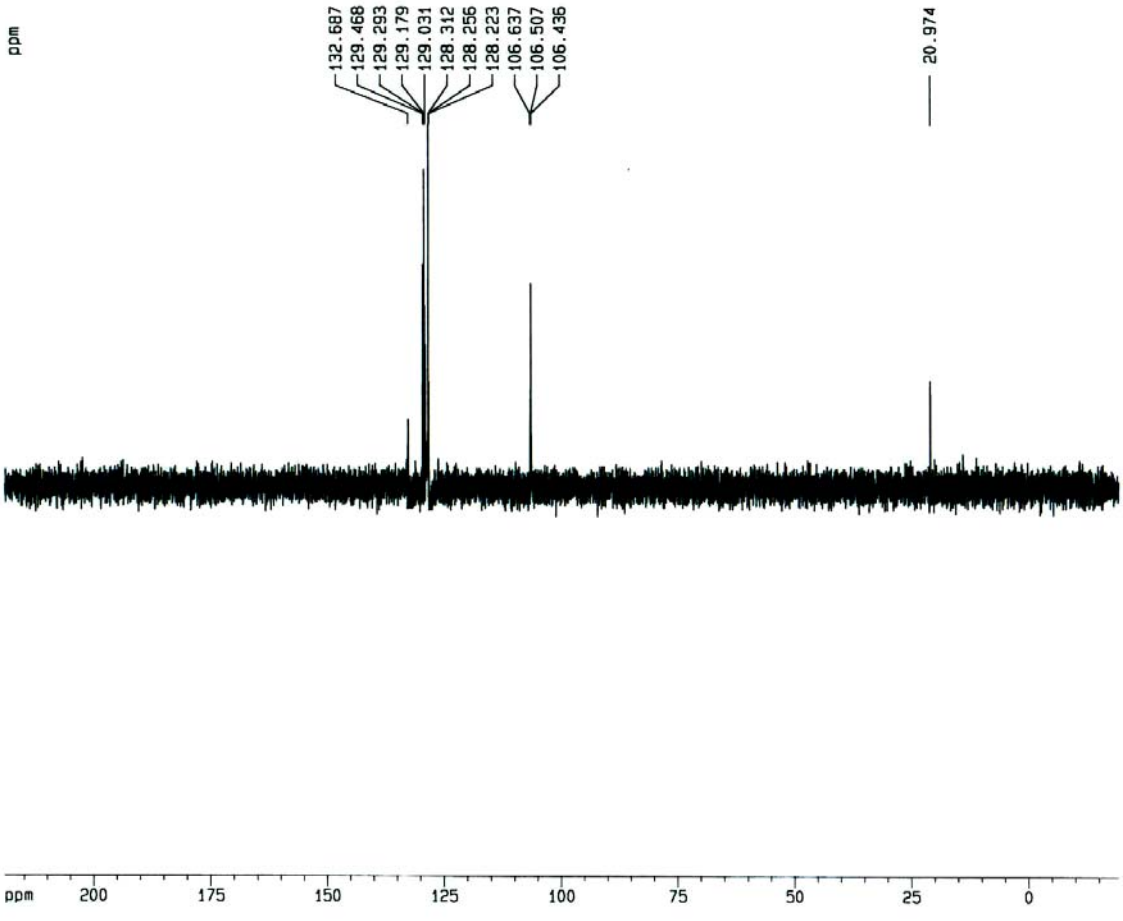
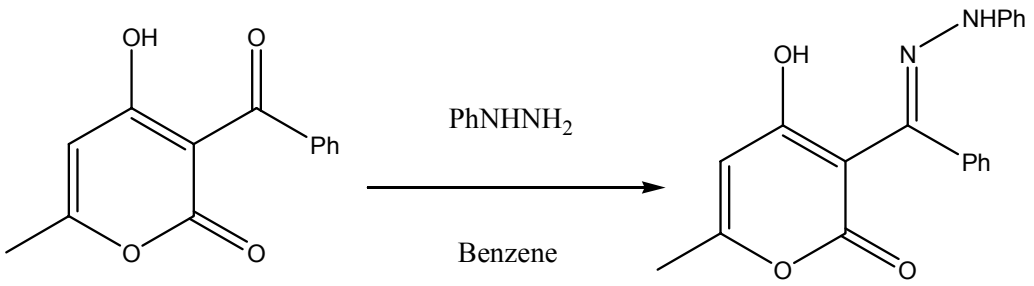


Figure 32: (a) ^{1}H-NMR of compound **26**; (b) ^{13}C-NMR of compound **26** and (c) ^{13}C-NMR DEPT 135 of compound **26**.

As observed in ^{13}C-DEPT 135 spectrum (Figure 32(c)), the six signals at δ 197.6, 183.8, 169.2, 162.8, 138.3, and 102.4 disappear which is consistent with their assignment to the four quaternary carbons of the pyrone ring, the carbonyl of the benzoyl side chain, and C-1 quaternary carbon of the phenyl ring. The positive signals due to the three CH type carbons of the phenyl ring are observed at δ 132.8, 129.1, and 128.2, while the C-5 carbon of the pyrone ring is observed at δ 106.5. The last positive signal due to the methyl carbon of the pyrone ring appears as a singlet at δ 20.97.



(26) **(27)**

Scheme 33: Synthesis of 4-hydroxy-6-methyl-3-(1-(2-phenylhydrazono)benzyl)-2*H*-pyran-2-one **(27)**.

According to the work of Gelin, C. and colleagues,[3] 4-hydroxy-6-methyl-3-(1-(2-phenylhydrazono)benzyl)-2*H*-pyran-2-one **(27)** was synthesized by treating **26** with phenylhydrazine in benzene to give the N-phenylhydrazone **27** in 84 % yield, mp 158-159 ^{o}C (Lit.[3] mp 160 ^{o}C) (Scheme 33).

(a)

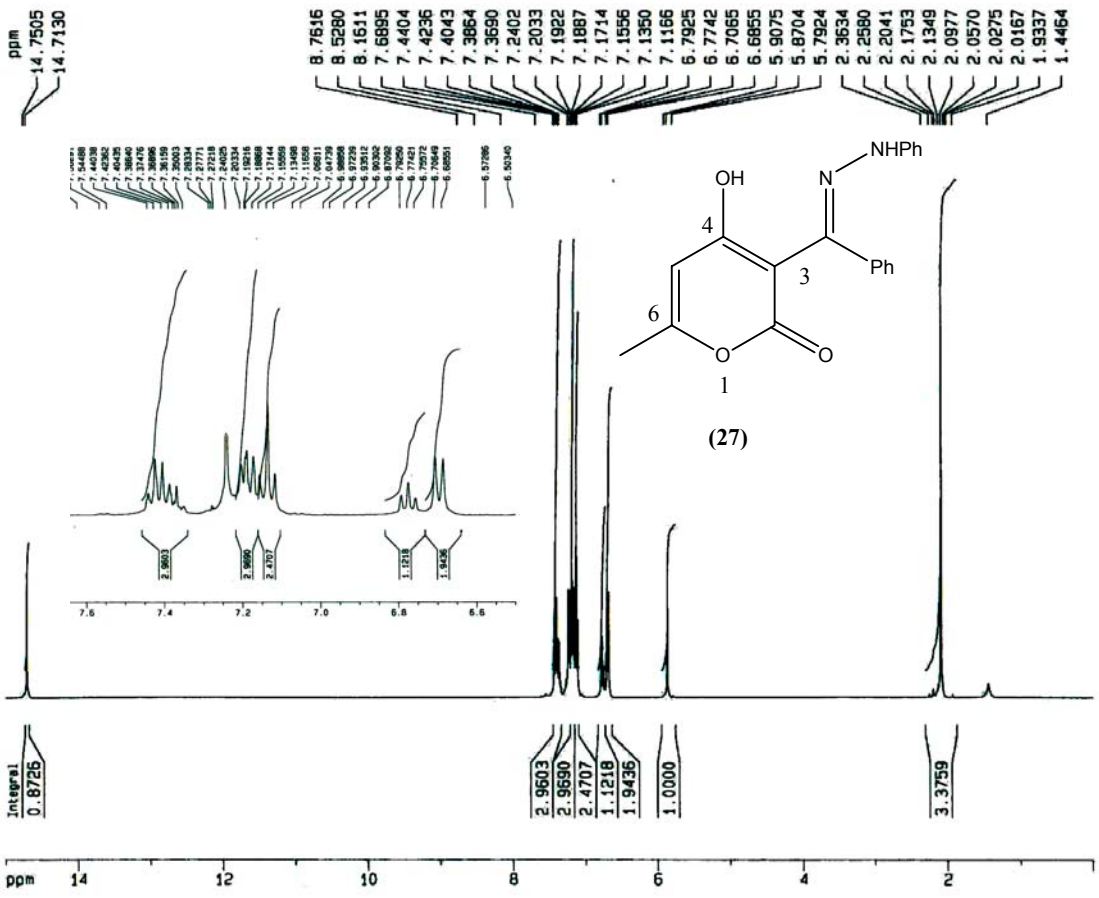
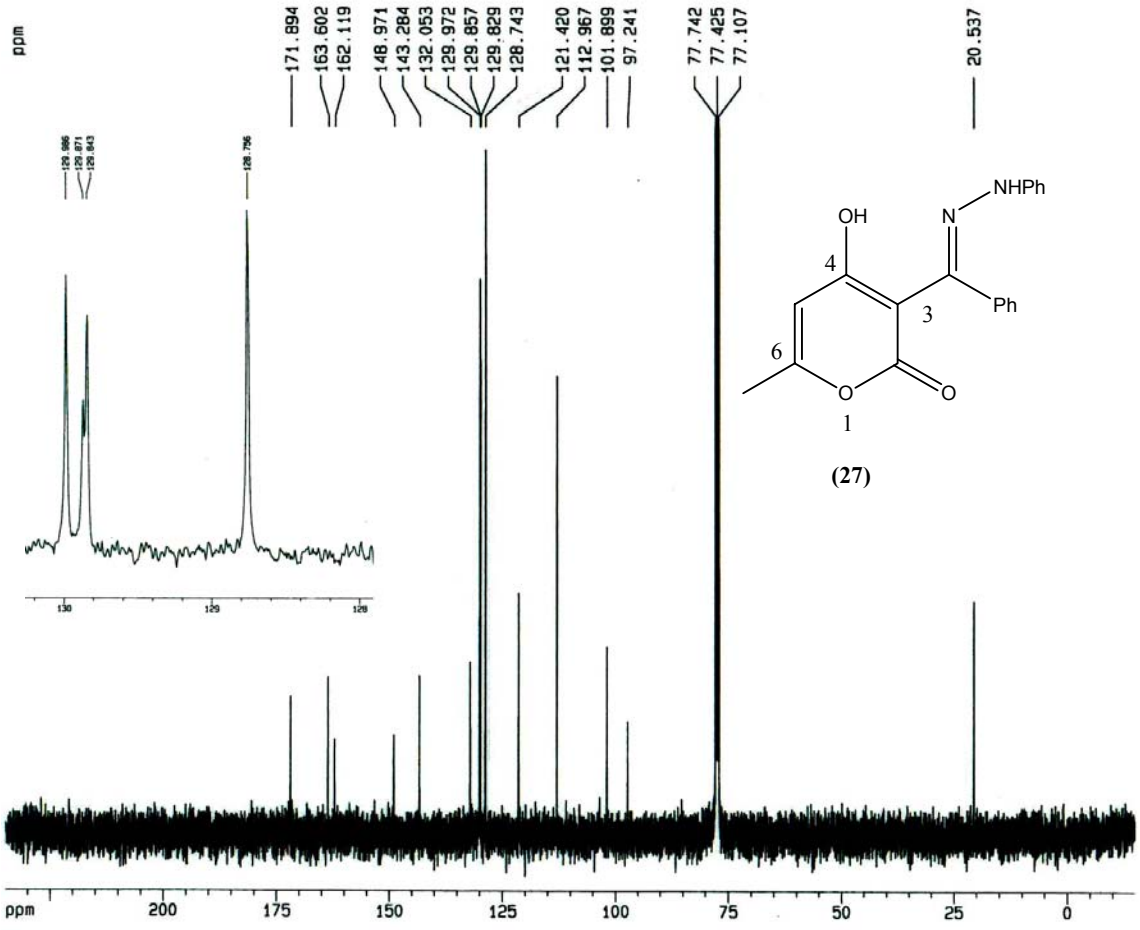


Figure 33(a) shows that the ^{1}H-NMR spectrum of the yellow crystalline product is consistent with the structure of **27.** Two key signals are observed in the spectrum as a 1H singlet at δ 5.79 and a 3H singlet at δ 2.10 due to the C-5 proton and the C-6 methyl group, respectively. In addition, the two triplets at δ 7.13 (2H; J = 7.6 Hz) and 6.77 (1H; J = 7.1 Hz) and a doublet at δ 6.69 (2H; J = 8.1 Hz) are due to the absorptions of the N-phenyl ring protons at the meta, para, and ortho positions, respectively. On the other hand, the phenyl ring protons of the hydrazone side chain appear as a multiplet at δ 7.40 (3H) for the meta and para positions, and the multiplet signal at δ 7.19 (2H) for

the ortho protons. The furthest down field proton at δ 14.7 is due to the enol proton. When compound **27** was treated with D_2O, this signal disappeared.

(b)



The ^{13}C-NMR spectrum (Figure 33(b)) is also consistent with the structure **27**. The enol carbon of the pyrone ring absorbs the furthest downfield at δ 171.9, while the signal at δ 148.9 was assigned to the hydrazone carbon. The C-2, C-3, C-5, and C-6 carbons of the pyrone ring appear at δ 163.6, 97.24, 101.9, and 162.1 respectively. The N-phenyl ring carbons due to C-1, ortho, meta, and para are observed at 143.3, 112.9, 128.8, and 121.4, respectively. On the other hand, the phenyl ring carbons of the

hydrazone side chain due to C-1, ortho, meta, and para are observed at δ 131.2, 130.0, 129.8, and 129.9, respectively. Finally, the furthest upfield signal at δ 20.54 is due to the methyl carbon. These assignments are consistent with the ^{13}C-DEPT 135 spectrum (Figure 33(c)).

(c)

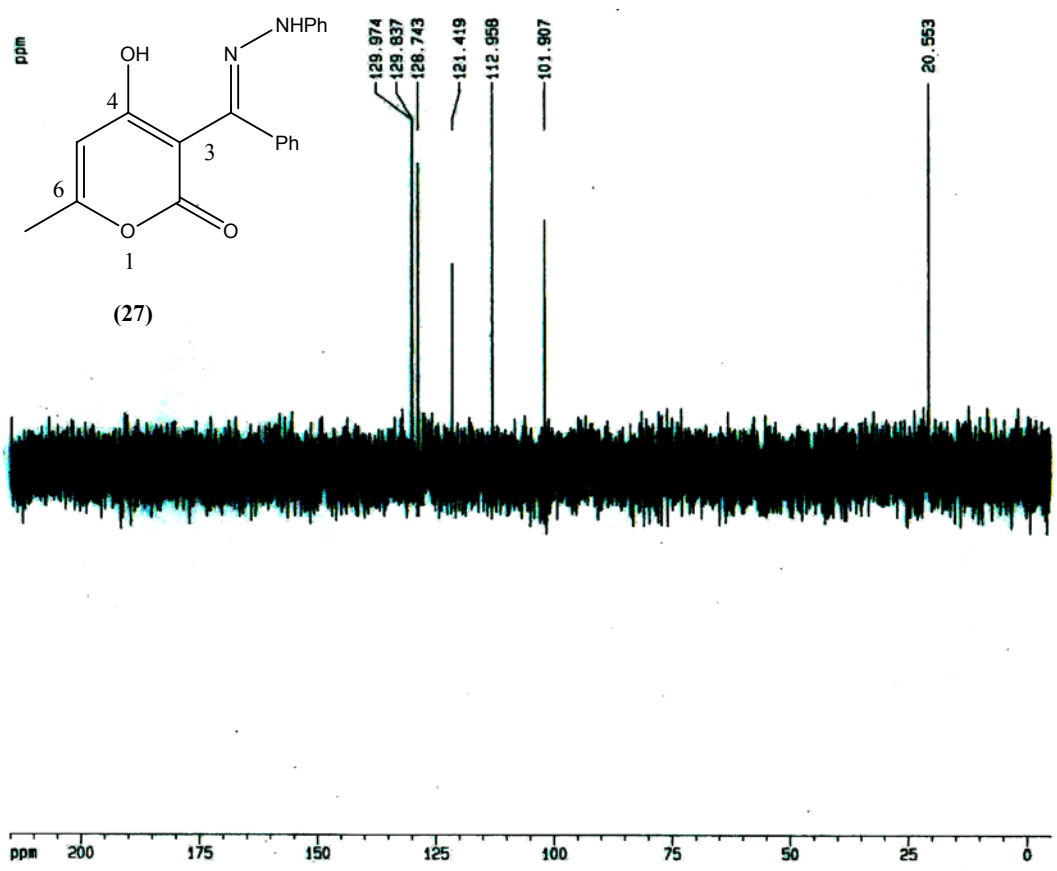
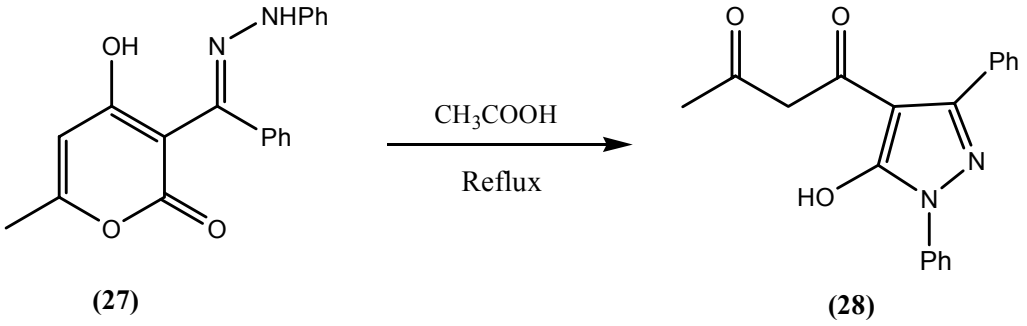


Figure 33: (a) ^{1}H-NMR of compound **27**; (b) ^{13}C-NMR of compound **27**; (c) ^{13}C-NMR DEPT 135 of compound **27**.

The seven signals at δ 171.9, 163.6, 162.1, 148.9, 143.3, 132.1, and 97.2 disappeared which is consistent with their assignment to the seven quaternary carbons for the two C-1 carbons of the two phenyl rings, the four carbons of the pyrone ring, and the hydrazone carbon. The CH type carbons of the phenyl rings consistent with the positive signals are observed at δ 130.0, 129.9, 129.8, 128.8, 121.4, and 112.9, while the CH type carbon at C-5 and the methyl carbon of the pyrone ring also due to the positive signals appear at δ 101.9 and 20.55.



(27) **(28)**

Scheme 34: Synthesis of 1-(5-hydroxy-1,3-diphenyl-1*H*-pyrazol-4-yl)butane-1,3-dione **(28)**.

Isomerization of compound **27** in refluxing acetic acid gave 1-(5-hydroxy-1,3-diphenyl-1*H*-pyrazol-4-yl)butane-1,3-dione **(28)** in 75% yield, mp 146-147^{o}C (Lit.[3] mp 148^{o}C) (Scheme 34).

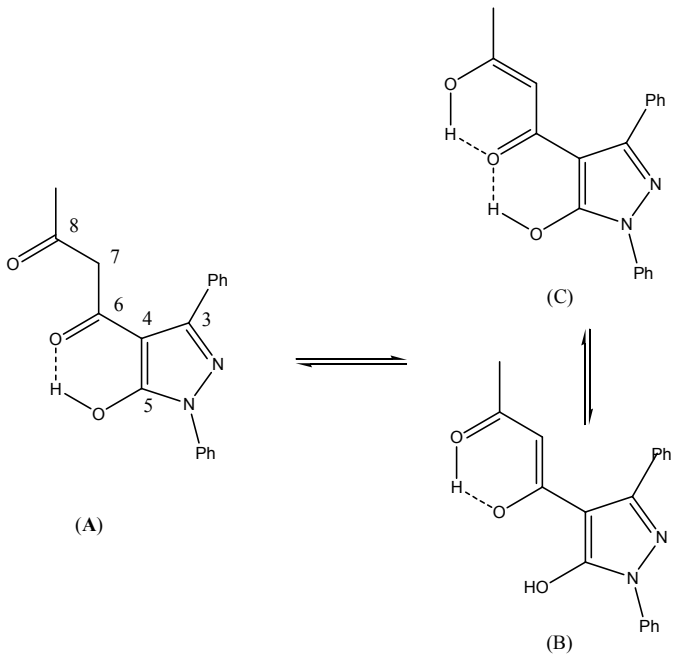
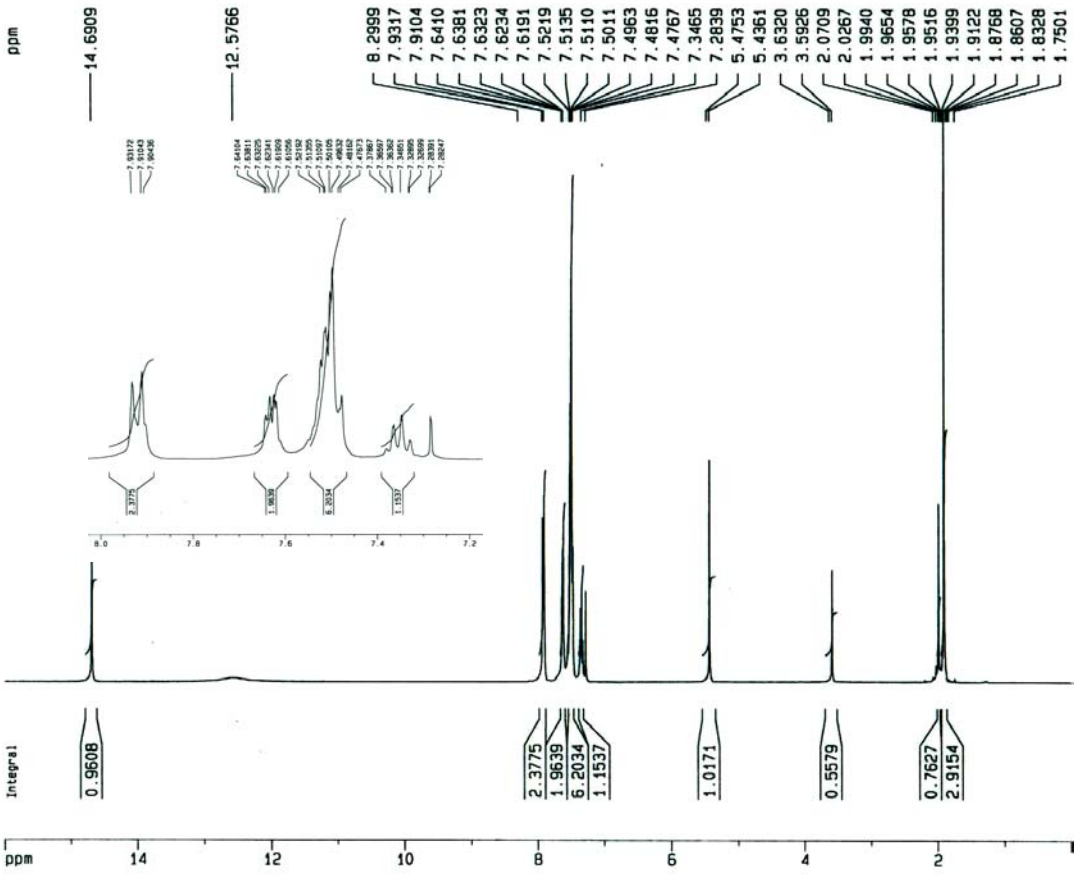


Figure 34: Tautomerization of compound **28**

(a)

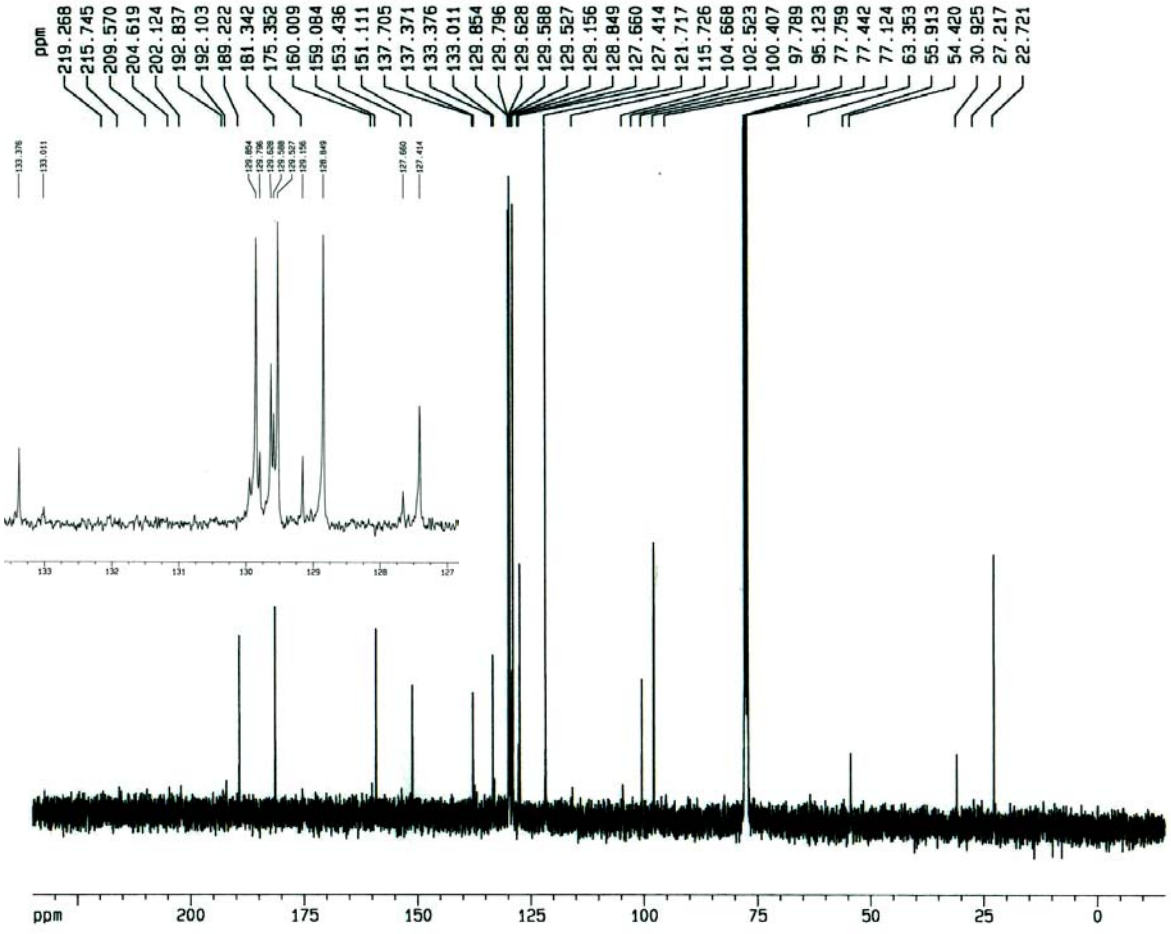


The ^{1}H-NMR in Figure 35(a) shows that compound **28** in deuteriochloroform exists as an equilibrium mixture of keto form A and an enol form which is the average of B and C. The enol form (B $\rightleftharpoons$ C) can be detected by the singlets at δ 5.47 and 1.91 due to the C-7 vinyl and C-8 methyl group, while the singlets at δ 3.59 and 2.03 result from the C-7 methylene and C-8 methyl protons of the keto tautomer A. Based on the integral rises of 1.017 and 0.5579, respectively for the vinyl and methylene proton signals, the enol to keto ratio was calculated to be 3.64 to 1.

The signals at δ 14.7 and 12.6 are due to protons bonded to oxygen atoms. The sharp enolic signal at δ 14.7 is consistent with the strongly chelated hydroxyl proton on the side chain of the enol tautomer (B $\rightleftharpoons$ C), while the broad signal at δ 12.6 is consistent with the more acidic proton at the C-5 hydroxyl group.

In addition, the ^{1}H-NMR also shows a 2H doublet (J = 8.3 Hz) at δ 7.91, a 2H triplet at δ 7.63 (J = 7.6 Hz), and a 1H triplet at δ 7.34 (J = 6.8 Hz) characteristic of the N-phenyl protons in the ortho, meta, and para positions respectively of the phenyl ring. The 5H multiplet signal at δ 7.50 was assigned to all phenyl protons of the pyrazole ring at C-3.

(b)



The ^{13}C-NMR spectrum (figure 35(b)) in $CDCl_3$ solution of compound **28** gives rise to two resonances for all the carbon atoms corresponding to the enol and keto tautomers. It is known that a hydrogen-bonded carbonyl carbon resonates at lower field than a corresponding free carbonyl carbon and that an enolic carbon atom resonates at higher field than a corresponding keto carbon atom, according to literature reported.[3] The C-6 resonance of the enol form (B $\rightleftharpoons$ C) would be at a lower field than the C-8 carbon atom. From the chemical shift values, respectively at δ 189.2 and 181.3, it can be reasonably concluded that the enol tautomer contributes mainly to the tautomeric

population in $CDCl_3$ solution. The characteristic ^{13}C-NMR spectrum of the enol tautomer at δ 189.2, 181.3, 97.79, and 22.72 is consistent with C-6, C-8, C-7, and methyl C-8 on the side chain ring, respectively. The pyrazole carbons due to C-5, C-3, and C-4 were assigned to δ 159.1, 151.1, and 100.4, respectively. In addition, the N-phenyl carbons due to C-1 and para positions absorb at δ 137.7 and 127.4, while the ortho and meta carbons appear as two singlets at δ 121.7 and 129.9 respectively. On the other hand, the phenyl carbons at C-3 side chain ring due to C-1 and para positions were assigned to δ 133.4 and 129.6, while the otho and meta carbons appear at δ 128.8 and 129.5. However, the keto tautomer A could not be completely assigned in the ^{13}C-NMR spectrum because of the low intensity of the signals of this minor tautomer. However, the ^{13}C-NMR spectrum exhibits some key signals which could be assigned to the keto tautomer A. The signals at δ 54.42 and 30.92 are due to at C-7 methylene carbon and C-8 methyl group on the side chain, respectively.

These assignments are consistent with the NMR CH-correlation of compound **28** (Figure 35(c)).

In order to confirm the ^{1}H and ^{13}C-NMR spectral assignments, the two dimensional CH correlation spectrum (Figure 35(c)) was recorded. The spectrum of the B and C tautomers reveals that the high intensity of the carbon signals at δ 22.72, which was assigned to the methyl carbon, correlates with the 3H singlet at δ 1.91 in the ^{1}H spectrum. The signal in the ^{13}C spectrum at δ 97.79, which was assigned to the vinyl carbon, correlates with a 1H singlet at δ 5.47. As expected, the three N-phenyl carbon signals at δ 129.9, 127.4, and 121.7 correlate with the phenyl proton signals at δ 7.63, 7.34, and 7.91 due to the meta, para, and ortho positions, respectively.

(c)

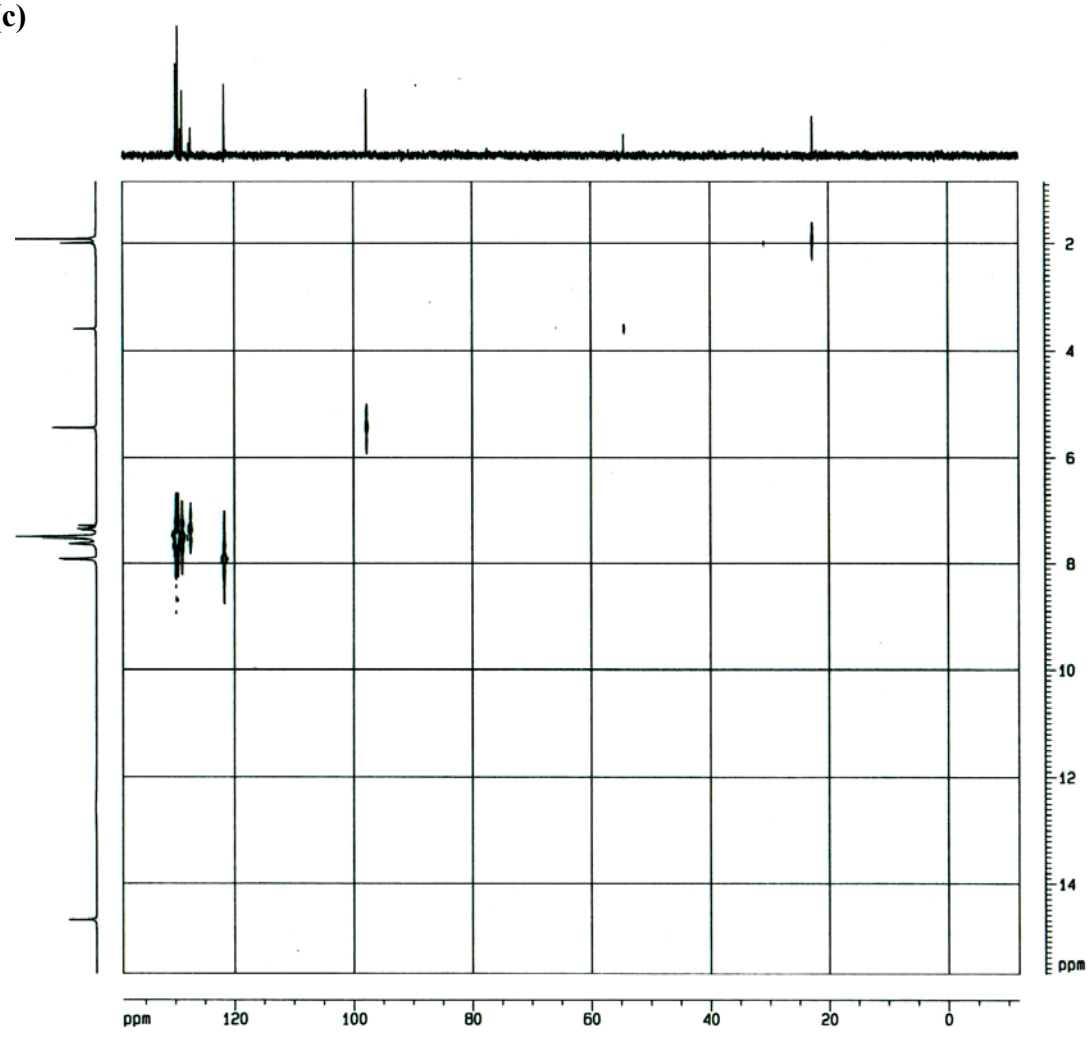
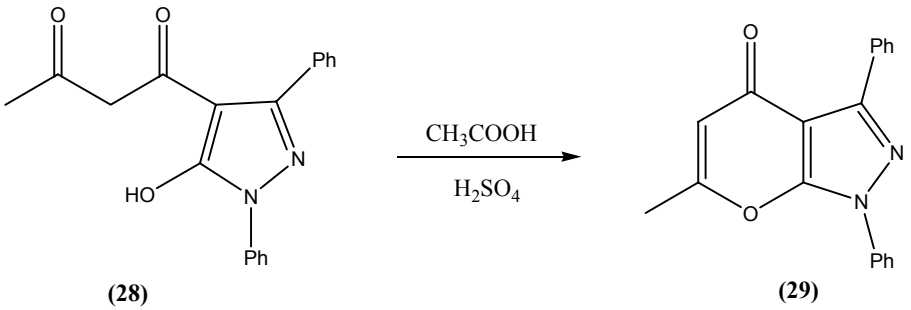


Figure 35: (a) ^{1}H-NMR of compound **28**; (b) ^{13}C-NMR of compound **28**; (c) NMR CH- correlation of compound **28**.

The phenyl carbons at positon 3 of the pyrazole ring due to δ 129.6, 129.5, and 128.8, which correlate with the multiplet signal at δ 7.50. In addition, in the two dimensional spectrum of the A tautomer reveals that the ^{13}C spectrum at δ 54.42 correlates with the proton signal at δ 3.59 due to methylene protons and a low intense signal at δ 30.92 of the ^{13}C spectrum correlates with the 3H singlet at δ 2.03 due to the C-8 methyl group.



(28) **(29)**

Scheme 35: Synthesis of 6-methyl-1,3-phenylpyrano[2,3-*c*]pyrazole-4(1*H*)-one **(29)**.

The ring closure of **28** to 6-methyl-1,3-phenylpyrano[2,3-*c*]pyrazole-4(1*H*)-one **(29)** was achieved by refluxing **28** in acetic acid in the presence of sulfuric acid to obtain **29** in a yield of 74%, mp 170-171°C (Lit.[3] mp 171°C) (Scheme 35).

(a)

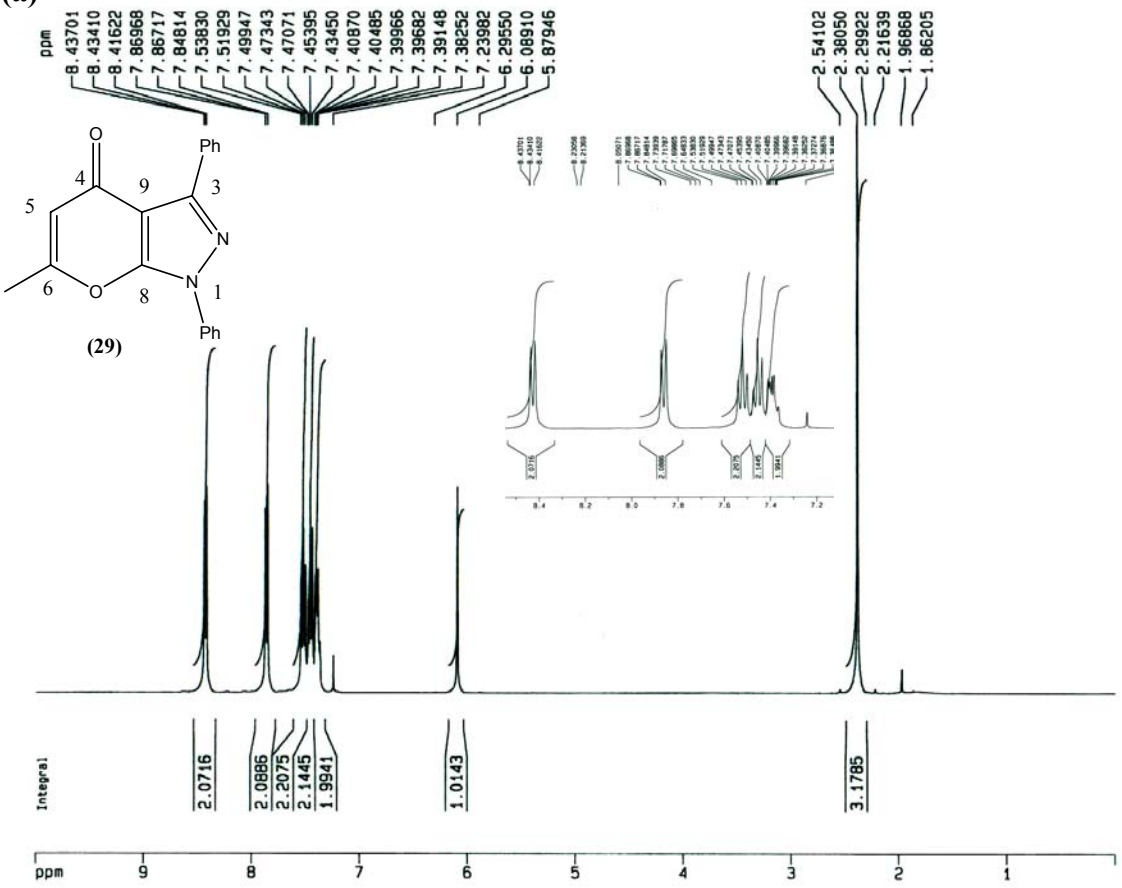
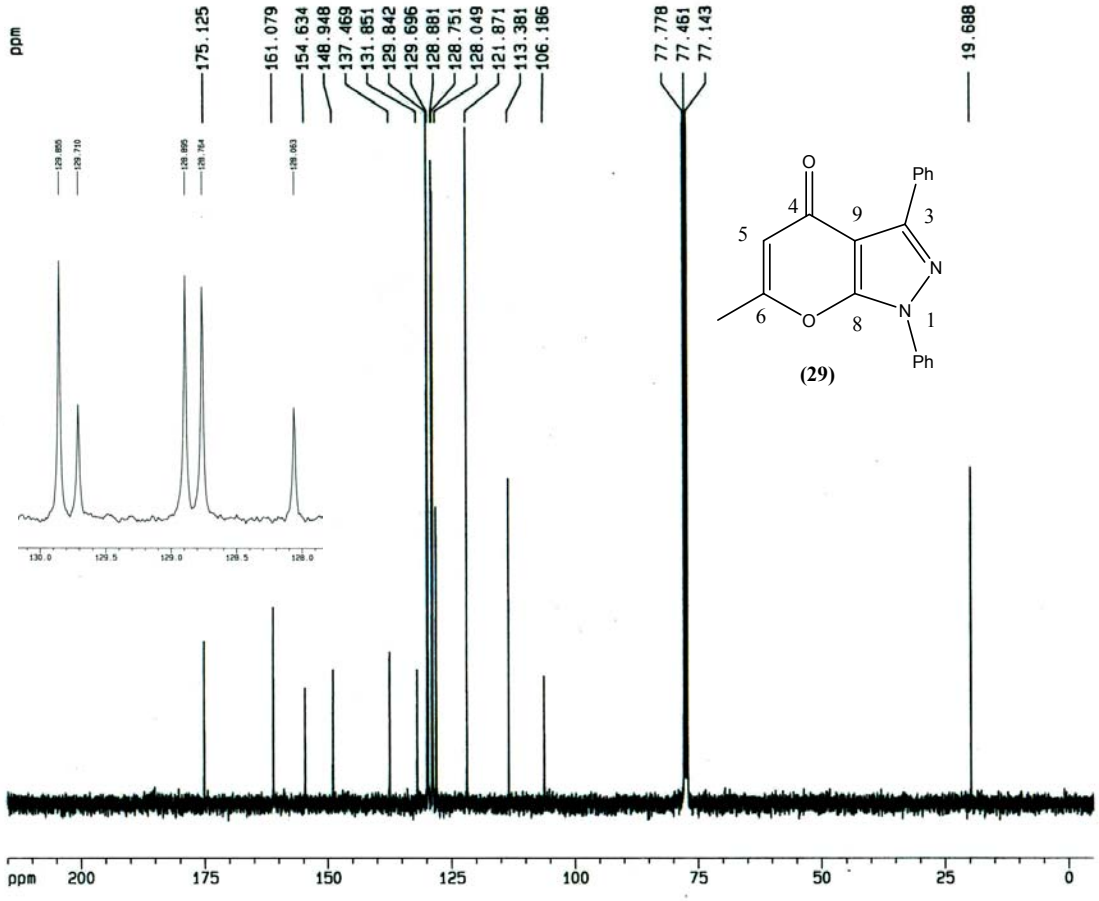


Figure 36(a) shows that the ^{1}H-NMR spectrum of the colorless crystals obtained in the previous experiment is consistent with the structure of **29.** The two key signals due to C-5 and methyl protons are shown as a 1H singlet at δ 6.08 and a 3H singlet at δ 2.38, respectively. The 1H multiplet signal at δ 7.36, the 2H triplet signal at δ 7.52 (J = 7.6 Hz), and the 2H doublet signal at δ 7.85 (J = 8.6 Hz) are due to absorptions of the N-phenyl protons at the para, meta, and ortho positions, respectively. In addition, the phenyl protons at the C-3 side chain ring due to para, meta, and ortho protons appear as the 1H multiplet signal at δ 7.36, the 2H triplet signal at δ 7.43 (J = 7.8 Hz), and the 2H doublet signal at δ 8.42 (J = 7.2 Hz), respectively.

(b)



(29)

The ^{13}C-NMR spectrum (Figure 36(b)) is also consistent with the structure **29**. The carbonyl carbon absorbs the furthest downfield at δ 175.1. The signals at δ 154.6 and δ 106.2 were assigned to the bridgehead carbons at positions 8 and 9, respectively. The C-5 and C-6 carbons are observed at δ 113.4 and 161.1, respectively, the C-3 imine carbon was assigned to the signal at δ 148.9. The N-phenyl carbons due to C-1 and para positions absorb at δ 137.5 and 128.1, respectively, while the ortho and meta positions appear as two singlets at δ 121.9 and 129.9. In addition, the phenyl carbons of the C-3 side chain ring due to C-1 and para positions are observed at δ 131.9 and 129.7, respectively, while the ortho and para carbons appear at δ 128.9 and 128.8. Finally, the methyl carbon is shown at δ 19.69.

(c)

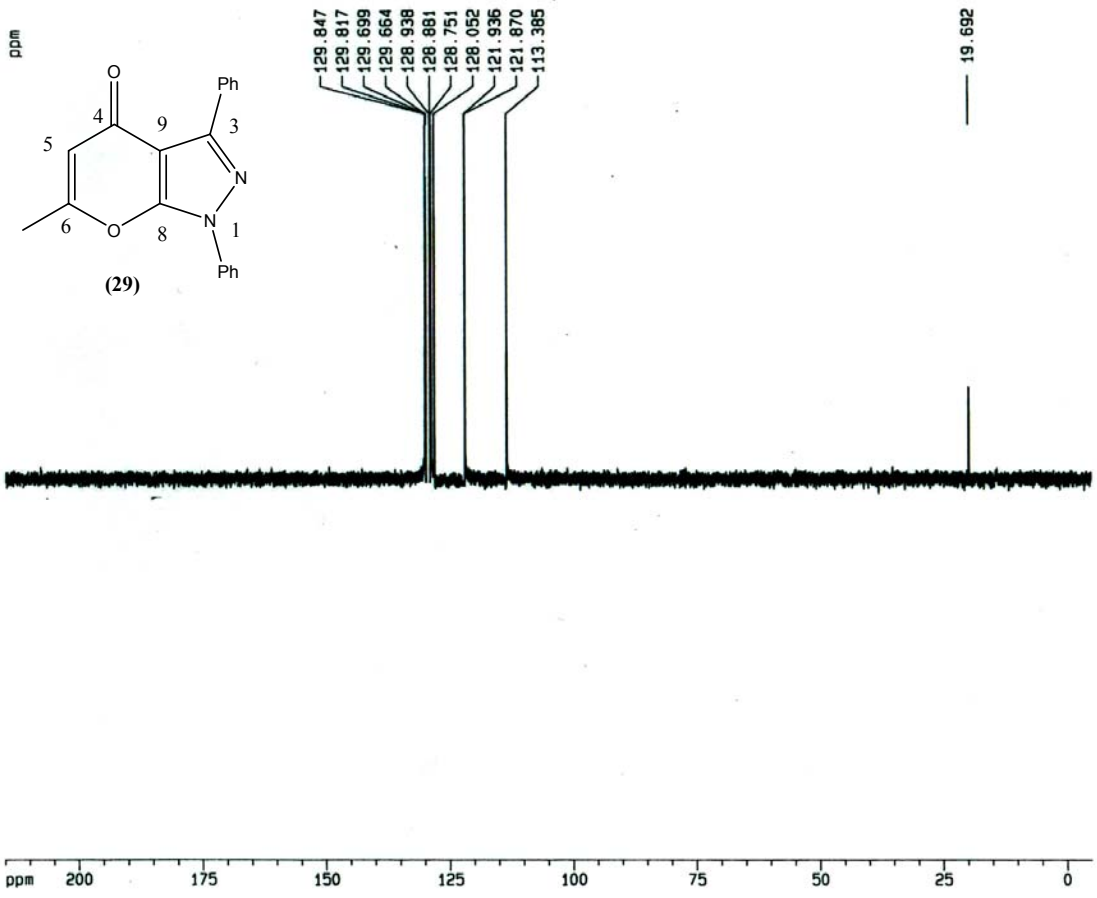
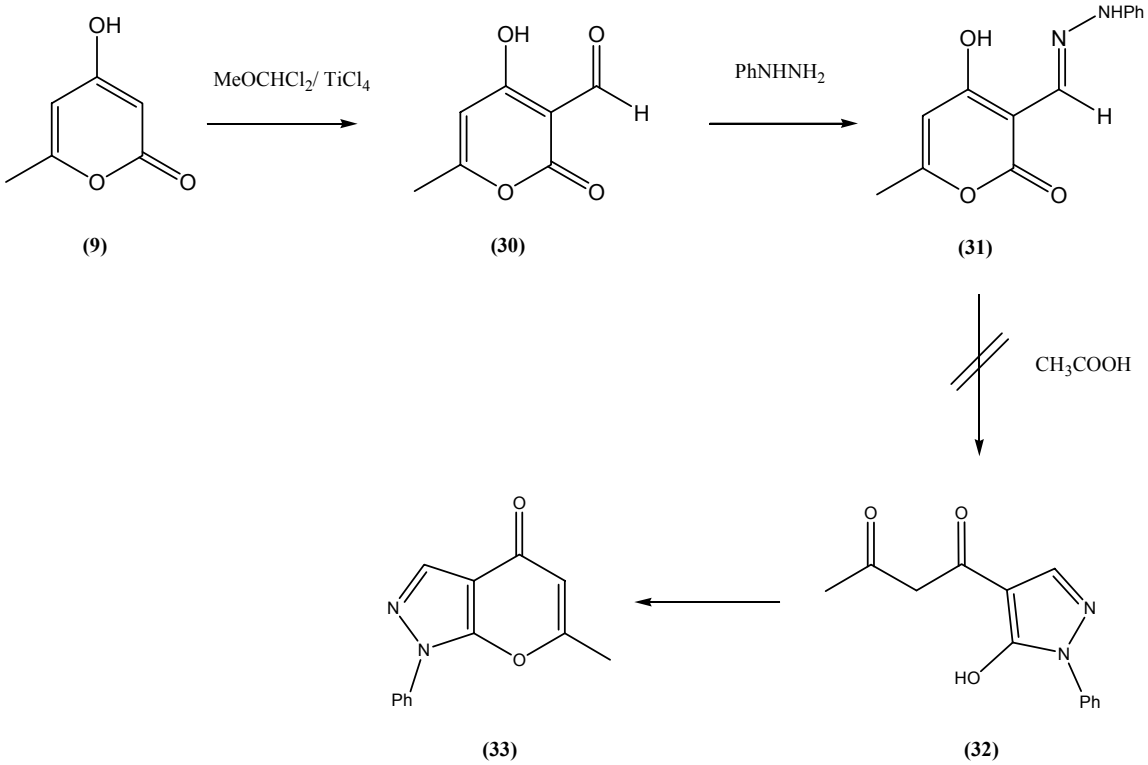


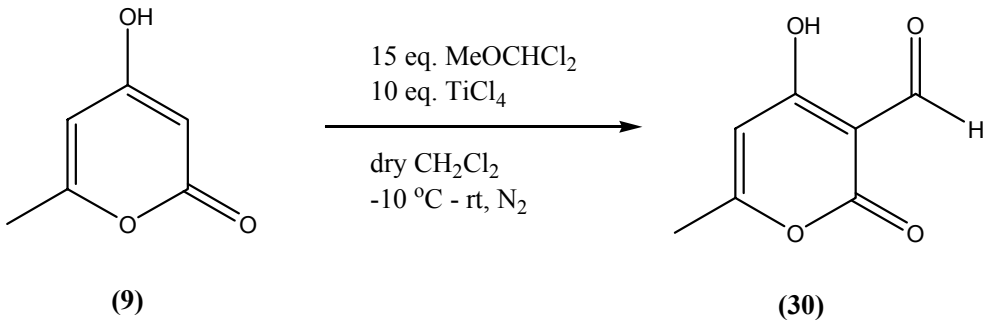
Figure 36: (a) ^{1}H-NMR of compound **29**; (b) ^{13}C-NMR of compound **29**; (c) ^{13}C-NMR DEPT 135 of compound **29**.

These assignments are consistent with the ^{13}C-DEPT 135 spectrum (Figure 36(c)). The six signals at δ 175.1, 161.1, 154.6, 148.9, 137.5, 131.9, and 106.2 disappeared which is compatible with their assignment to the seven quaternary carbons of the structure. In addition, the positive signals at δ 129.9, 129.7, 128.9, 128.8, 128.1, and 121.9 are due to the six CH type carbons of both phenyl rings, while the positive signals due to the CH type carbon at C-5 and methyl carbon appear at δ 113.4 and 19.7, respetively.

In order to utilized this approach to synthesize a pyranoprazole that is unsubstituted at position 3 of the pyrazole ring, the formylated dehydroacetic acid derivative **30** is required.



T. Shimizu and colleague[8] have reported that **30** can be prepared by the regioselective introduction of a formyl group at the C-3 position of the commercially available 4-hydroxy-6-methyl-2-pyrone **(9)** as shown in Scheme 36.



(9) **(30)**

Scheme 36: Synthesis of 4-hydroxy-6-methyl-2-oxo-2*H*-pyran-3-carbaldehyde **(30)**.

According to their procedure,[8] **9** was treated with excess dichloromethyl methyl ether ($MeOCHCl_2$)-$TiCl_4$ in dry CH_2Cl_2 under a continuous nitrogen flow while raising the reaction temperature from -10°C to room temperature over a period of one day. This produced the 4-hydroxy-6-methyl-2-oxo-2*H*-pyran-3-carbaldehyde **(30)** in a yield of 71%, mp 93-94°C (Lit.[8] mp 108°C).

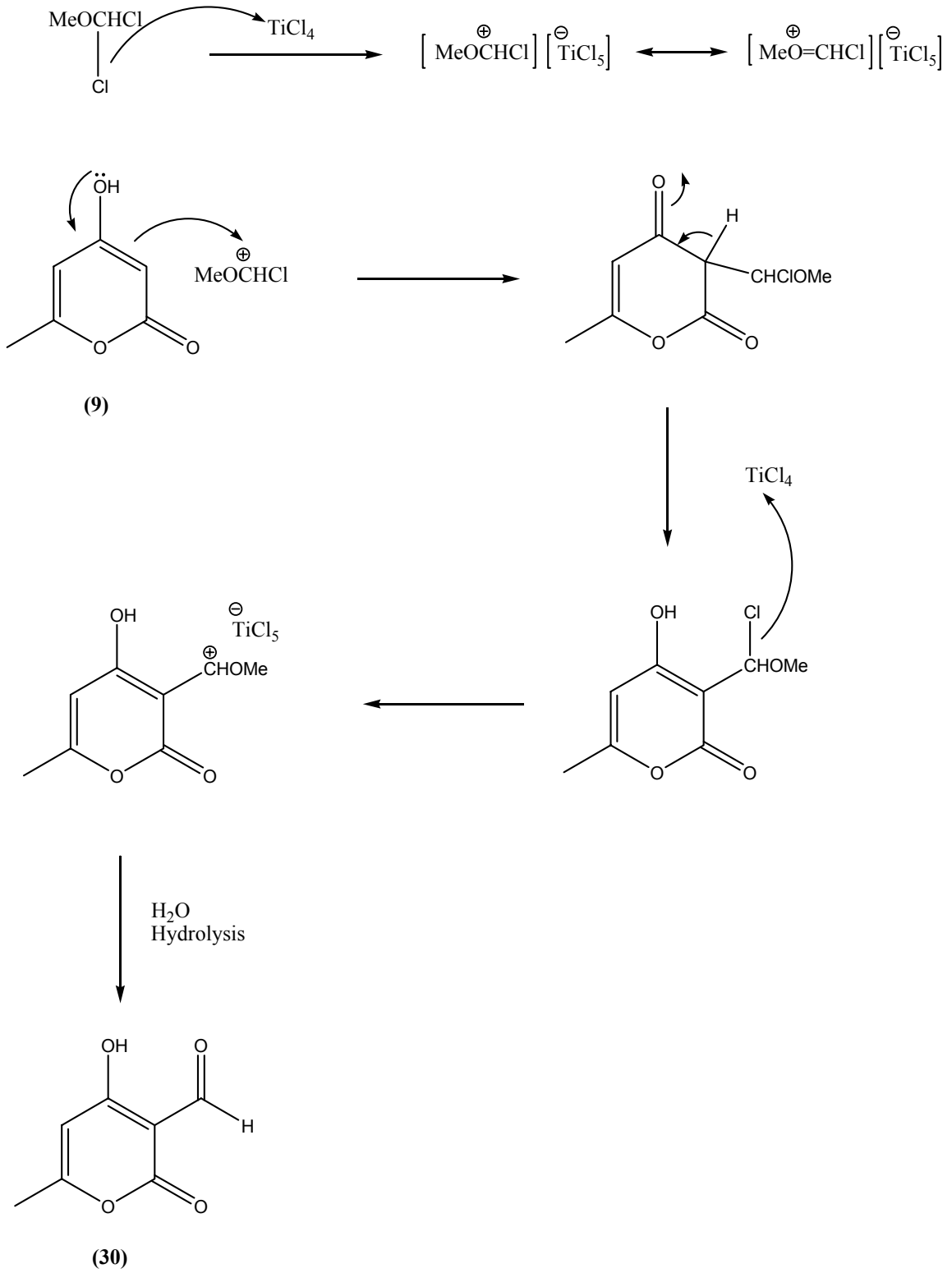
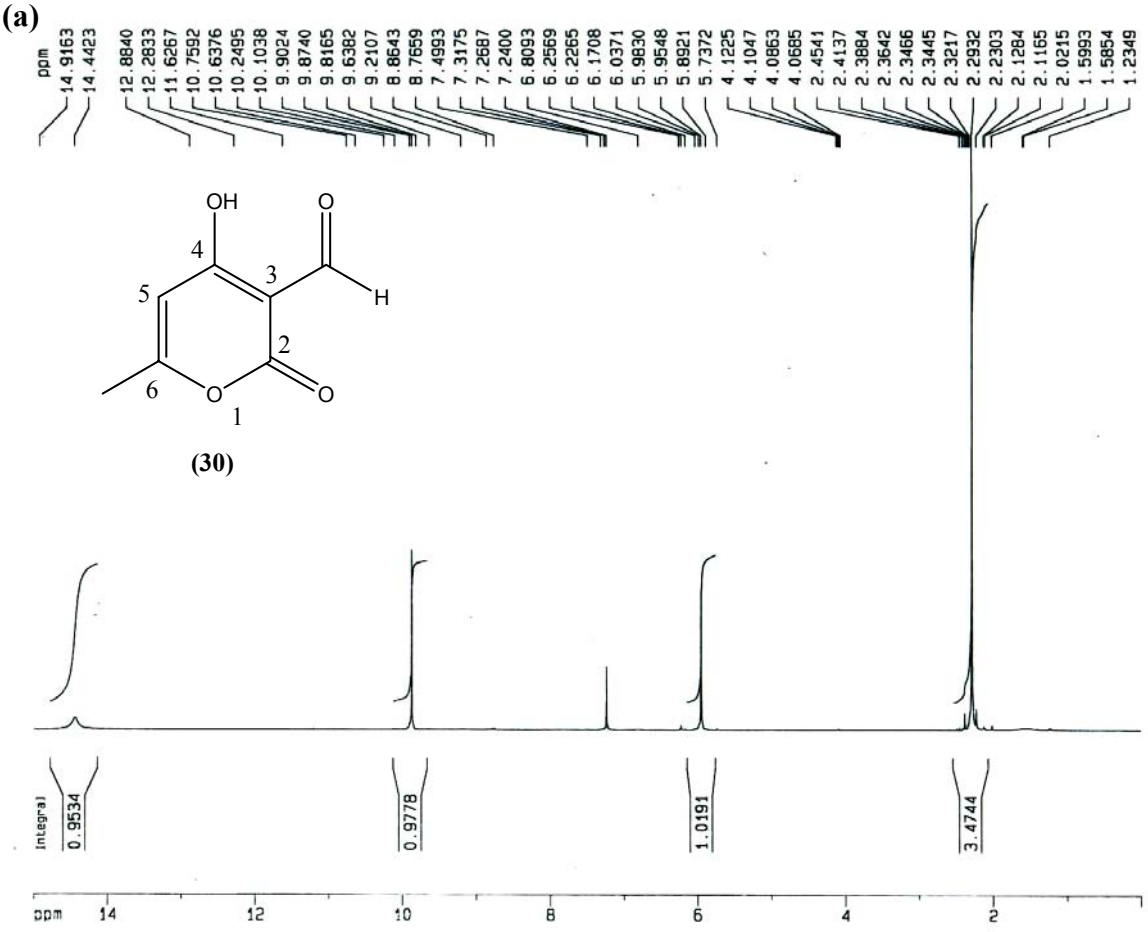


Figure 37: Mechanism of the formation **30**

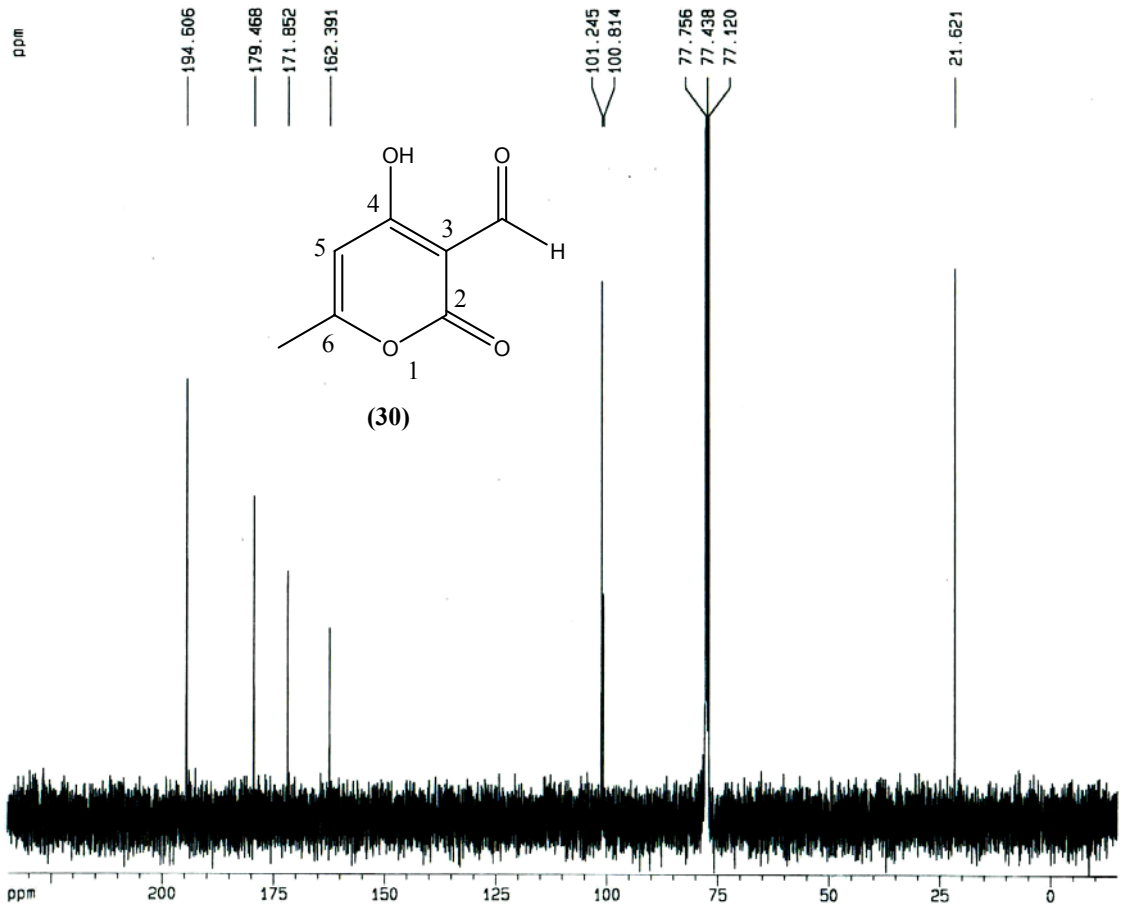
(a)



(30)

Figure 38(a) shows that the ^{1}H-NMR spectrum of the white solid compound is consistent with the structure of **30**. The key proton at C-5 appears as a 1H singlet at δ 5.89, while the methyl protons appear as a 3H singlet at δ 2.29. The formyl proton appears as a 1H singlet at δ 9.82 confirming that the 2-pyrone ring has been formylated. Finally, the broad signal at δ 14.4 is due to the enol proton. As expected for protons bonded to O atom, when compound **30** was treated with D_2O, this signal disappeared.

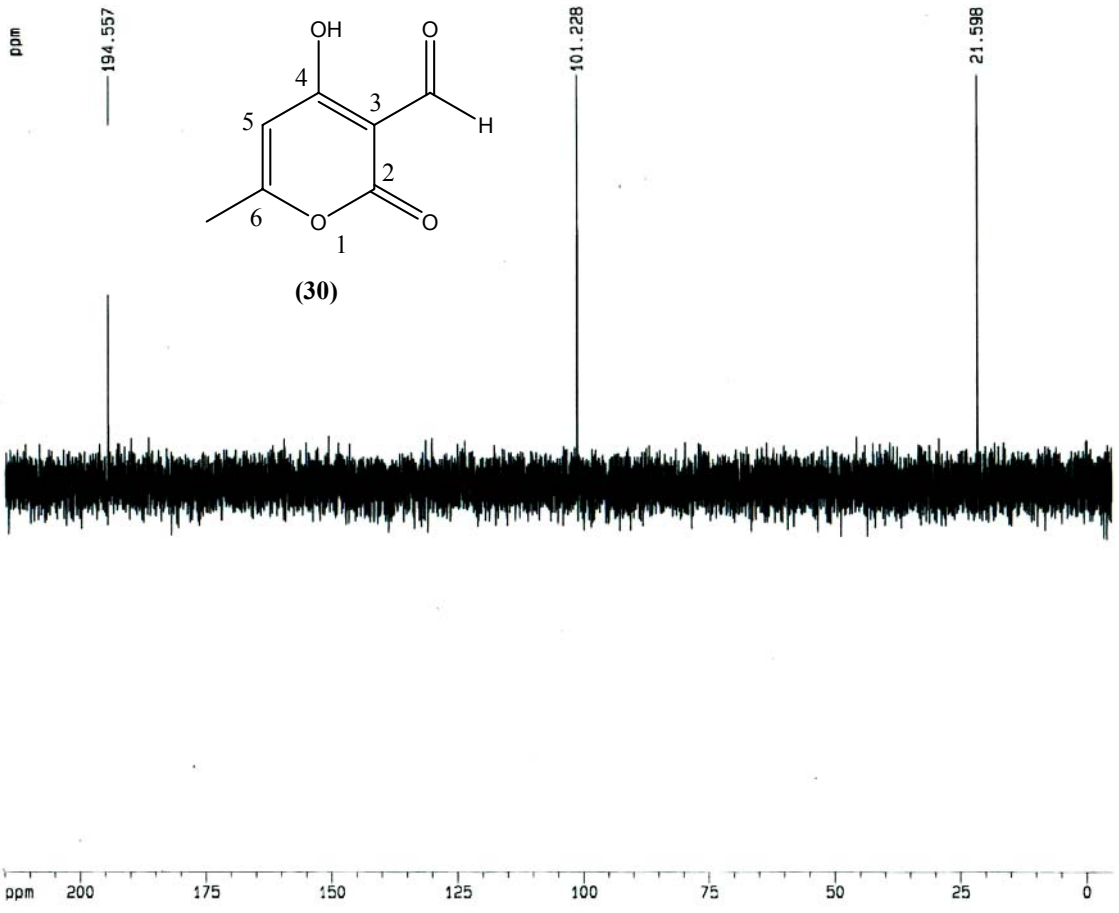
(b)



(30)

The ^{13}C-NMR spectrum (Figure 38(b)) is also compatible with the structure of **30**. The formyl carbon absorbs the furthest downfield at δ 194.6. The CH carbon due to C-5 and methyl carbons due to C-6 appear as the intense signals at δ 101.2 and 21.62, respectively. In addition, the quaternary carbons due to C-2, C-3, C-4, and C-6 of the structure absorb at δ 171.9, 100.8, 179.5, and 162.4, respectively.

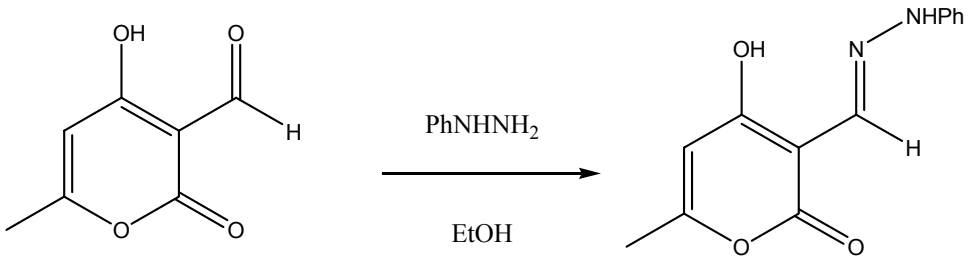
(c)



(30)

Figure 38: (a) ^{1}H-NMR of compound **30**; (b) ^{13}C-NMR of compound **30** and (c) ^{13}C-NMR DEPT 135 of compound **30**.

These assignments are consistent with the ^{13}C-DEPT 135 spectrum (Figure 8-2 (c)). The four signals at δ 179.5, 171.9, 162.4, and 100.8 disappeared which is consistent with their assignment to the four quaternary carbons of the structure. In addition, the signals at δ 194.6, 101.2, and 21.6 still appear in the positive direction due to the two CH type carbons and the methyl carbon.

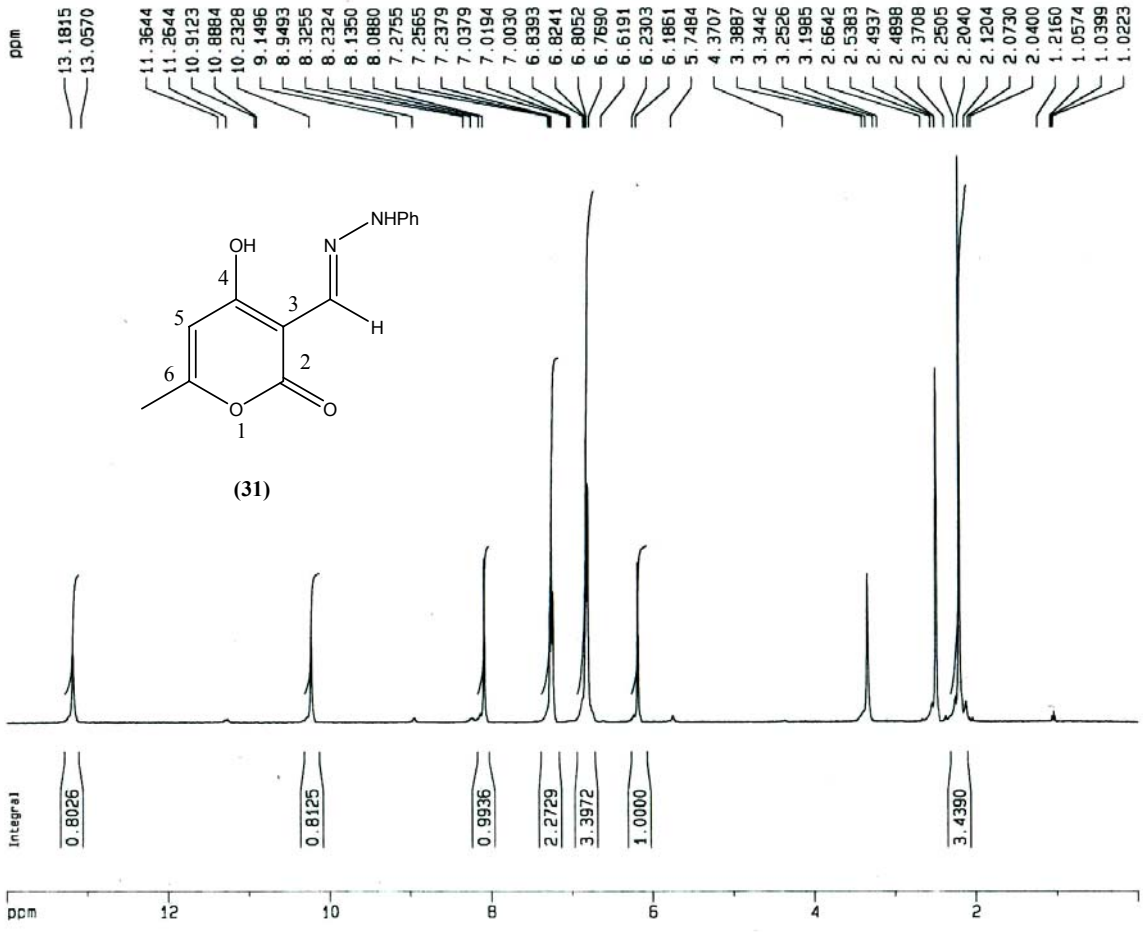


(30) **(31)**

Scheme 37: Synthesis of 4-hydroxy-6-methyl-3-(1-(2-phenylhydrazono)methyl)-2*H*-pyran-2-one **(31)**.

Based on procedure,[3] used to synthesize other N-phenylhydrazones, 4-hydroxy-6-methyl-2-oxo-2*H*-pyran-3-carbaldehyde **(30)** was treated with phenylhydrazine in ethanol at 80^{o}C to yield the new N-phenylhydrazone, 4-hydroxy-6-methyl-3-(1-(2-phenylhydrazono)methyl)-2*H*-pyran-2-one **(31)** in a yield of 81%, mp 212-213^{o}C (Scheme 37).

(a)

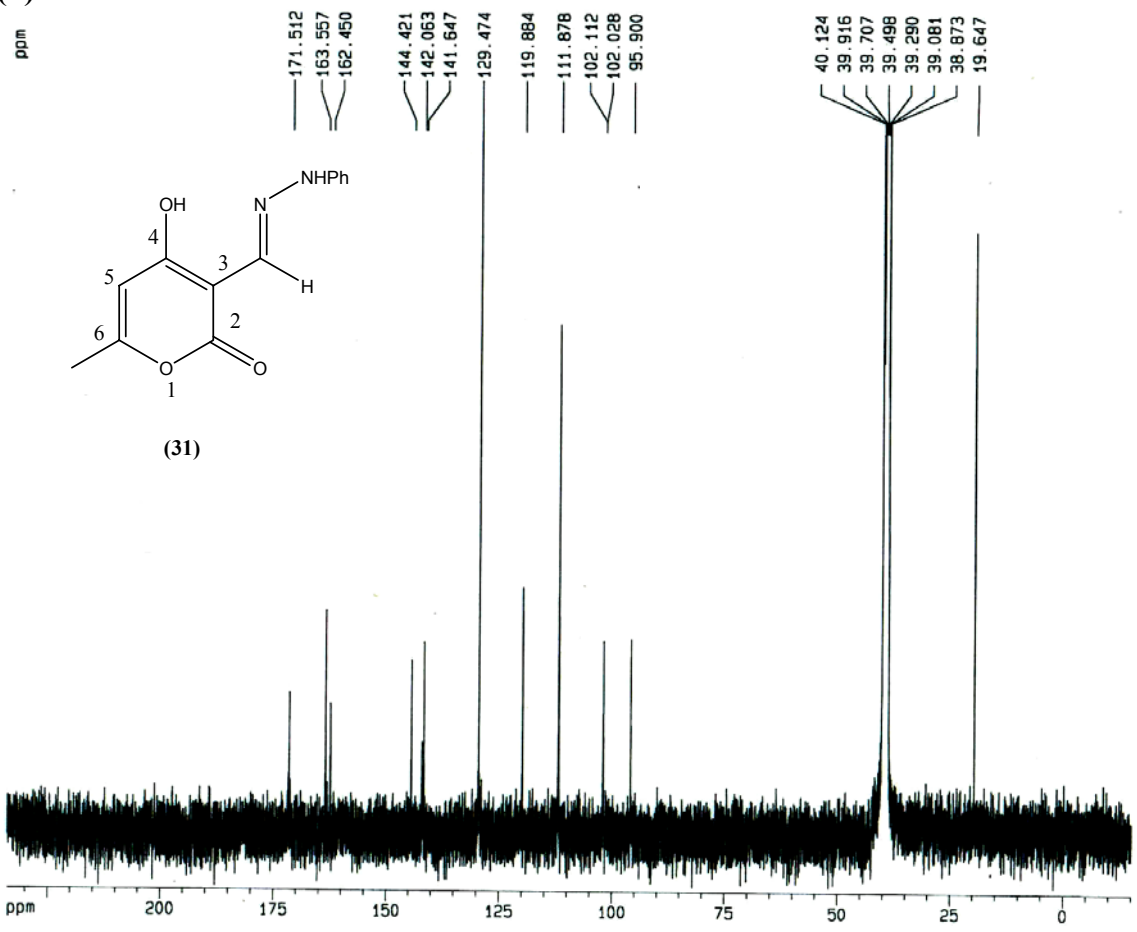


(31)

Figure 39(a) shows that the ^{1}H-NMR spectrum of the yellow crystalline product in DMSO solution is consistent with the structure of **31.** The methyl protons appear as a 3H singlet at δ 2.20. The 3H multiplet at δ 6.67 is due to absorptions of the phenyl ring protons at the ortho and para positions, while the 2H triplet signal at δ 7.12 (J = 7.8 Hz) is due to the protons in the meta positions. The proton due to C-5 appears as a 1H singlet at δ 6.05, while the imine proton appears as a 1H singlet at δ 7.95. Finally, the signals due to the enol and amino protons appear as a 1H signal at δ 13.2 and a 1H

signal at δ 10.2, respectively. As expected for protons bonded to O and N, when compound **31** was treated with D_2O, these signals disappeared.

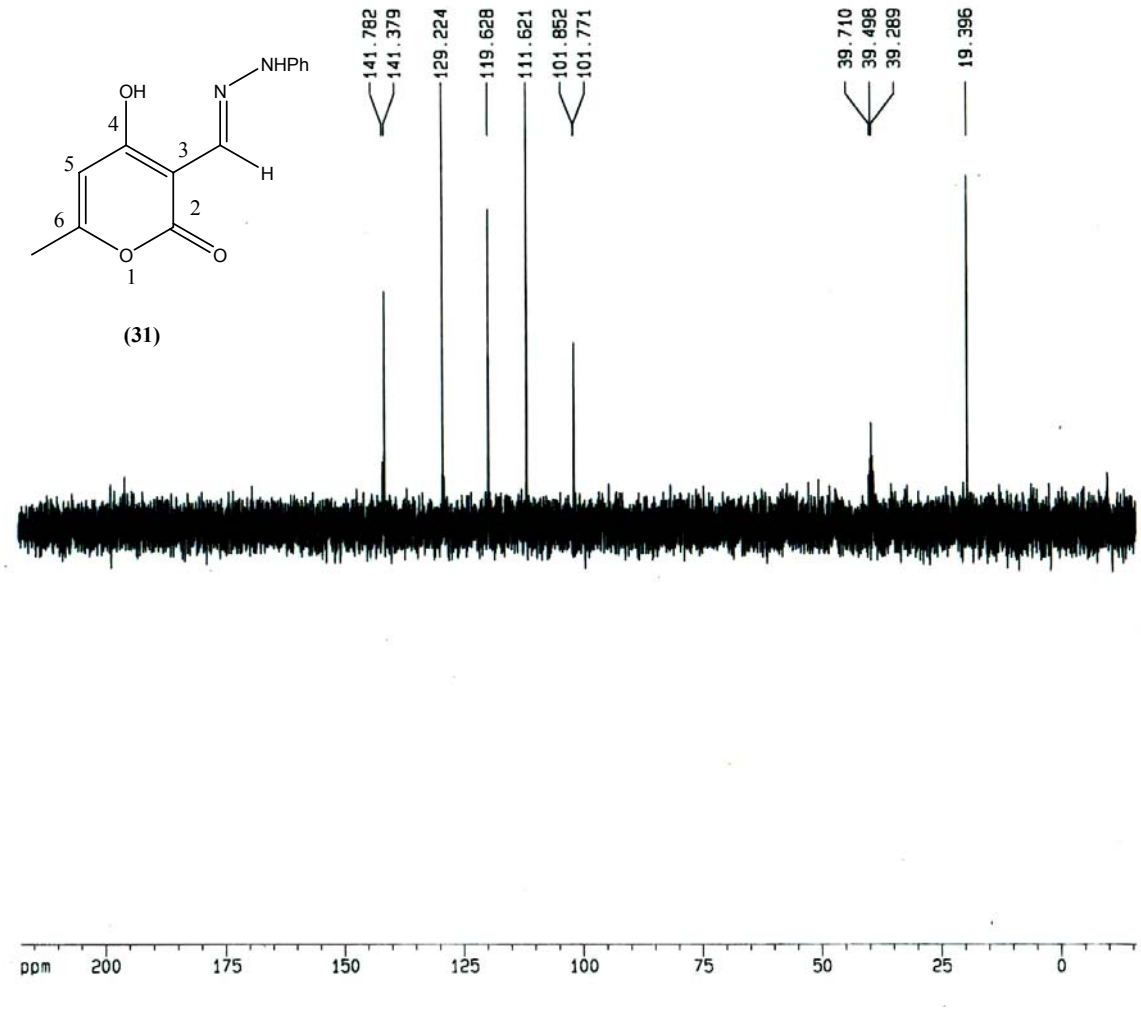
(b)



The ^{13}C-NMR spectrum (Figure 39(b)) is also consistent with the structure **31**. The C-4 enol carbon absorbs the furthest downfield at δ 171.5, while the signal at δ 141.6 was assigned to the hydrazone carbon. The C-5 CH carbon and C-6 methyl carbon appear as the strong signals at δ 102.0 and 19.65, respectively. In addition, the quaternary carbons at C-2, C-3, and C-6 of the structure absorb at δ 163.6, 95.90, and 162.4, respectively. The carbons of the phenyl ring due to C-1 and the para position absorb at δ 144.4 and 119.9 respectively, while the ortho and meta carbons appear as

two singlets at δ 111.9 and 129.9. These assignments are consistent with the ^{13}C-DEPT 135 spectrum (Figure 39(c)).

(c)

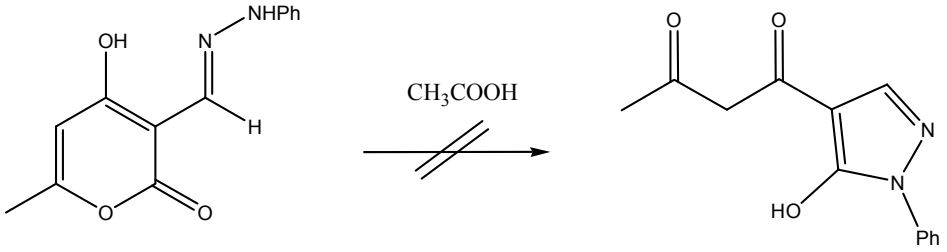


(31)

Figure 39: (a) ^{1}H-NMR of compound **31**; (b) ^{13}C-NMR of compound **31**; (c) ^{13}C-NMR DEPT 135 of compound **31**.

The five signals at δ 171.5, 163.6, 162.4, 144.4, and 95.90 disappeared which is consistent with their assignment to the five quaternary carbons of the structure. In contrast, the signals at δ 141.4, 129.2, 119.6, 111.6, 101.0, and 19.6 which still appear

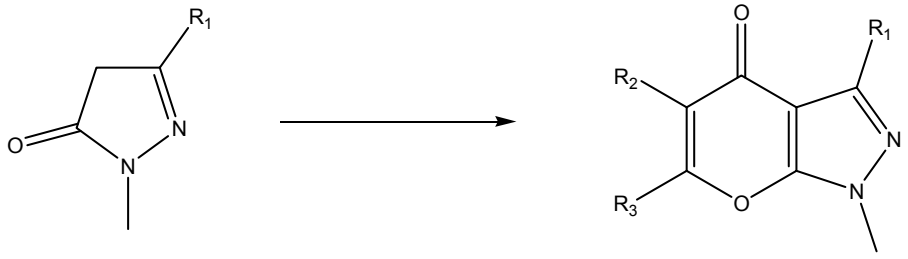
in the positive direction are due to the CH type carbon of hydrazone group, the three CH type carbons of the phenyl ring, the CH type carbon of the pyrone ring, and the methyl carbon.



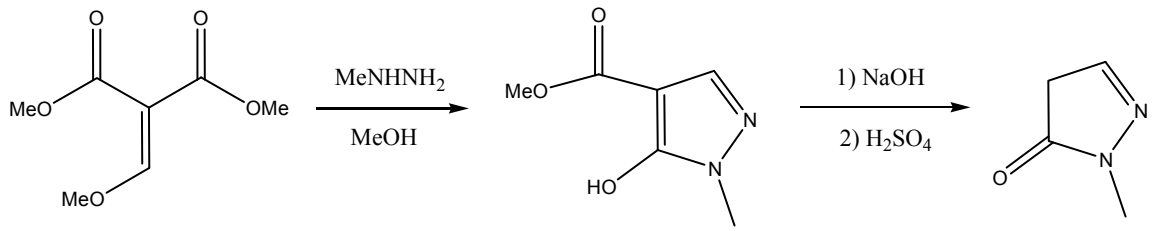
(31) **(32)**

The isomerization of **31** to **32** in the refluxing acetic acid for an 1 hour was unsuccessful, the starting material was therefore recovered. Upon prolong refluxing in acetic acid, the decomposition of **31** was observed.

Since the approach shown above was unsuccessful, the approach shown below was suggested. Work in this laboratory has already confirmed that 3-substituted pyrazolones can be converted to pyranopyrazoles substituted at position 3 of

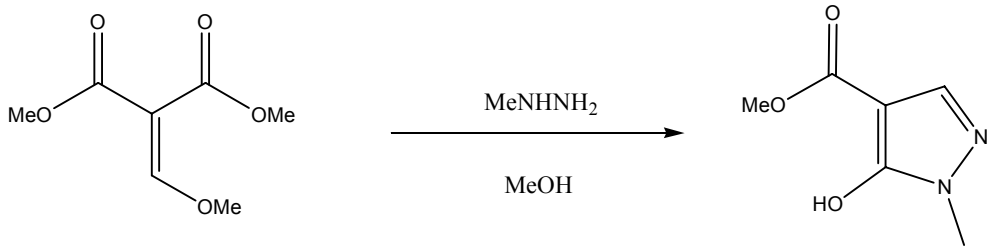


the pyrazole ring. In order to use this approach to synthesize a pyranopyrazole unsubstituted at position 3 of the pyrazole ring requires the availability of the pyrazolone unsubstituted at position 3.



(34) **(35)** **(36)**

The pyrazolone unsubstituted at position 3 is a known compound[9] which has been synthesized by Tietze and colleague[9] from dimethyl(methoxymethylene)malonate **(34)** as shown above.

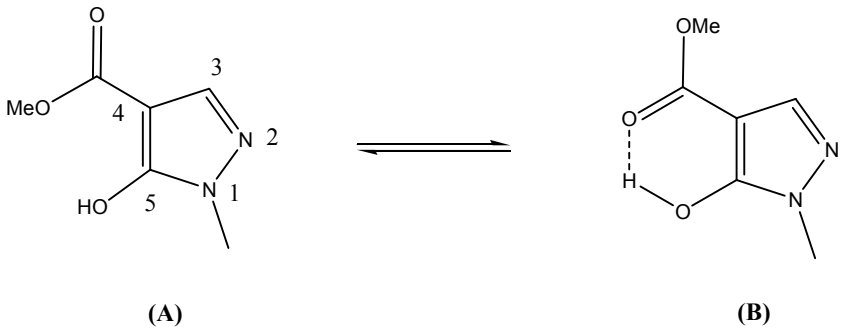


(34) **(35)**

Scheme 38: Synthesis of methyl 5-hydroxy-1-methyl-1*H*-pyrazole-4-carboxylate **(35)**.

According to this method,[9] reaction of dimethyl(methoxymethylene)malonate **(34)** with methylhydrazine in methanol afforded the white product methyl 5-hydroxy-1-

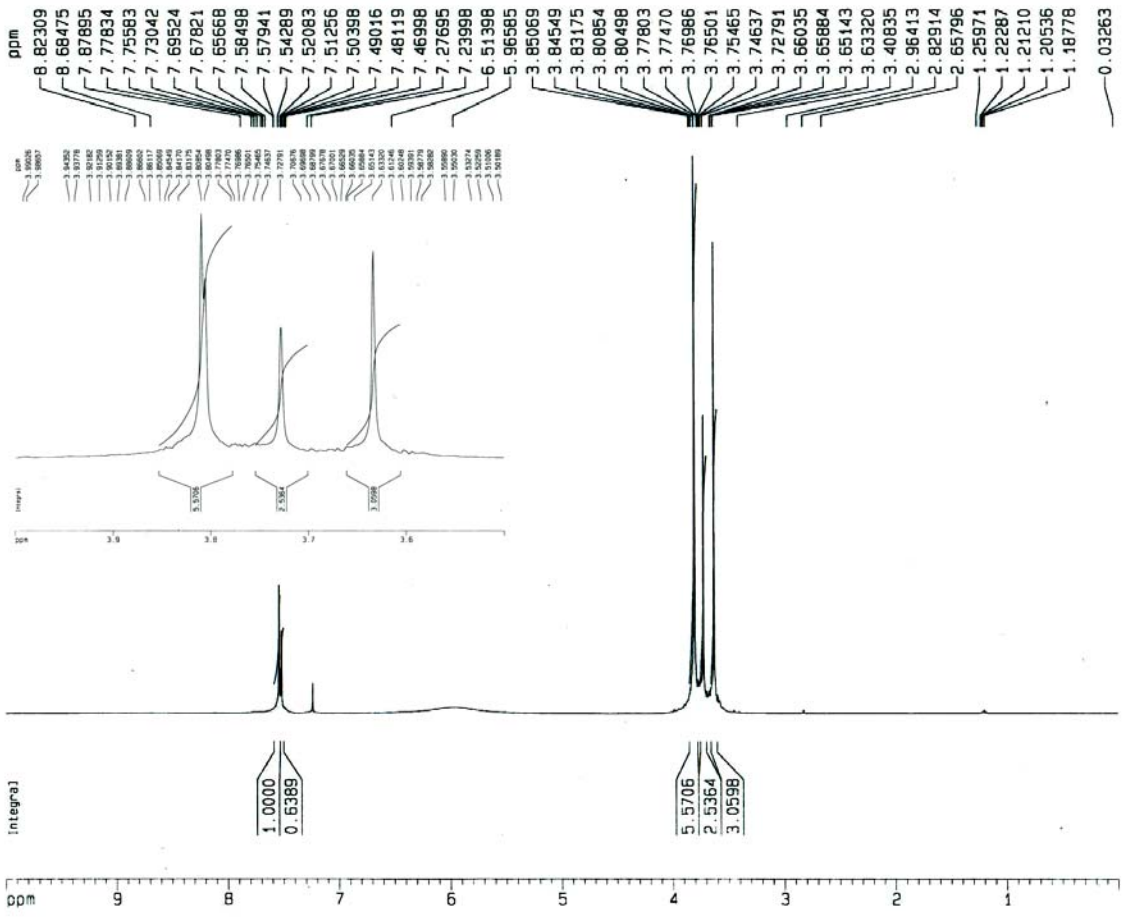
methyl-1*H*-pyrazole-4-carboxylate **(35)** in a yield of 76%, mp 122-123^{o}C (Lit.[9] 125-126^{o}C) (Scheme 38).



(A) **(B)**

Figure 40: Equilibrial intramolecular hydrogen bonding of compound **35**.

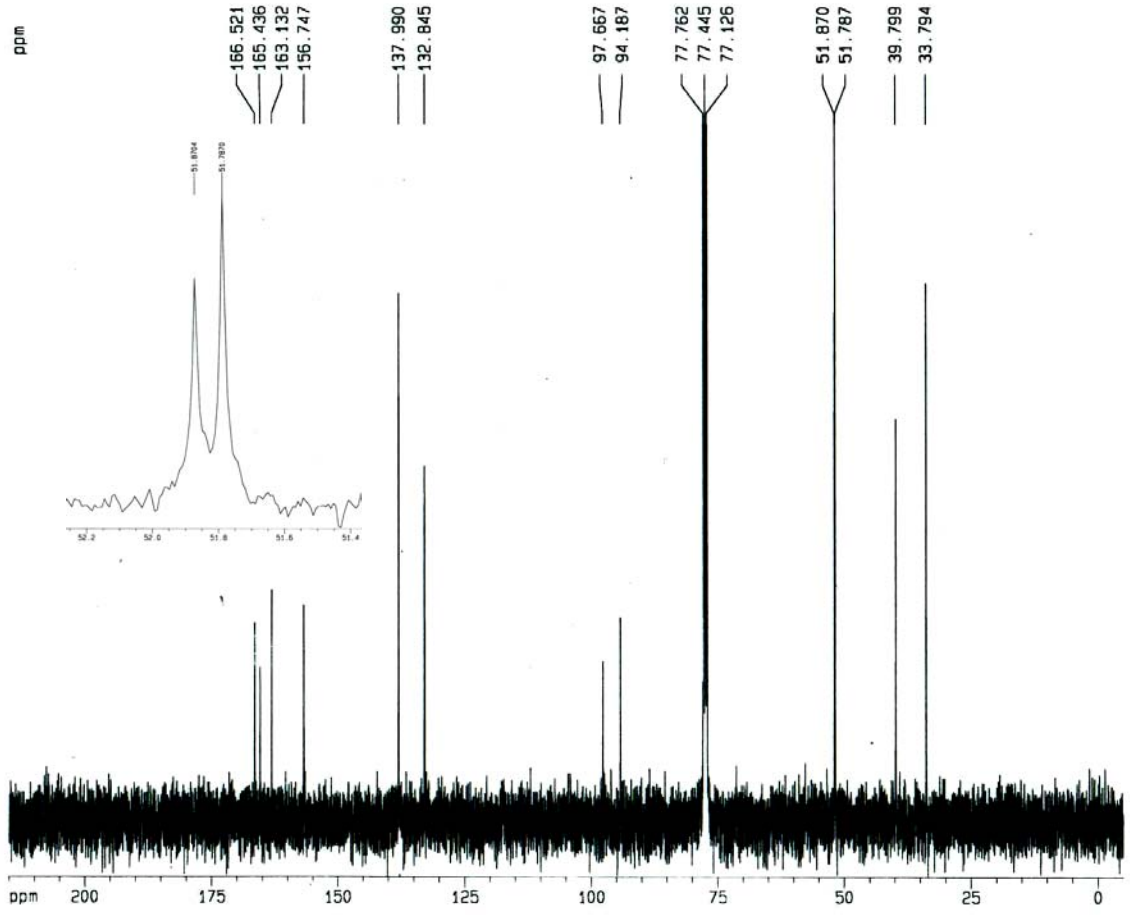
(a)



The ^{1}H-NMR spectrum (Figure 41(a)) shows that **35** is an equilibrium mixture of conformers A and B. The equilibrium between OH-non-intramolecular hydrogen bonding form A and OH-stabilized by an intramolecular hydrogen bonding form B is expected to be slow on the NMR time scale so that both forms are expected to be detected as distinct species.

The methyl ester proton in the pyrazole ring of both forms is most easily detected by the signal at δ 3.73 for the A conformer and at δ 3.63 for the B conformer. The very broad signal at δ 5.96 is more consistent with the more acidic, C-5 non-hydrogen bonded hydroxyl proton in conformer A. The singlet signals at δ 3.80 (3H) and 3.81 (3H) were assigned to N-methyl protons in conformers A and B, respectively. Thus, the singlet signals at δ 3.72 (3H) and 3.63 (3H) were assigned to the methyl ester protons in conformers A and B, respectively. Based on the integral rises of 2.54 and 3.06 respectively for these signals, and noting that they are both due to 3H signals, the conformer A to B ratio is calculated to be 1 to 1.21.

(b)



The ^{13}C-NMR spectrum (figure 41(b)) in $CDCl_3$ solution of compound **35** shows one set of signals for conformer A and one set for conformer B. Thus, the signal at δ 165.4 was assigned to the carbonyl carbon of the ester function as conformer A while the carbons at C-3, C-4, and C-5 of the pyrazole ring appear at δ 132.8, 97.7, and 156.7, respectively. The carbons of the N-methyl and O-methyl groups gave signals at δ 39.8, 51.9, respectively. The analogous carbon atoms of conformer B led to signals at δ 166.5, 137.9, 94.2, 163.1, 33.8, and 51.8, respectively.

(c)

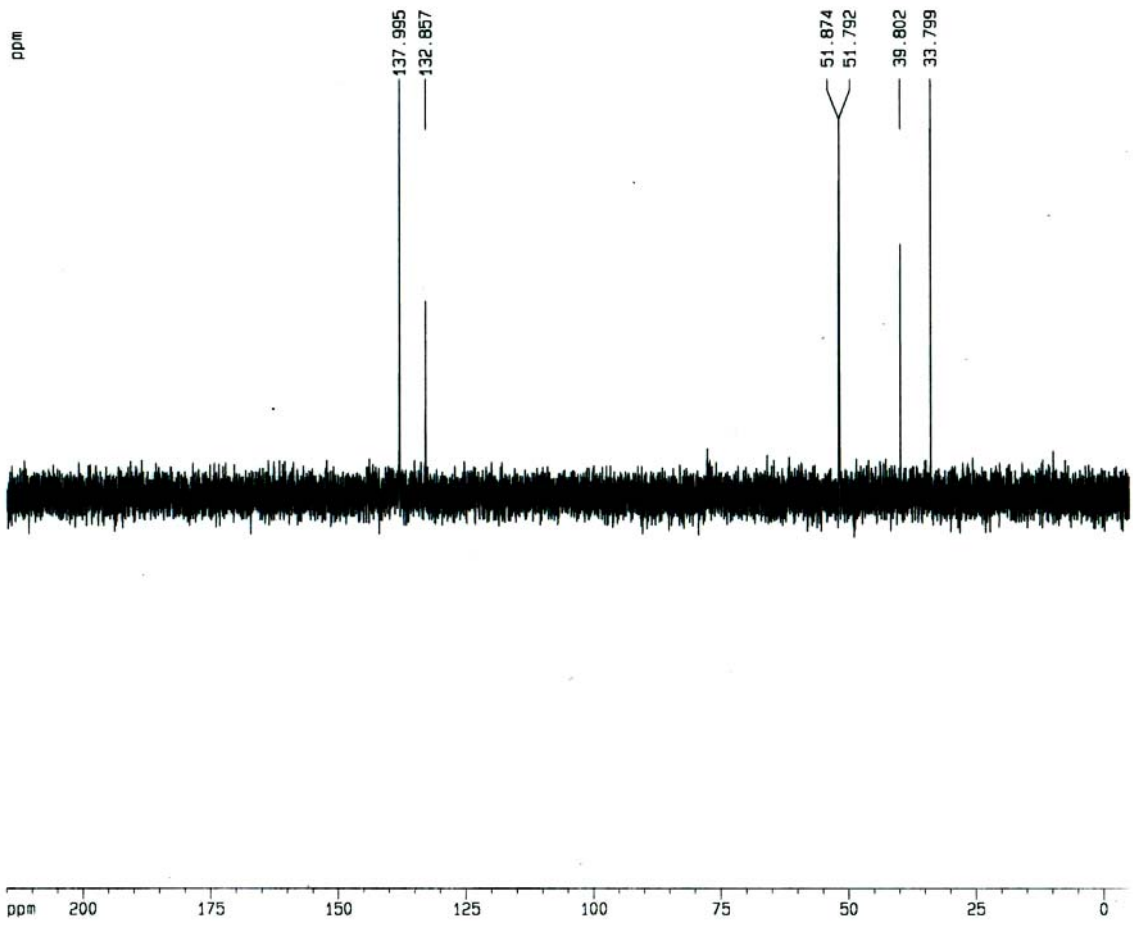
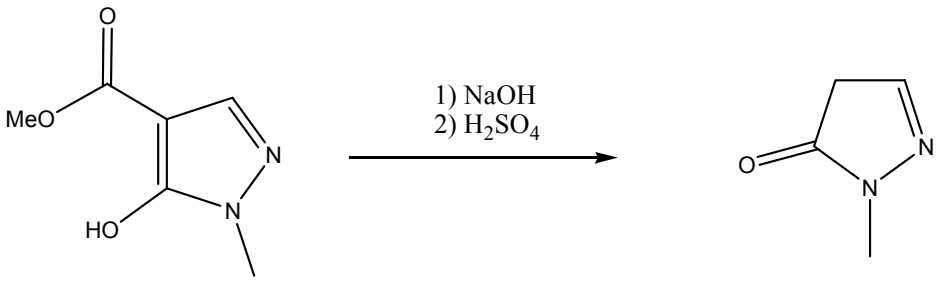


Figure 41: (a) ^{1}H-NMR of compound **35**; (b) ^{13}C-NMR of compound **35**; (c) ^{13}C-NMR DEPT 135 of compound **35**.

As expected, the ^{13}C-NMR DEPT 135 (figure 41(c)) of compound **35** shows that the six signals at δ 166.5, 165.4, 163.1, 156.7, 97.67, and 94.19 are consistent with the two sets of the quaternary signal of the A and B conformers. In contrast, the signals at δ 137.9, 132.8, 51.87, 51.79, 39.79, and 33.79 appear in the positive direction which is consistent with their assignment to the two sets of A and B conformers. These signals are due to the CH type carbon on the pyrazole ring and the two methyl type carbons on N and O atoms.



(35) **(36)**

Scheme 39: Synthesis of 1-methyl-1*H*-pyrazol-5(4*H*)-one **(36)**.

As reported in the literature[9] saponification of ester **35** followed by acidification and heating led to decarboxylation and to the formation of 1-methyl-1*H*-pyrazol-5(4*H*)-one **(36)** in a yield of 73%, mp 109-110°C (Lit.[9] 110-111.5°C) (Scheme 39).

(a)

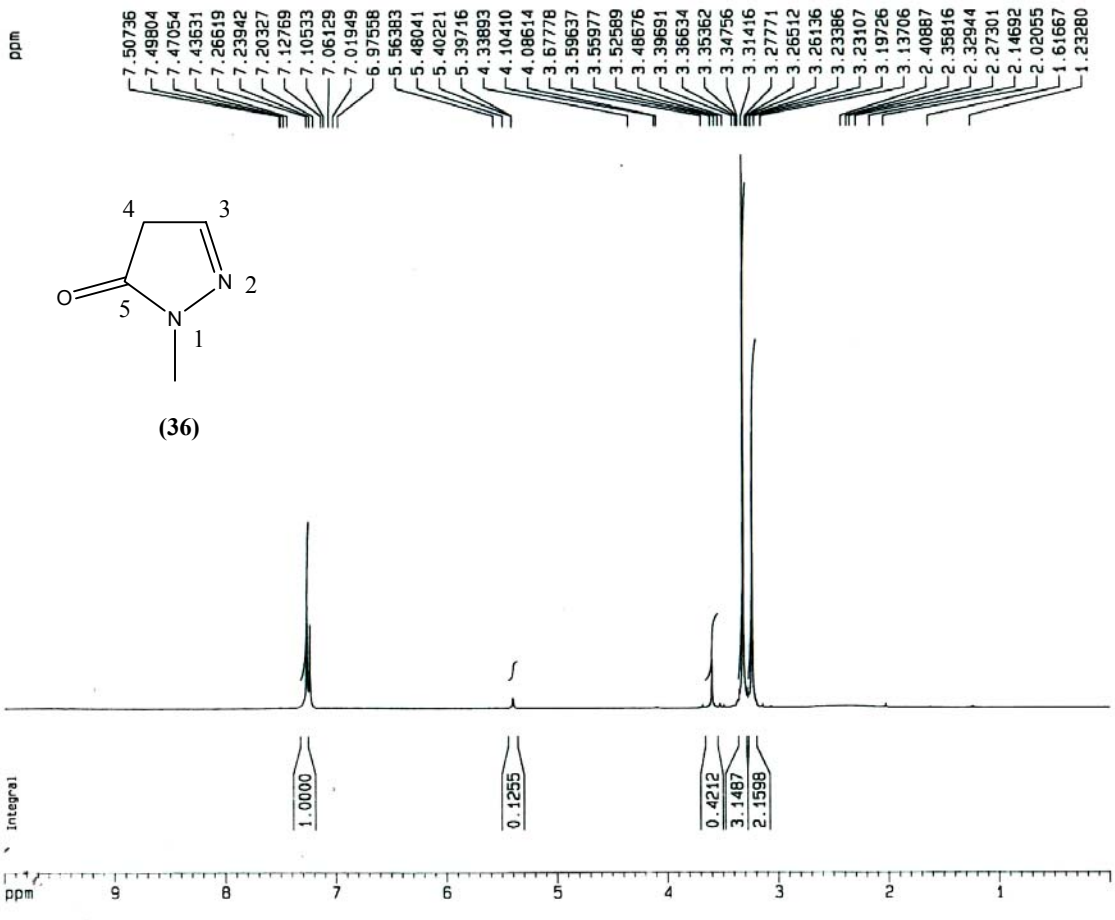
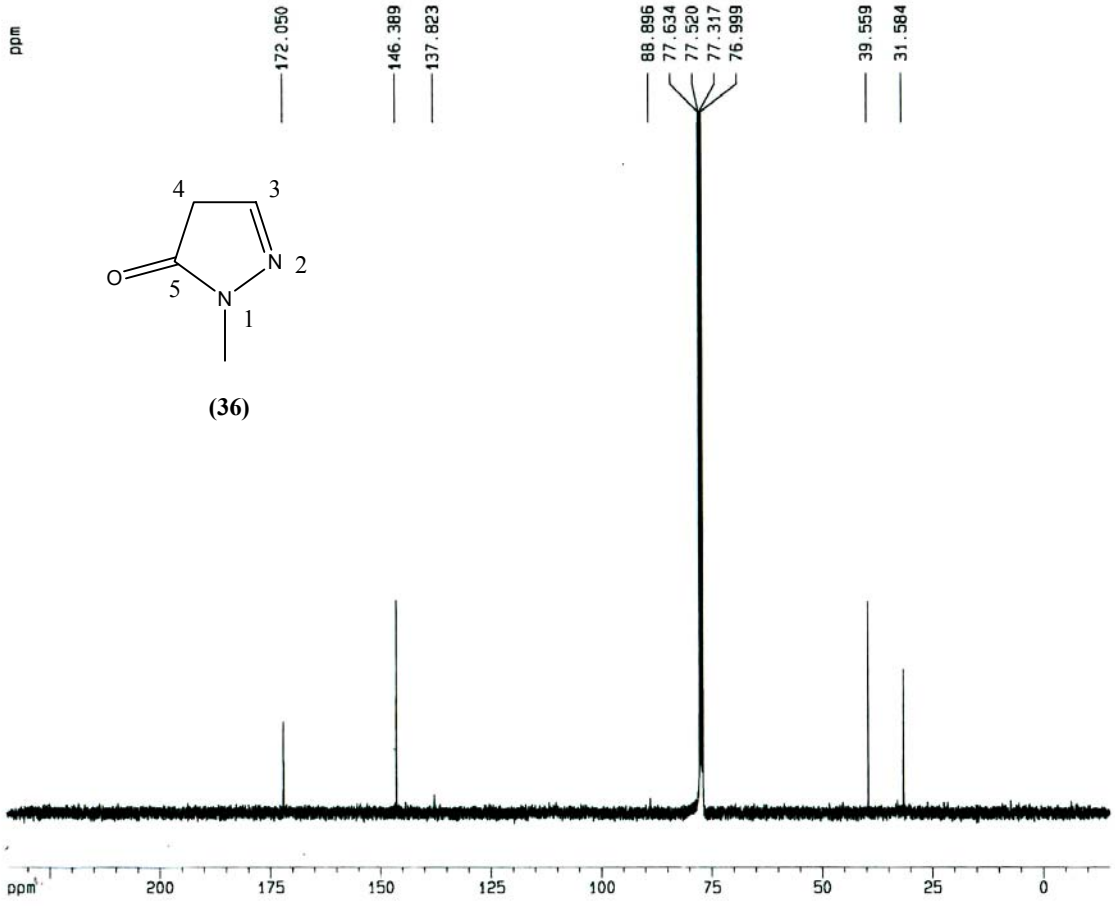


Figure 42(a) shows that the ^{1}H-NMR spectrum of the white solid compound is consistent with the structure of **36.** The proton at C-3 of the pyrazolone ring appears as a singlet at δ 7.27 (1H). The protons of the N-methyl group appear as a 3H singlet at δ 3.31. Finally, the α-carbonyl protons of the pyrazolone ring appear as a 2H singlet at δ 3.19.

(b)



(36)

The ^{13}C-NMR spectrum (Figure 42(b)) is also compatible with the structure of **36**. The carbonyl carbon of the pyrazolone ring absorbs the furthest downfield at δ 172.0. Unambiguously, the sp^2 carbon at C-3 absorbs at δ 146.4, while the signal at

39.56 is due to the α-carbonyl carbon of the pyrazolone ring. Finally, the N-methyl carbon absorbs the furthest highfield at δ 31.58.

(c)

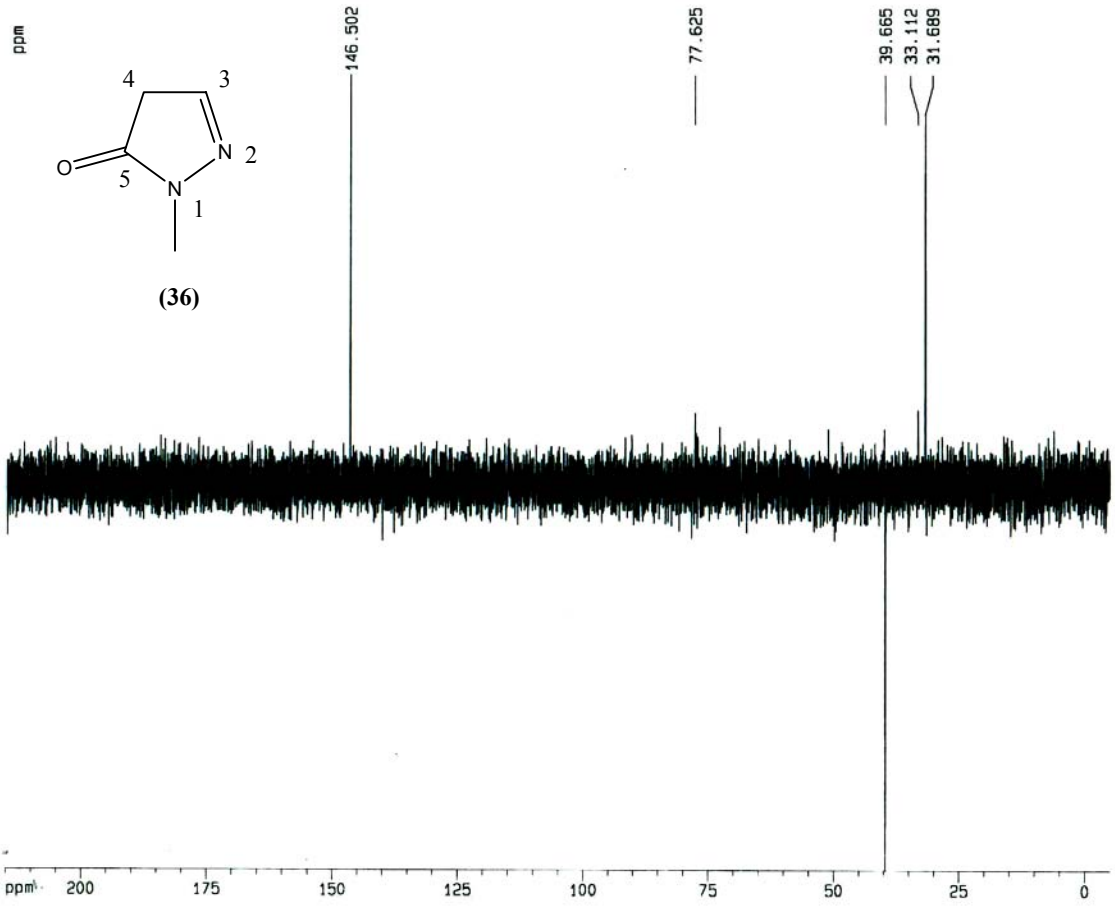
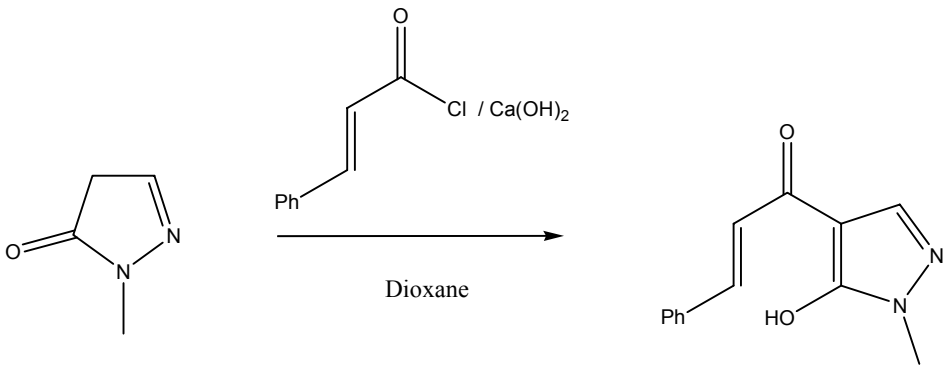


Figure 42: (a) ^{1}H-NMR of compound **36**; (b) ^{13}C-NMR of compound **36** and (c) ^{13}C-NMR DEPT 135 of compound **36**.

These assignments are consistent with the ^{13}C-DEPT 135 spectrum (Figure 42(c)). As expected, the signal at δ 172.0 disappeared which is consistent with the quaternary carbon of the carbonyl carbon of the pyrazolone ring. But, the signals at δ 146.4 and 31.58 still appear in the positive direction, which is consistent with the assignment to the CH type carbon of the pyrazolone ring and the methyl carbon of the

N atom. The signal at δ 39.56, however, appears in the negative direction confirming that this signal is due to a CH_2 type carbon of the pyrazolone ring.



(36) **(37)**

Scheme 40: Synthesis of (*E*)-1-(5-hydroxy-1-methyl-1*H*-pyrazol-4-yl)-3-phenylprop-2-en-1-one **(37)**.

Based on synthetic approach by Heinisch, G. and colleagues,[4] pyrazolone **36** was treated with *trans*-cinnamoyl chloride in a dioxane slurry of calcium hydroxide. This led to C-acylation and the formation of (*E*)-1-(5-hydroxy-1-methyl-1*H*-pyrazol-4-yl)-3-phenylprop-2-en-1-one **(37)** in a yield of 45%, mp 136-137^{o}C, (Lit.[10] mp 140-142^{o}C) (Scheme 40). The proposed mechanism of this reaction was shown in figure 43.

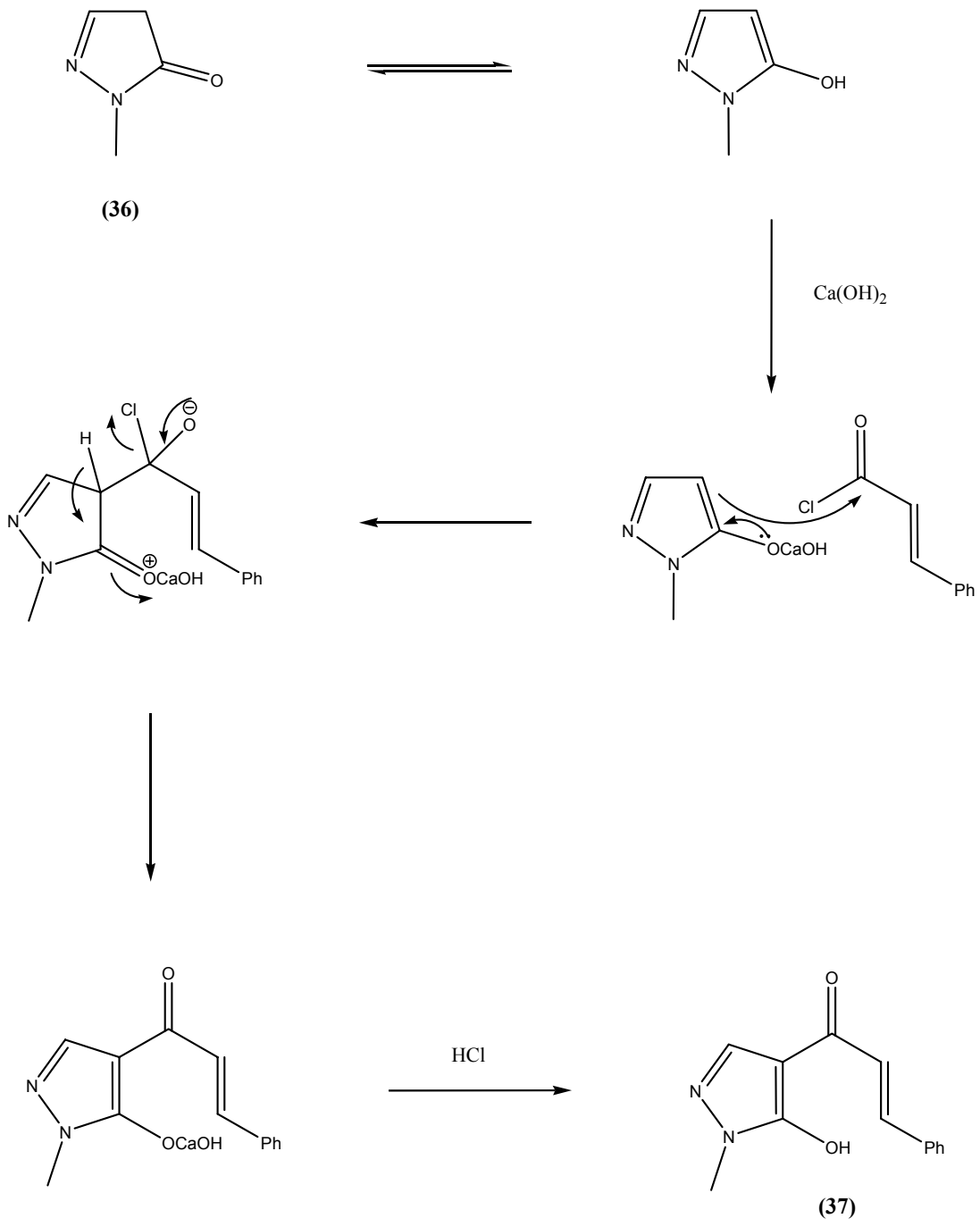


Figure 43: Mechanism of the formation **37**

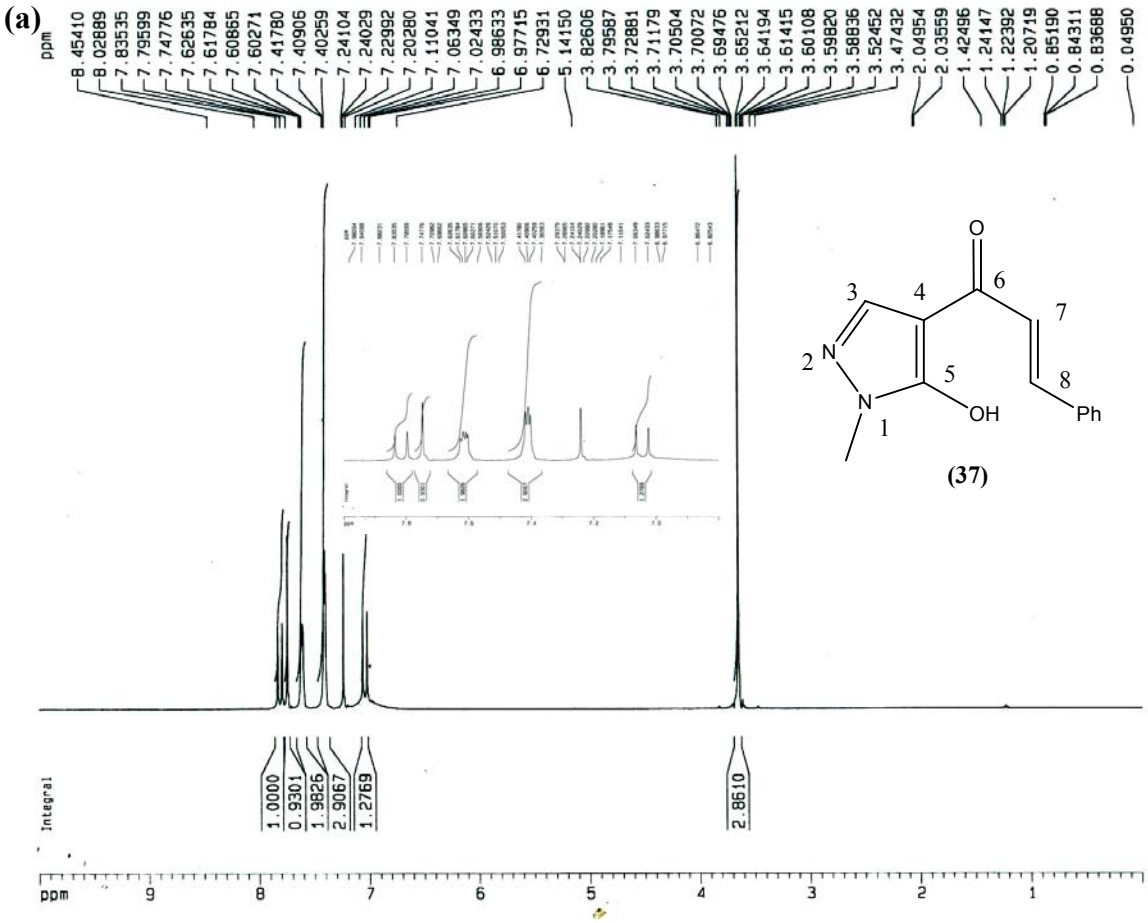


Figure 45(a) shows that the ^{1}H-NMR spectrum of the brown-yellow crystalline needles is consistent with the structure of **37**. The proton at C-3 of the pyrazole ring appears as a 1H singlet at δ 7.75, while N-methyl protons appear as a 3H singlet at δ 3.65. The 1H doublet at δ 6.98 (J = 15.8 Hz) of the proton α to the carbonyl moiety (COC**H**=) shows a markedly smaller chemical shift than that of the corresponding a 1H doublet at δ 7.80 (J = 15.8 Hz) of the β-proton (=C**H**Ph). A possible explanation for this phenomenon is that the β-proton is shifted downfield due to the partially positive charge by delocalized electron of the C=O moiety. The magnitude of the coupling constant is consistent with the trans configuration as indicated by the Karplus equation.

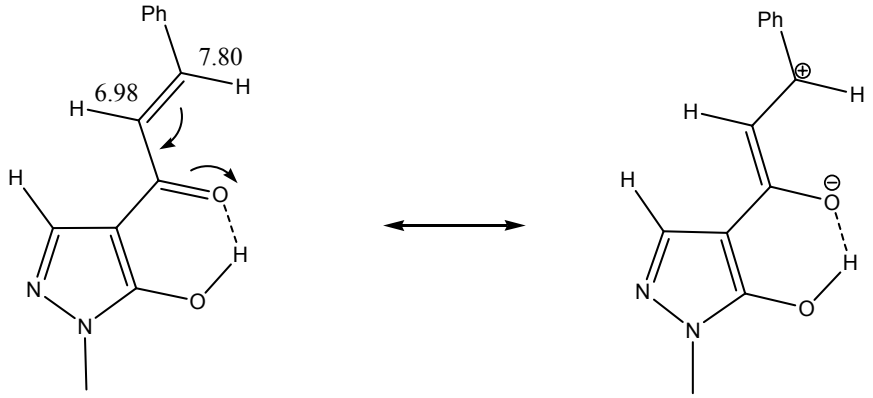
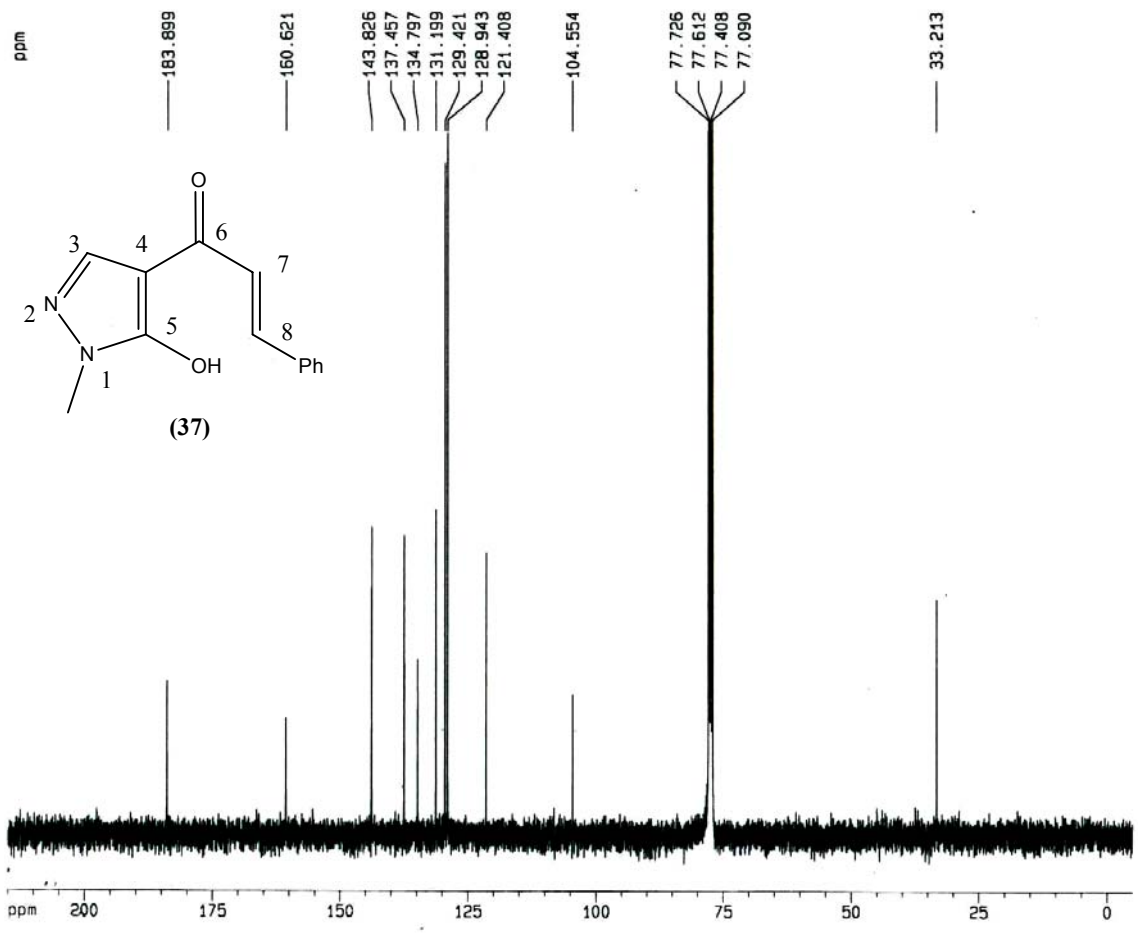


Figure 44: Diagnostic ^{1}H-NMR chemical shifts in **37**

Finally, the phenyl protons appear as a 2H multiplet at δ 7.60 for the ortho protons, while the mata and para protons are observed in the same position as a 3H multiplet at δ 7.40.

(b)



The ^{13}C-NMR spectrum (Figure 45(b)) is also consistent with the structure **37**. The carbonyl carbon of the acyl side chain absorbs the furthest downfield at δ 183.9. The C-3, C-4, and C-5 carbons of the pyrazole ring are assigned to the signal at δ 137.5, 104.6, and 160.6, respectively. The phenyl ring carbon attached to the nitrogen atom and at the para position absorb at δ 134.8 and 131.2 respectively, while the carbons atom at meta and ortho positions appear as two singlets at δ 129.4 and 128.9, respectively. As expected, the ^{13}C-NMR chemical shifts of the α-alkene carbon atom appears at δ 121.4 (CO**C**H=) which the β-carbon is downfield at δ 143.8 (=**C**HPh). Unambiguously, the N-methyl carbon of the pyrazole ring is observed at δ 33.21.

(c)

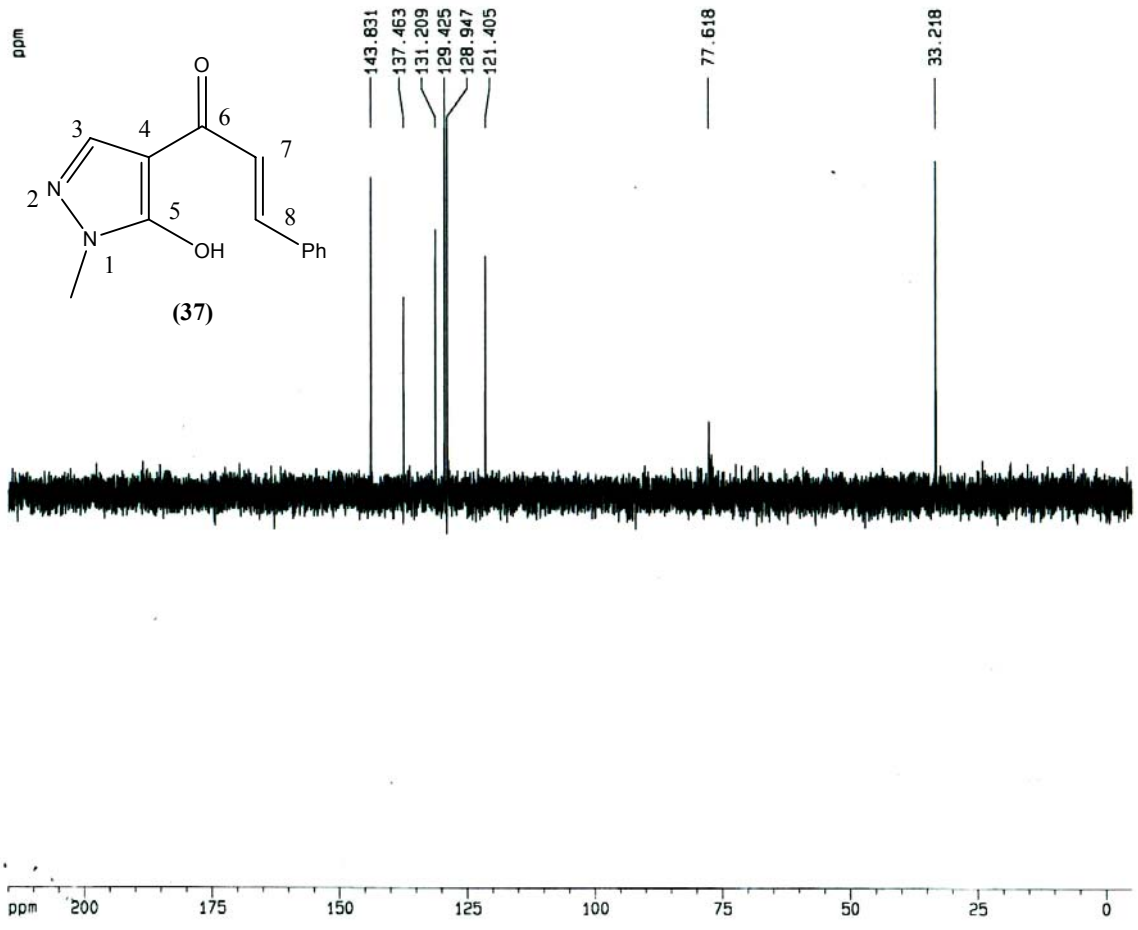
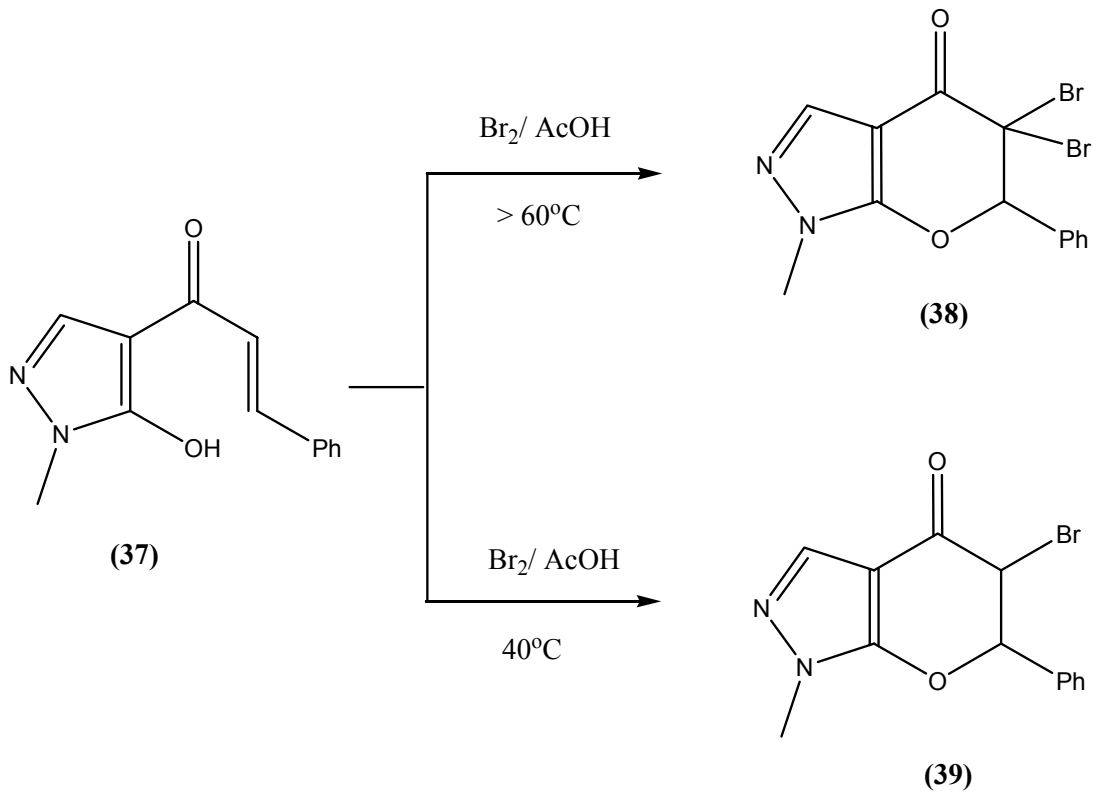


Figure 45: (a) ^{1}H-NMR of compound **37**; (b) ^{13}C-NMR of compound **37**; (c) ^{13}C-NMR DEPT 135 of' compound **37**.

As expected, the ^{13}C-NMR DEPT 135 (figure 45(c)) of compound **37** shows that the four signals at δ 183.9, 160.6, 134.8, and 104.6 disappeared which is consistent with their assignment to the quaternary carbons of **37** due to the carbonyl carbon, C-4 and C-5 carbon atoms of the pyrazole ring, and the quaternary carbon of the phenyl ring. On the other hand, the signals at δ 143.8, 137.5, 131.2, 129.4, 128.9, 121.4, and 33.21 appear in the positive direction which is consistent with their assignment to the CH type carbon on the pyrazole ring, the two type α and β alkene carbons, the three CH type carbons of the phenyl ring at ortho, meta, and para positions, and the N-methyl carbon of the pyrazole ring.



Scheme 41: Synthesis of 5-bromo-1-methyl-6-phenyl-5,6-dihydropyrano[2,3-*c*]pyrazole-4(1*H*)-one **(39)**.

Surprisingly, the bromination of **37** with bromine in acetic acid at greater than 60^{o}C led to the formation of the unexpected 5,5-dibromo-1-methyl-6-phenyl-5,6-dihydropyrano[2,3-*c*]pyrazol-4(1*H*)-one **(38)** in a yield of 33%, mp 176-177^{o}C. In contrast, when the reaction was carried out below 40^{o}C, the new compound 5-bromo-1-methyl-6-phenyl-5,6-dihydropyrano[2,3-*c*]pyrazole-4(1*H*)-one **(39)** was formed in a yield of 88%, mp 177-178^{o}C (Scheme 41). While, the reasons are unclear for the formation of this unexpected product **38**, the E1 reaction could be a competitive reaction of the bromonium ion at the higher temperature. Ionization is favored by: (1) formation of the stable benzyl carbonium ion; (2) relief of ring strain by opening of the three member ring; (3) the higher ionizing strength of the acetic acid solvent. Once ionization has occurred, the carbonium ion is subject to two competing reactions: cyclization (S_N1) back to the bromonium ion or proton removal (E1) to yield the bromoalkene **38a**. At the higher temperature, the E1 path would be faster than the S_N1 path. The bromoalkene **38a** would then undergo bromine addition as shown in Figure 46 to give **38**.

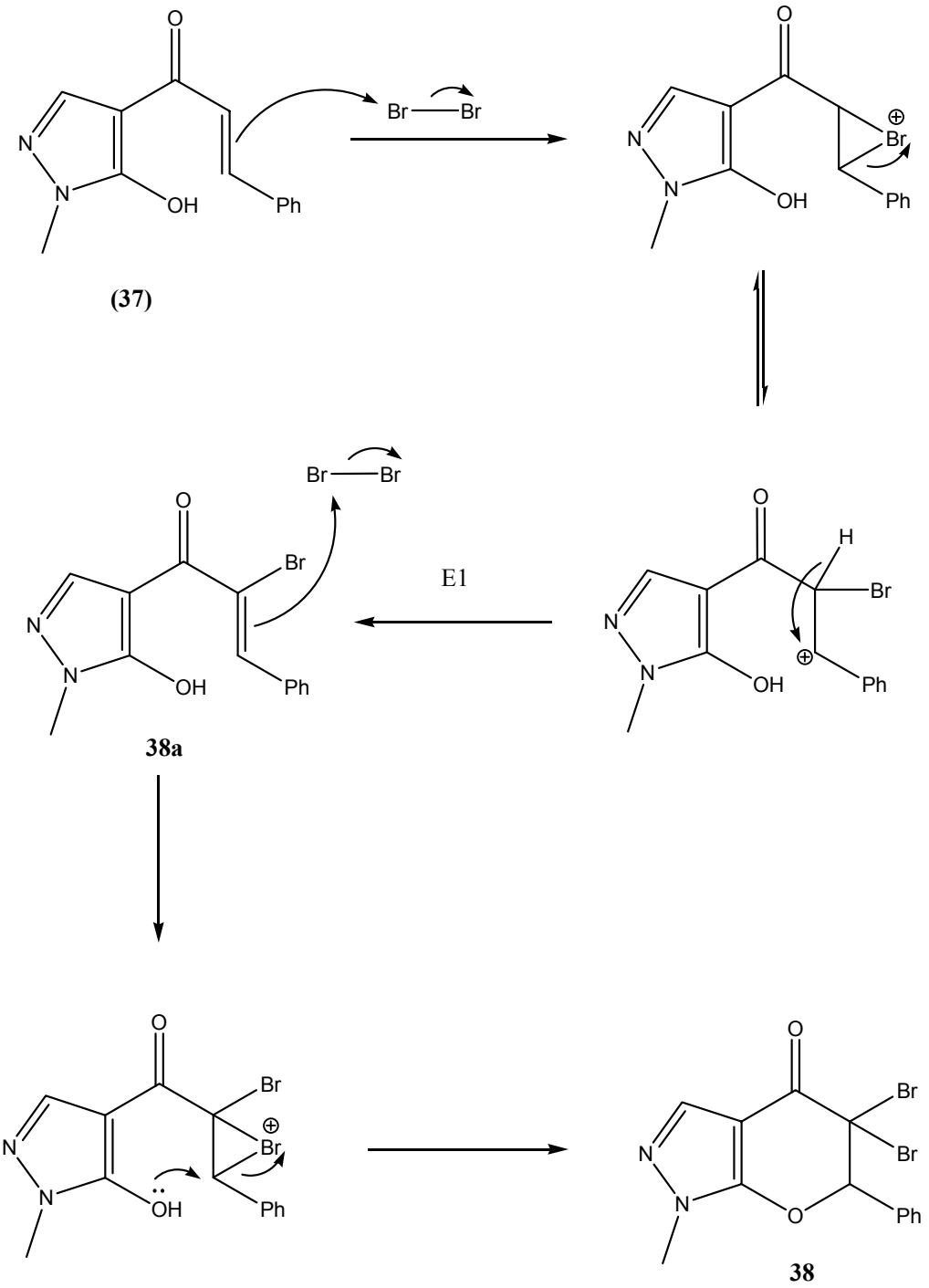
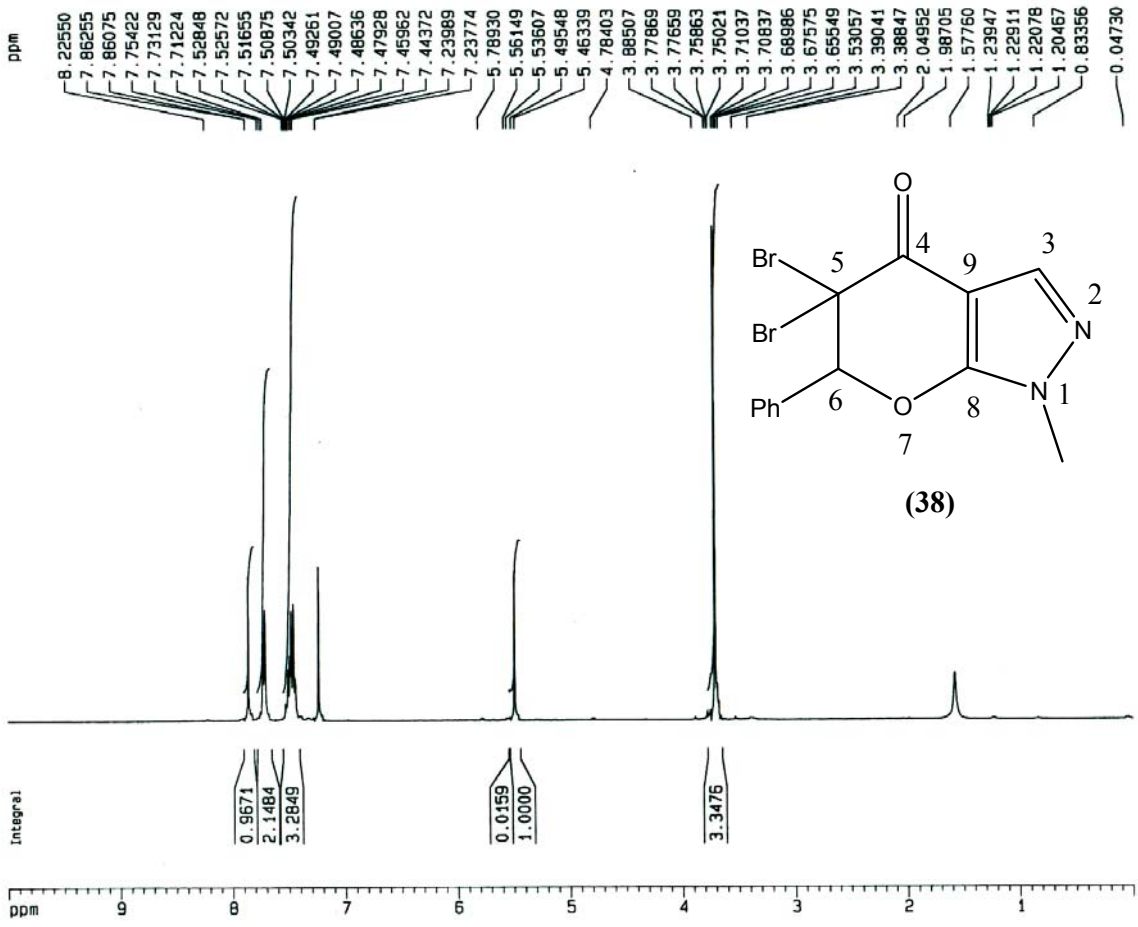


Figure 46: Mechanism of the formation **38**

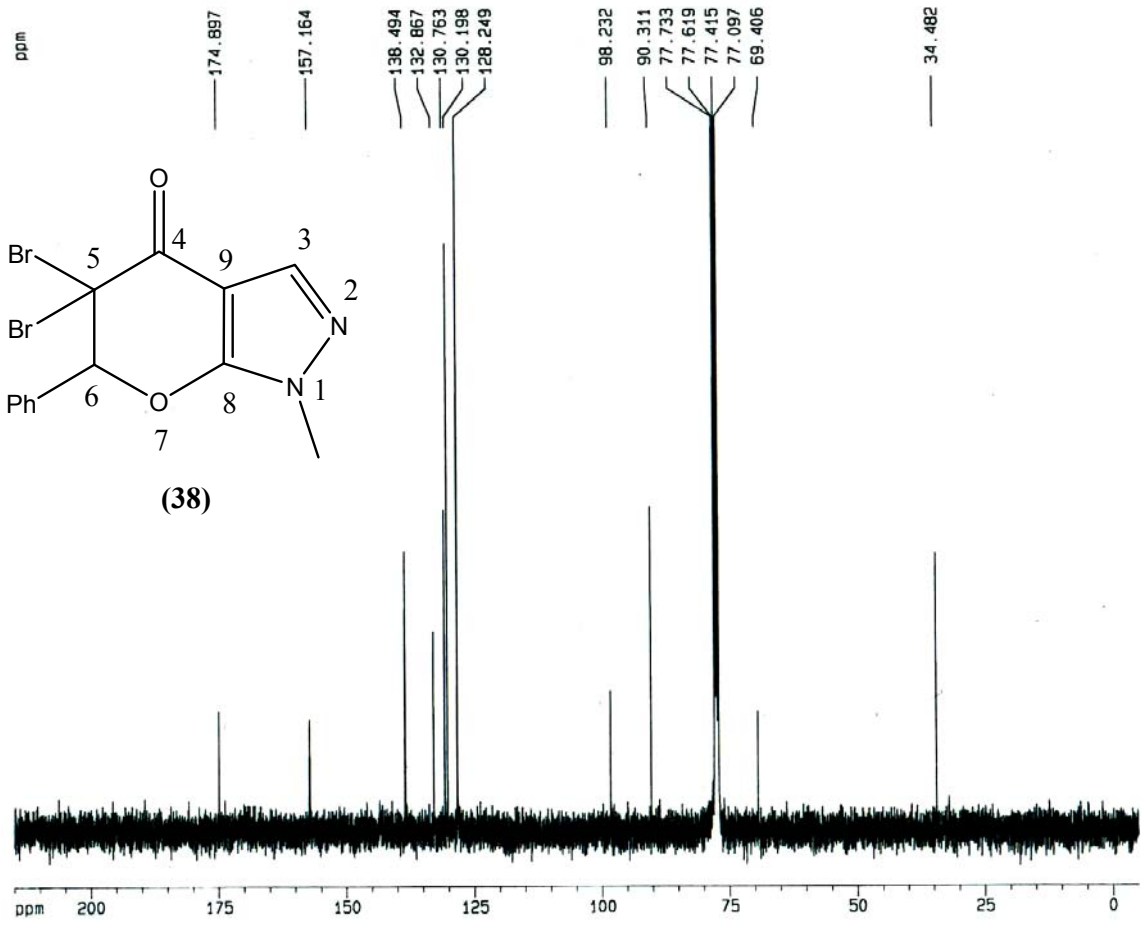
(a)



(38)

Figure 47(a) shows that the ^{1}H-NMR spectrum of the white crystalline product is consistent with the structure of **38**. The proton at C-3 of the pyrazole ring appears as a 1H singlet at δ 7.86, while the N-methyl protons are shown as a 3H singlet at δ 3.71. The 3H multiplet signals at δ 7.45 are due to absorptions of the protons at the meta and para positions of the phenyl ring, while the 2H doublet (J = 8 Hz) signal at δ 7.71 is due to the ortho protons. Finally, the signal due to the C-6 proton of the pyrone ring appears as a singlet at δ 5.49.

(b)



(38)

The ^{13}C-NMR spectrum (Figure 47(b)) is also consistent with structure **38**. The carbonyl carbon of the pyrone ring absorbs the furthest downfield at δ 174.9. The signals at δ 157.2 and δ 98.23 were assigned to the bridgehead carbons at positions 8 and 9, respectively. The sp^3 carbons of the pyrone ring in positions 5 and 6 appear at δ 69.40 and 90.31, respectively. The C-3 carbon of the pyrazole ring was assigned to the signal at δ 138.5. The phenyl ring carbons attached to the nitrogen atom and at the para position absorb at δ 132.9 and 130.8 respectively, while the ortho and meta carbons in

the phenyl ring appear as two singlets at δ 128.2 and 130.2, respectively. Finally, the N-methyl carbon of the pyrazole ring is shown at δ 34.48.

(c)

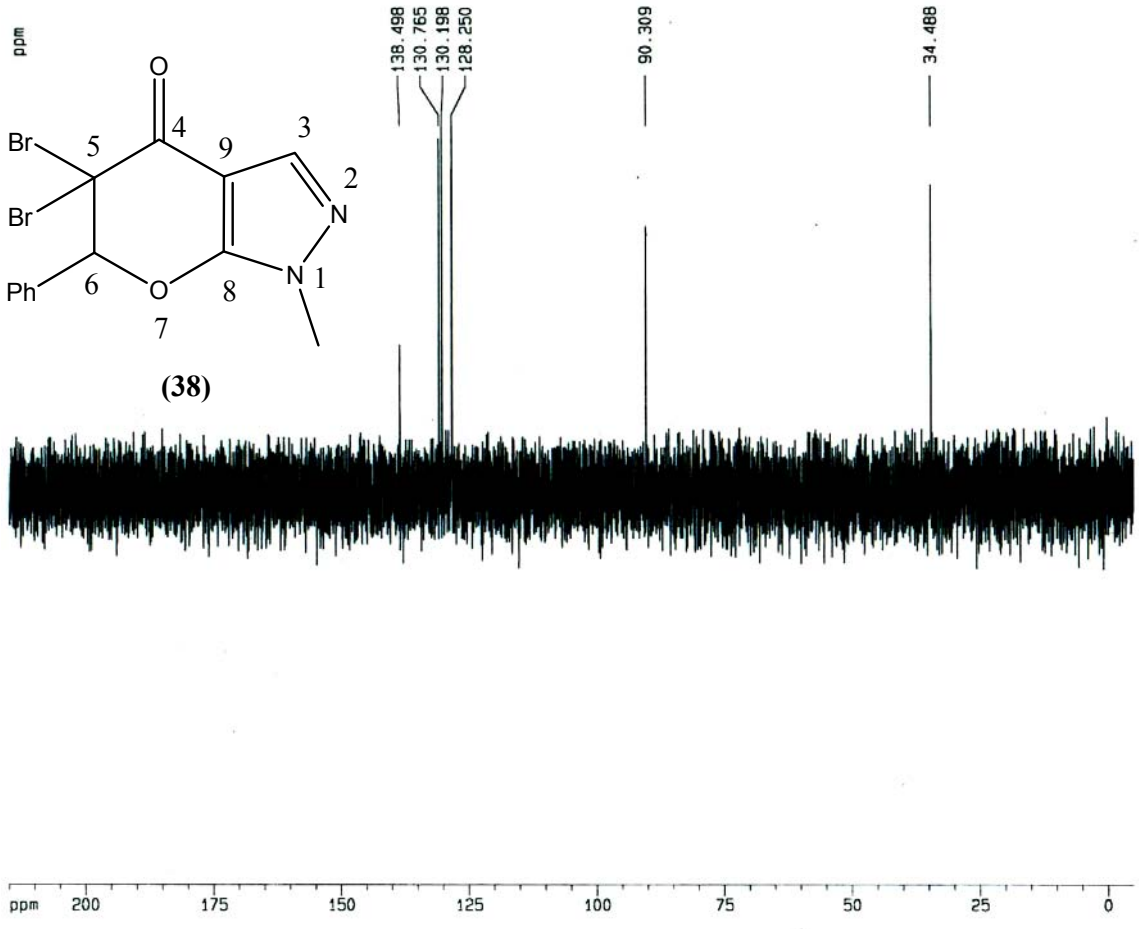
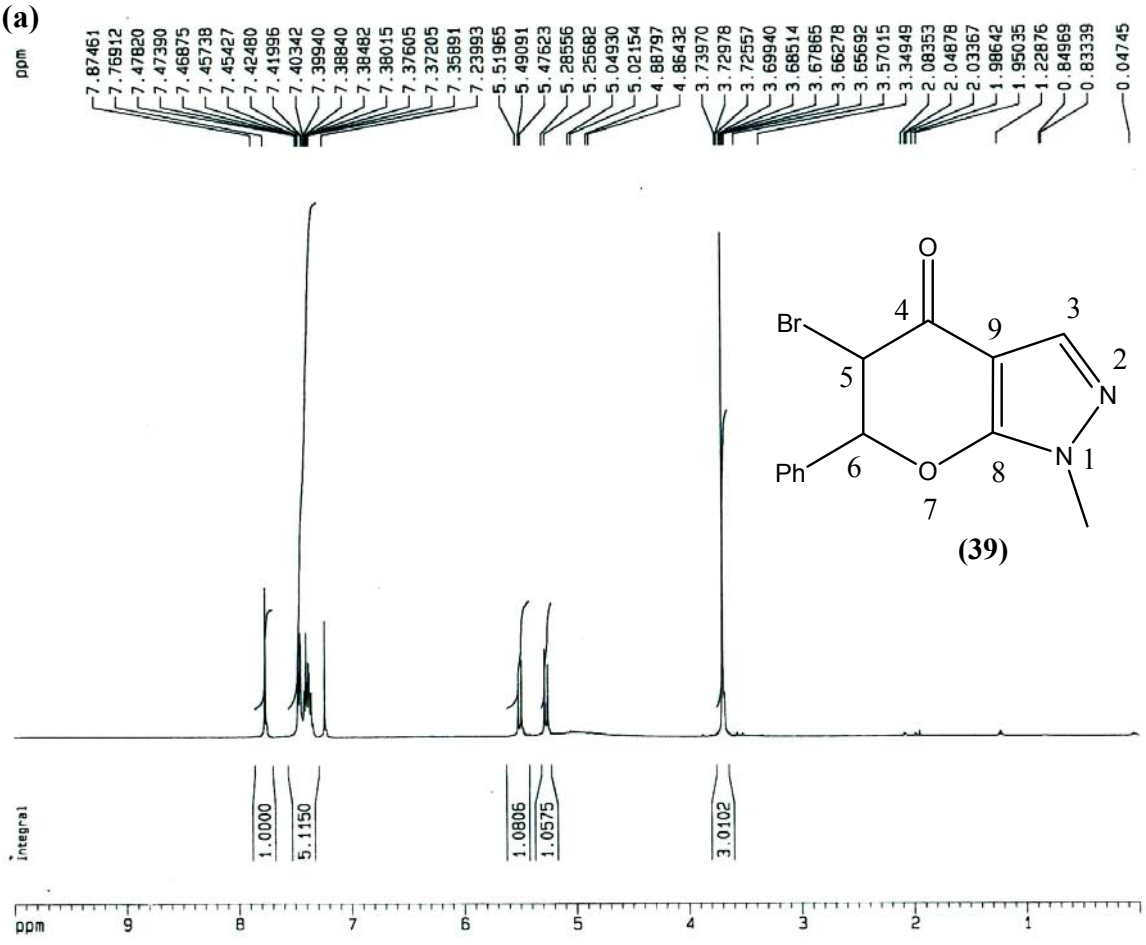


Figure 47: (a) ^{1}H-NMR of compound **38**; (b) ^{13}C-NMR of compound **38**; (c) ^{13}C-NMR DEPT 135 of compound **38**.

These assignments are consistent with the ^{13}C-DEPT 135 spectrum (Figure 47(c)). The five signals at δ 174.9, 157.2, 132.9, 98.32, and 69.40 disappeared which is consistent with their assignment to the five quaternary carbons. These signals are due to the two carbons in the pyrone ring, two carbons in the fused ring, and one carbon in the

phenyl ring. In addition, the signals at δ 138.5, 130.8, 130.2, 128.2, 90.31, and 34.48 still appear in the positive direction which is consistent with their assignment to the three CH type carbons of phenyl ring, the two CH type carbons of the pyrone and pyrazole rings, and the N-methyl carbon of the pyrazole ring.

(a)

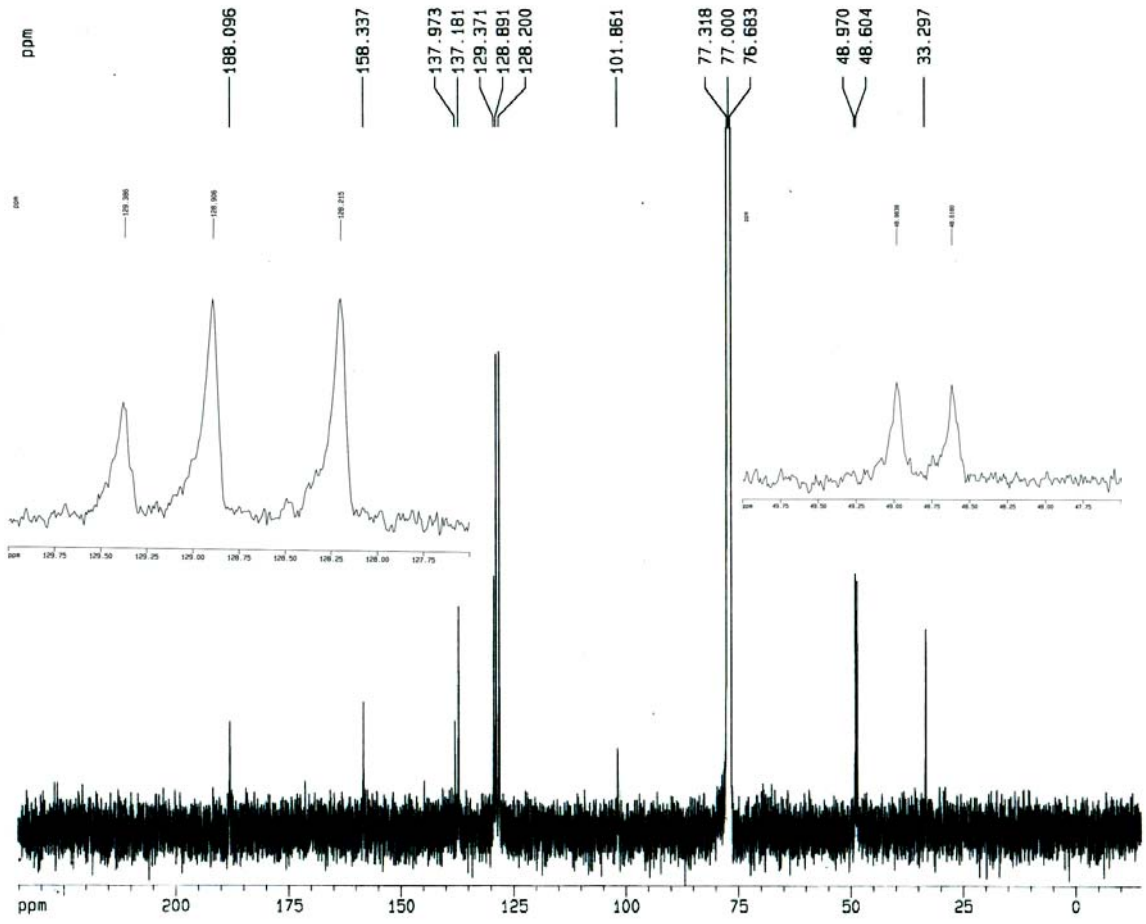


(39)

Figure 48(a) shows that the ^{1}H-NMR spectrum of the white crystalline product obtained when the bromination was carried out at lower temperature consistent with structure of **39**. The proton at C-3 of the pyrazole ring appears as a 1H singlet at δ 7.77, while the N-methyl protons are shown as a 3H singlet at δ 3.69. The 3H multiplet signals at δ 7.37 are due to absorptions of the protons at the meta and para positions,

while the 2H multiplet signal at δ 7.42 is due to ortho protons of the phenyl ring. Finally, the signal due to the C-6 proton of the pyrone ring appears as a 1H doublet (J = 11.7 Hz) at δ 5.49, while the C-5 proton appears as a 1H doublet (J = 11.6 Hz) at δ 5.26. Based on the Karplus equation, this compound should be assigned to the cis isomer.

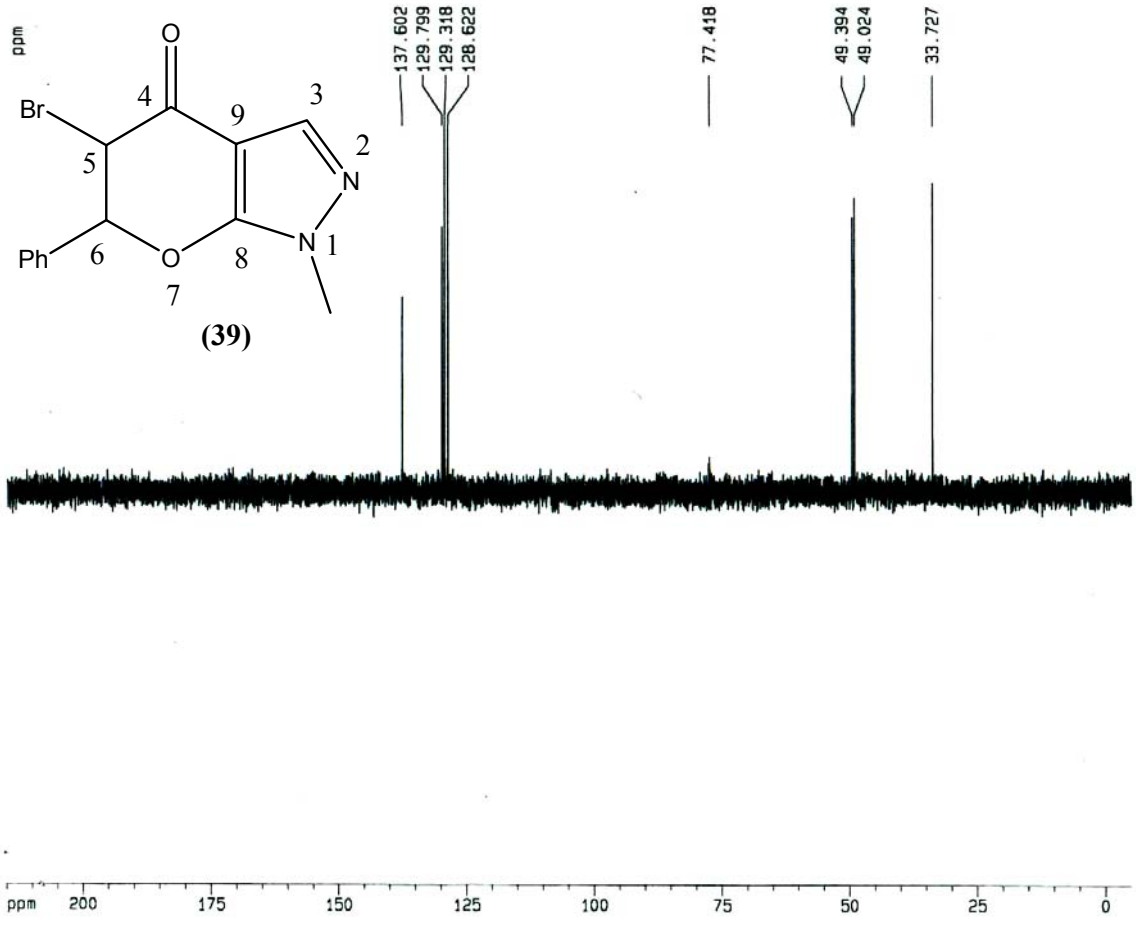
(b)



The ^{13}C-NMR spectrum (Figure 48(b)) is also consistent with the structure **39**. The carbonyl carbon of the pyrone ring absorbs the furthest downfield at δ 188.1. The signals at δ 158.3 and δ 101.9 were assigned to the bridgehead carbons at positions 8 and 9, respectively. The sp^3 carbons of the pyrone ring in positions 5 and 6 appear at δ

48.60 and 48.97, respectively. The C-3 carbon of the pyrazole ring was assigned to the signal at δ 137.2. The phenyl ring carbon attached to the nitrogen atom and at the para carbon absorb at δ 137.9 and 129.4 respectively, while the ortho and meta carbons in the phenyl ring appear as two singlets at δ 128.2 and 128.9, respectively. Finally, the N-methyl carbon of the pyrazole ring is shown at δ 33.29.

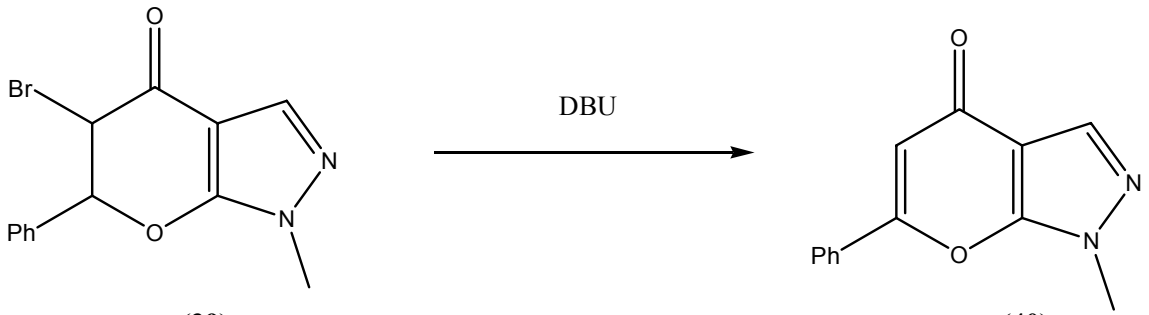
(c)



(39)

Figure 48: (a) ^{1}H-NMR of compound **39**; (b) ^{13}C-NMR of compound **39**; (c) ^{13}C-NMR DEPT 135 of compound **39**.

These assignments are also consistent with the ^{13}C-DEPT 135 spectrum (Figure 48(c)). The four signals at δ 188.1, 158.3, 137.9, and 101.9 disappeared which is consistent with their assignment to the four quaternary carbons. These signals are due to the carbonyl carbon in the pyrone ring, the two carbons in the fused ring, and one carbon in the phenyl ring. In addition, the signals at δ 137.2, 129.4, 128.9, 128.2, 48.97, 48.60, and 33.29 still appear in the positive direction which is consistent with their assignment to the three CH type carbons of phenyl ring, the two CH type carbons at C-5 and 6 of the pyrone, the CH type carbon at C-3, and the N-methyl carbon of the pyrazole ring.

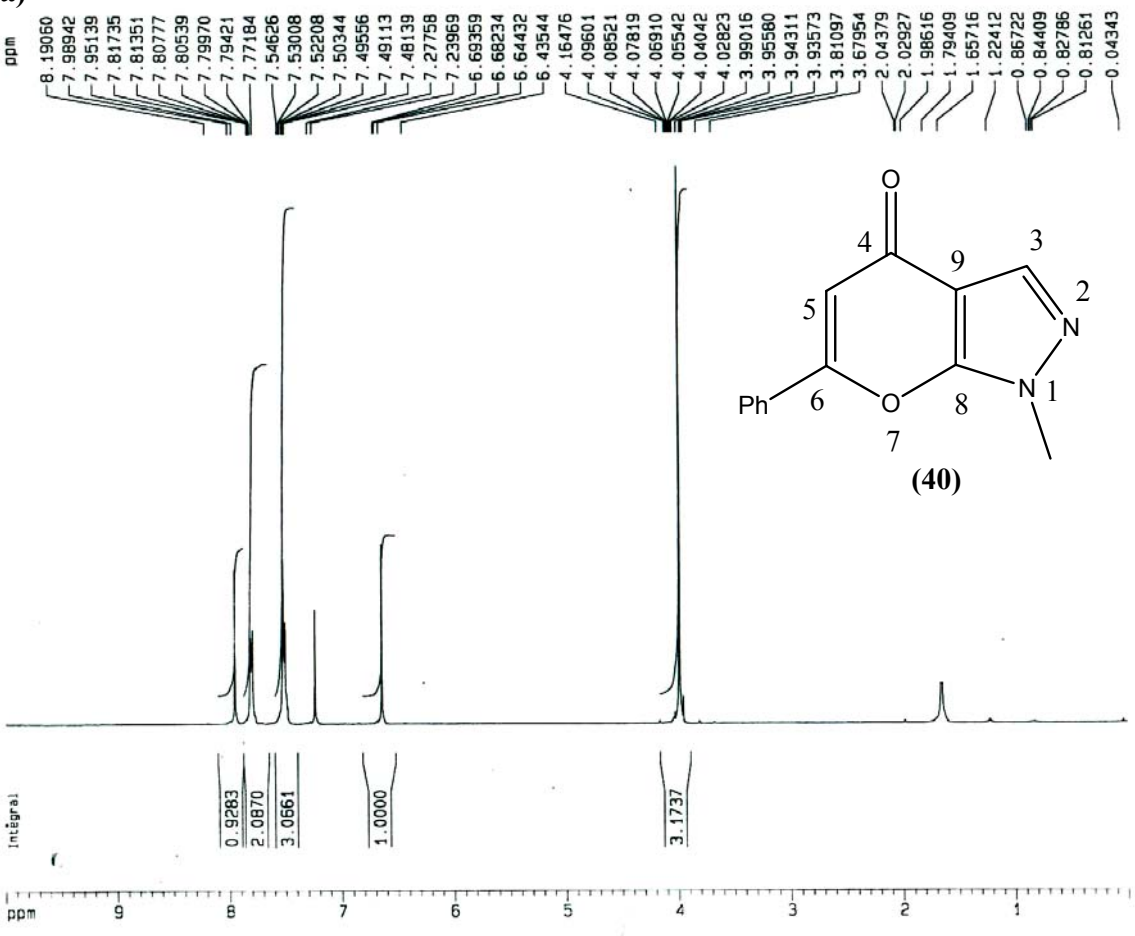


(39) **(40)**

Scheme 42: Synthesis of 1-methyl-6-phenylpyrano[2,3-*c*]pyrazole-4(1*H*)-one **(40)**.

The dehydrobromination of **39** to the new compound 1-methyl-6-phenylpyrano[2,3-*c*]pyrazole-4(1*H*)-one **(40)** was achieved by heating **39** in dioxane with an equivalent amount of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) at 90^{o}C to obtain **40** in a yield of 69%, mp 147-148^{o}C (Scheme 42).

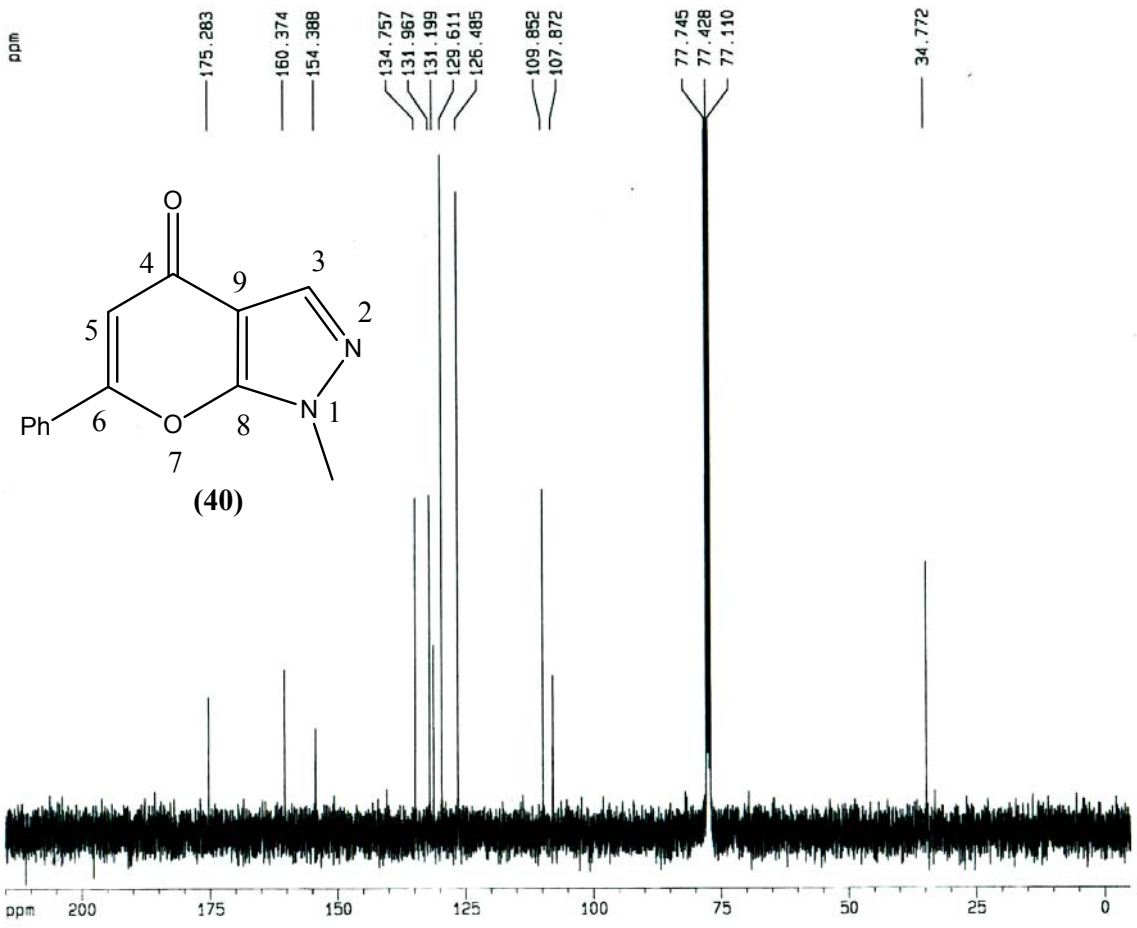
(a)



(40)

Figure 49(a) shows that the ^{1}H-NMR spectrum of the colorless crystalline product obtained in the previous experiment is consistent with the structure of **40**. The N-methyl protons of the pyrazole ring are shown as a 3H singlet at δ 3.99, while the C-3 proton appears as a 1H singlet at δ 7.95. The 2H multiplet at δ 7.77 is due to absorption of the protons at ortho positions, while the 3H multiplet at δ 7.52 is due to the meta and para protons of the phenyl ring. Finally, the key signal due to the C-5 proton of the pyrone ring appears as a 1H singlet at δ 6.64.

(b)

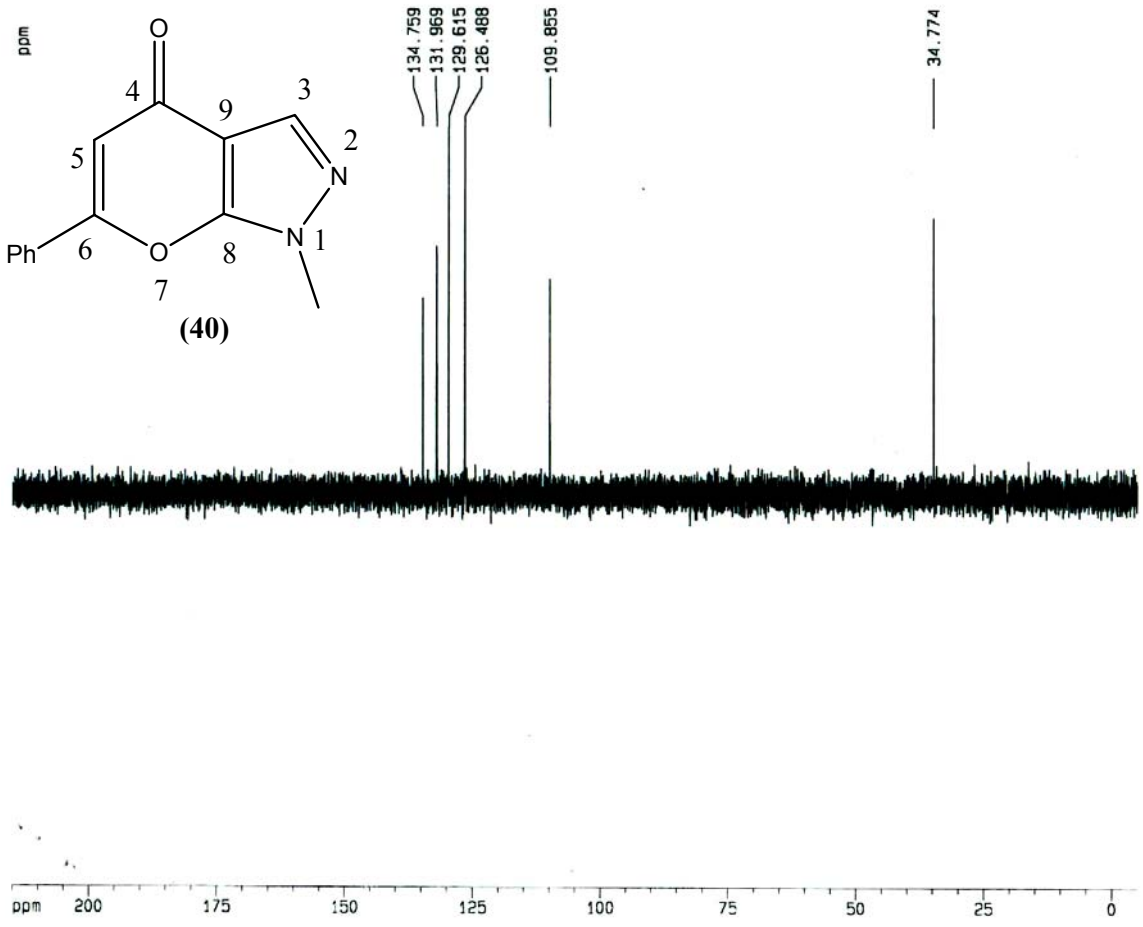


(40)

The ^{13}C-NMR spectrum (Figure 49(a)) is also consistent with the structure **40**. The carbonyl carbon of the pyrone ring absorbs the furthest downfield at δ 175.3. The signals at δ 154.4 and δ 107.9 were assigned to the bridgehead carbons at positions 8 and 9, respectively. The pyrone ring carbons at positions 5 and 6 appear at δ 109.8 and 160.4, respectively. The imine carbon of the pyrazole ring is assigned to the signal at δ 134.8. The phenyl ring carbon attached to the nitrogen atom and at the para carbon absorb at δ 131.2 and 131.9 respectively, while the ortho and meta carbons in the

phenyl ring appear as two singlets at δ 126.5 and 129.6, respectively. Finally, the N-methyl carbon of the pyrazole ring is shown at δ 34.77.

(c)

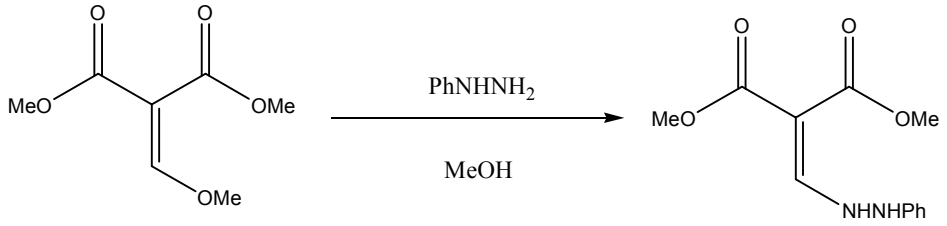


(40)

Figure 49: (a) ^{1}H-NMR of compound **40**; (b) ^{13}C-NMR of compound **40**; (c) ^{13}C-NMR DEPT 135 of compound **40**.

These assignments are consistent with the ^{13}C-DEPT 135 spectrum (Figure 49(c)). The five signals at δ 175.3, 160.4, 154.4, 131.2, and 107.9 disappeared which is consistent with their assignment to the five quaternary carbons. Thus, these two carbons are in the pyrone ring, one carbon is in the phenyl ring, and two carbons are in the fused

ring. In addition, the signals at δ 134.8, 131.9, 129.6, 126.5, 109.9, and 34.77 still appear in the positive direction which is consistent with their assignment to the three CH type carbons of the phenyl ring, the CH type carbons at C-3 of the pyrazole ring, the C-5 of the pyrone ring, and the N-methyl carbon of the pyrazole ring.

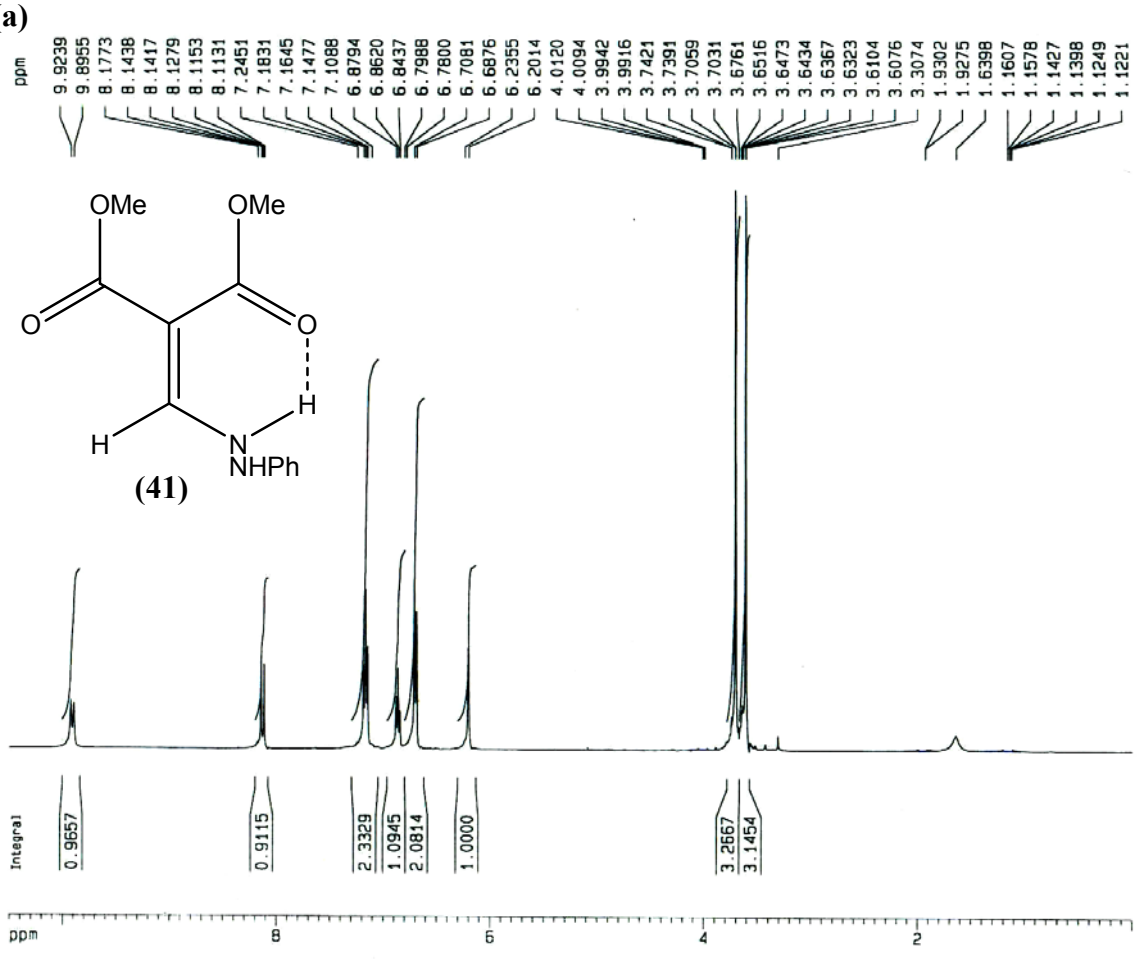


(34) **(41)**

Scheme 43: Synthesis of diethyl 2-[(2-phenylhydrazinyl)methylene]malonate **(41)**.

Previous attempts reported in the literature to isolate and purify diethyl 2-[(2-phenylhydrazinyl)methylene]malonate **(41)** have not been successful. In our laboratory, however, reaction of dimethyl(methoxymethylene)malonate **(34)** with phenylhydrazine in methanol afforded the white crystalline product **41** in a yield of 98%, mp 72-73^{o}C (Scheme 43).

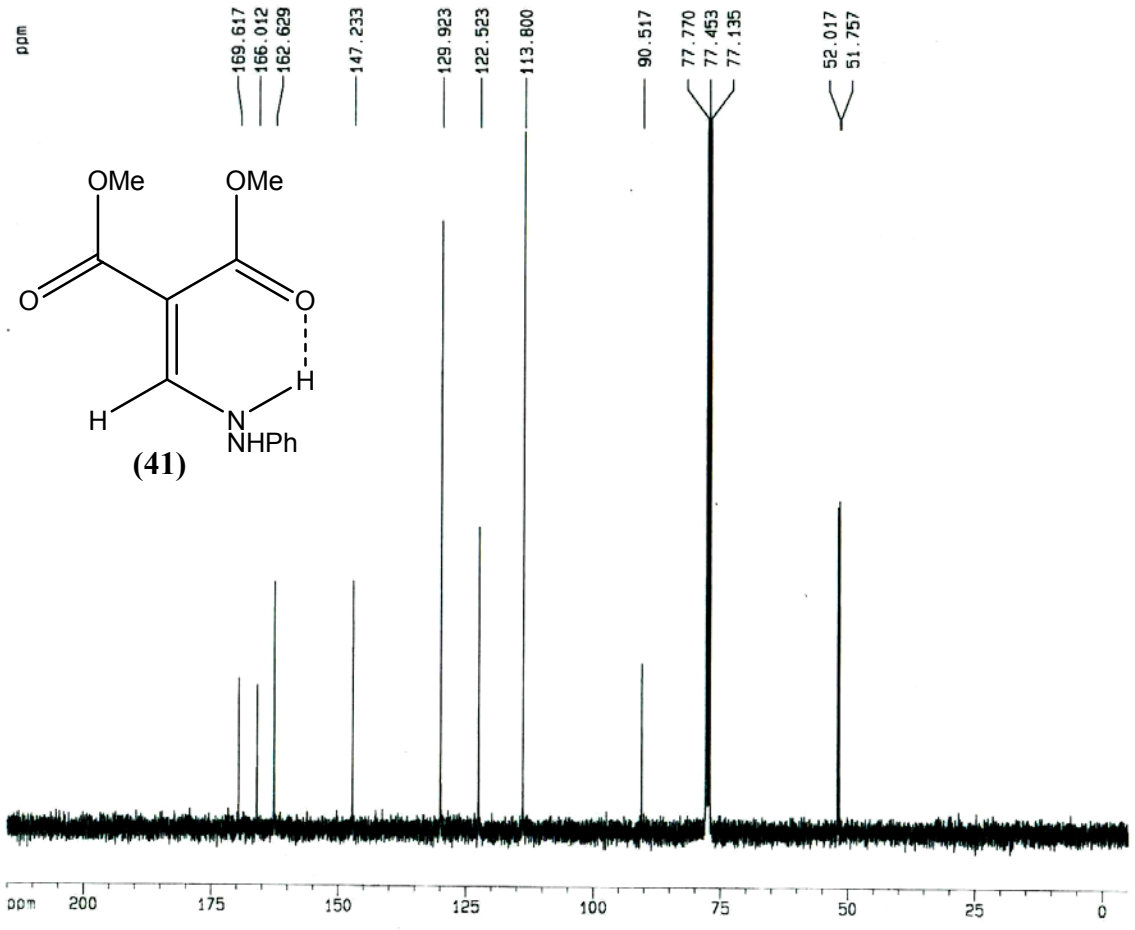
(a)



The ^{1}H-NMR spectrum indicates that in $CDCl_3$ solution compound **41** occurs as the intramolecular hydrogen bonded structure shown in Figure 50(a). As expected for this structure the ^{1}H-NMR spectrum shows two 3H singlets at δ 3.61 and 3.70 for the two non-equivalent CH_3O- groups and a pair of 1H doublets at δ 9.89 (J = 10.5 Hz) and δ 8.12 (J = 12.4 Hz) for the N-H and C-H protons of the =C**H**-N**H** moiety. The magnitude of the the coupling constant is consistent with the vicinal trans coupling rather than a free rotating system. The spectrum also shows a 1H singlet at δ 6.20 due to the proton bonded to nitrogen as well as a 2H triplet (J = 6.6 Hz) at δ 7.11, a 1H triplet (J = 7.6 Hz) at δ 6.78, and a 2H doublet (J = 8.6 Hz) at δ 6.69 assigned to the

phenyl protons at the meta, para, and ortho positions respectively. As required by these assignments, when treated with D_2O, both NH-NH signals at δ 9.58 and 6.20 disappeared and the 1H doublet at δ 8.12 collapsed to a singlet.

(b)



The ^{13}C-NMR spectrum shown in Figure 50(b) is also consistent with the suggested intramolecularly hydrogen bonded structure. Thus, the spectrum shows evidence for two non-equivalent methyl ester groups. The signals at δ 169.6 and 52.02 were assigned to the carbonyl and methyl carbons of the hydrogen bonded *Z*-ester carbonyl group while the signals at δ 166.0 and 51.76 were assigned to the carbonyl and methyl carbons of the non-hydrogen bonded *E*-ester group. In addition, the signals

at δ 162.6 and 90.51 are due to the carbons in the β and α positions of the **C**=**C**H fragment, respectively. The signals at δ 147.2, 129.9, 122.5, and 113.8 are consistent with the phenyl carbons at the quaternary, meta, para, and ortho positions, respectively.

(c)

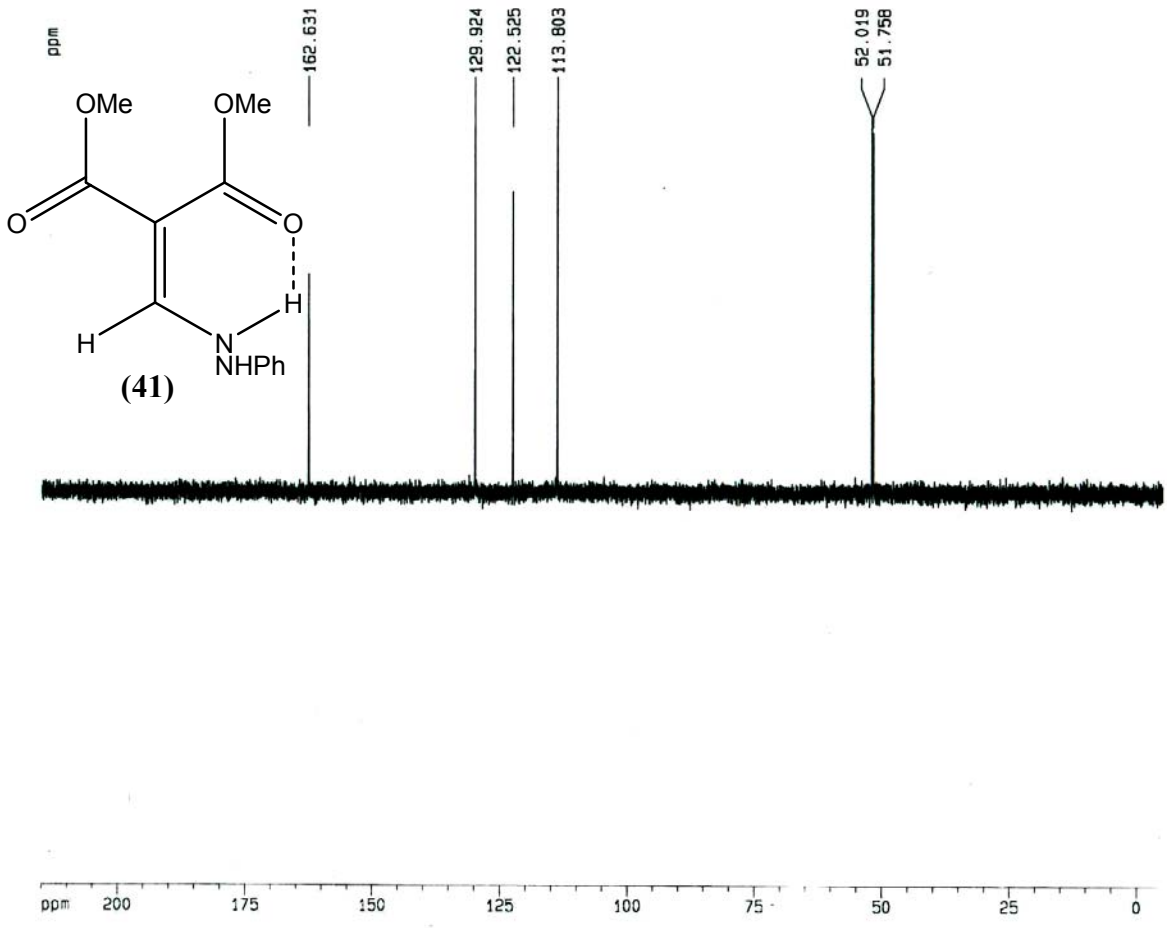
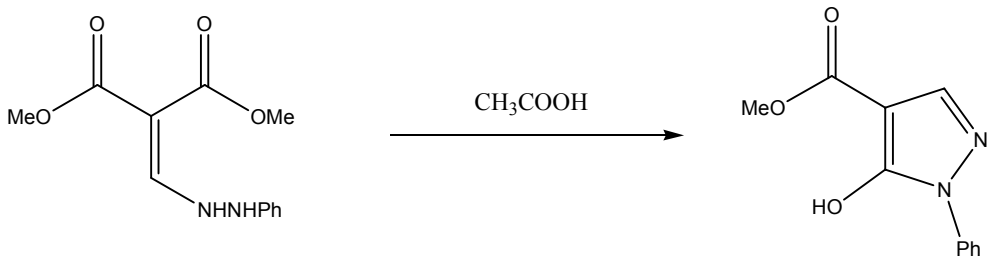


Figure 50: (a) ^{1}H-NMR of compound **41**; (b) ^{13}C-NMR of compound **41**; (c) ^{13}C-NMR DEPT 135 of compound **41**.

As expected, the four signals at δ 169.6, 166.0, 147.2, and 90.51 disappeared in the ^{13}C-DEPT 135 spectrum (Figure 50(c)).which is compatible with their assignment

to the two carbonyl carbons, the α carbon of the carbonyl group, and the quaternary carbon of the phenyl ring. In addition, the signals at δ 162.6, 129.9, 122.5, 113.6, 52.02, and 51.76 still appear in the positive direction which is consistent with their assignment to the three CH type carbons of the phenyl ring, the CH type carbon at β carbon of the carbonyl group, and the two methyl type carbons of the *E* and *Z*-ester.



(41) **(42)**

Scheme 44: Synthesis of methyl 5-hydroxy-1-phenyl-1*H*-pyrazole-4-carboxylate **(42)**.

Refluxing of **41** in acetic acid led to cyclization and the formation of the new compound methyl 5-hydroxy-1-phenyl-1*H*-pyrazole-4-carboxylate **(42)** in a yield of 85%, mp 151-153^{o}C (Scheme 44).

(a)

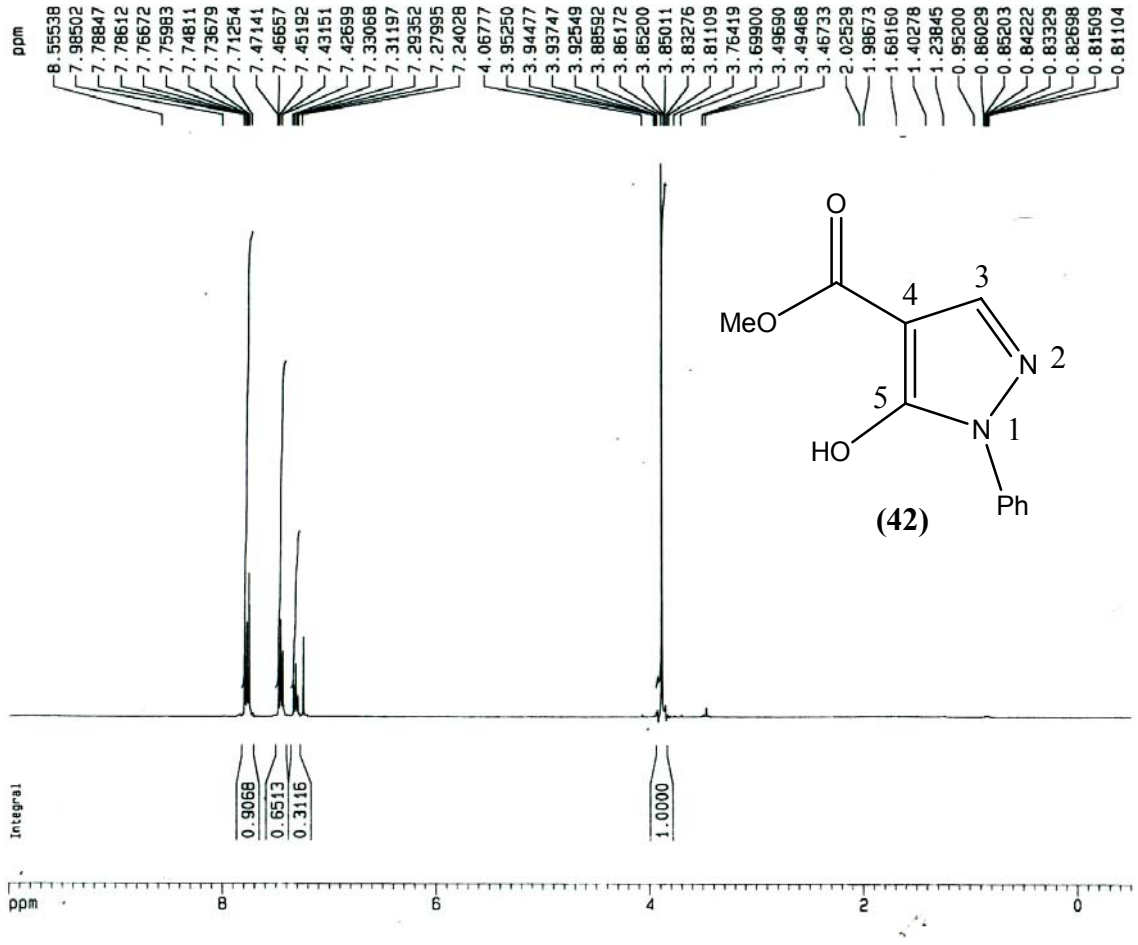
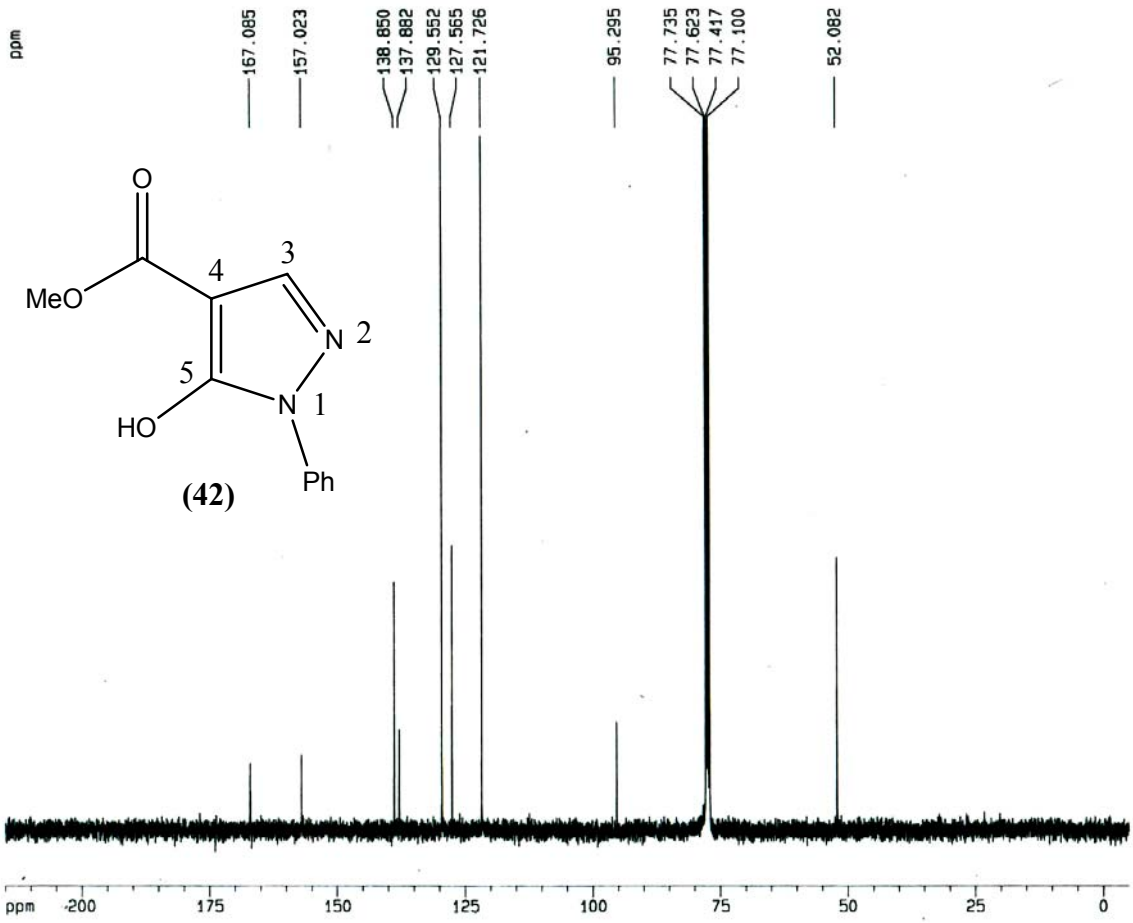


Figure 51(a) shows that the ^{1}H-NMR spectrum of the white solid compound is consistent with the structure of **42.** The proton at C-3 of the pyrazole ring appears as a 1H singlet at δ 7.71, while the protons of the O-methyl ester appear as a 3H singlet at δ 3.89. In addition, the 2H doublet (J = 7.6 Hz) at δ 7.74, the two triplets at δ 7.43 (2H; J = 7.8 Hz), and 7.29 (1H; J = 7.6 Hz) are characteristic of the phenyl protons at ortho, meta, and para positions, respectively.

(b)



The ^{13}C-NMR spectrum (Figure 51(b)) is also compatible with the structure **42**. The ester carbonyl carbon absorbs the furthest downfield at δ 167.1, while the signals at δ 157.0, 138.8, and 95.25 are consistent with the carbons at C-5, C-3, and C-4 of the pyrazole ring. In addition, the signals at δ 137.9, 129.6, 127.6, and 121.7 are due to the phenyl carbons at quaternary, meta, para, and ortho positions, respectively. Finally, the carbon of the O-methyl ester absorbs the furthest highfield at δ 52.08.

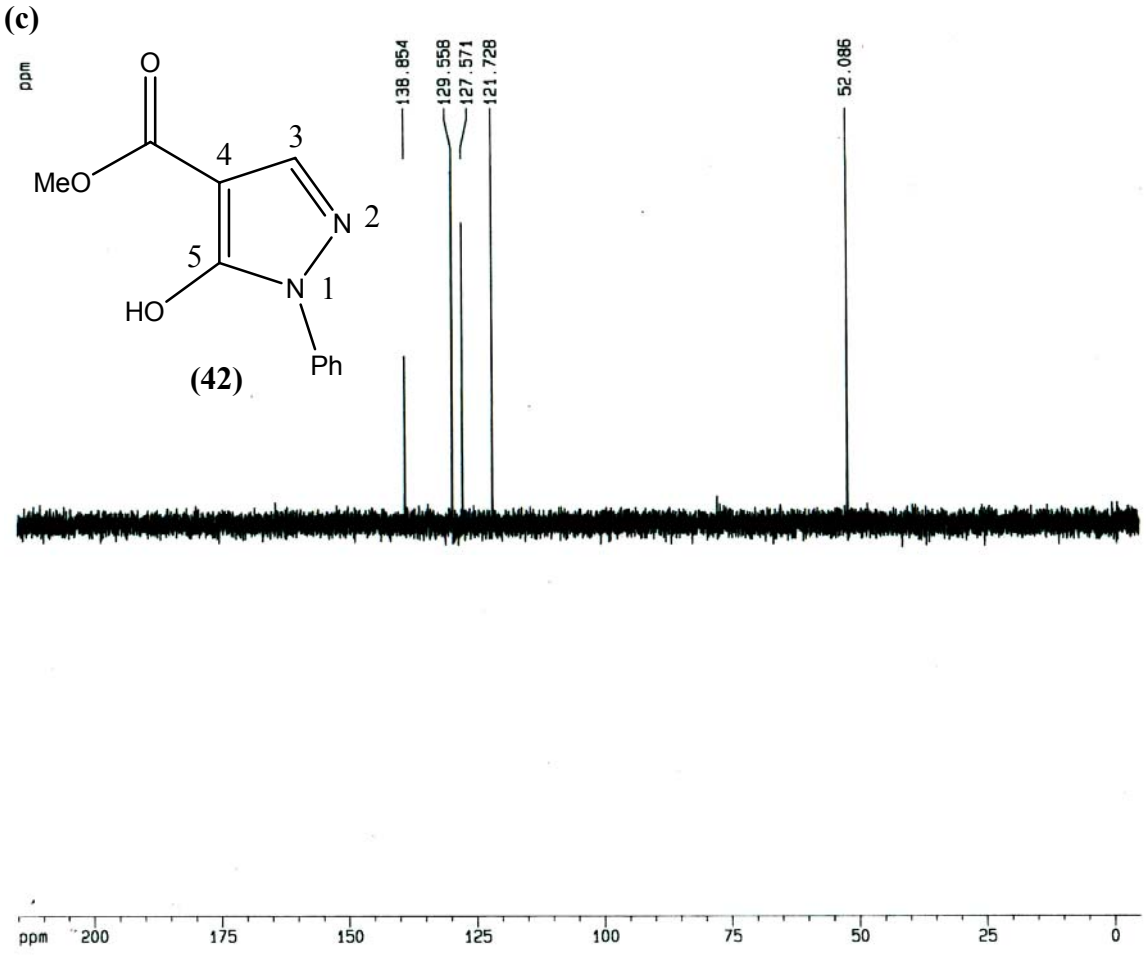
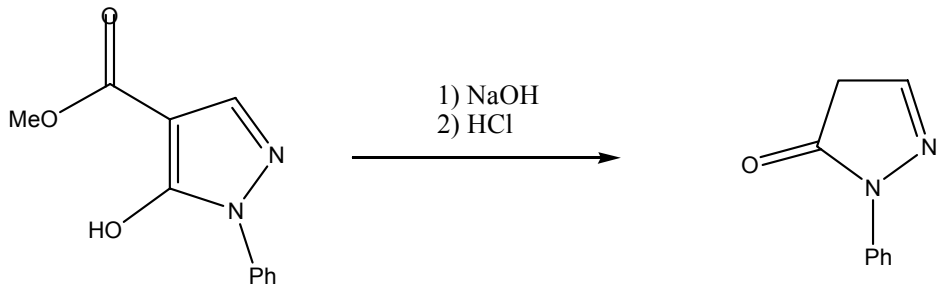


Figure 51: (a) ^{1}H-NMR of compound **42**; (b) ^{13}C-NMR of compound **42**; (c) ^{13}C-NMR DEPT 135 of compound **42**.

As expected, the four signals at δ 167.1, 157.0, 137.9, and 95.25 disappeared in the ^{13}C-DEPT 135 spectrum (Figure 51(c)).which is consistent with their assignment to the carbonyl carbon, the two quaternary carbon of the pyrazole ring, and the quaternary carbon of the phenyl ring. In addition, the signals at δ 138.8, 129.6, 127.6, 121.7, and 52.08 still appear in the positive direction which is consistent with their assignment to the three CH type carbons of the phenyl ring, the CH type carbon at C-3 of the pyrazole ring, and the O-methyl carbon of the ester side chain.



(42) **(43)**

Scheme 45: Synthesis of 1-phenyl-1*H*-pyrazol-5(4*H*)-one **(43)**

.

Methylester **42** was then saponified and decarboxylated as based on the literature procedure[9] to give 1-phenyl-1*H*-pyrazol-5(4*H*)-one **(43)** in a yield of 77%, mp 110-111°C (Lit.[11] 118°C) (Scheme 45).

(a)

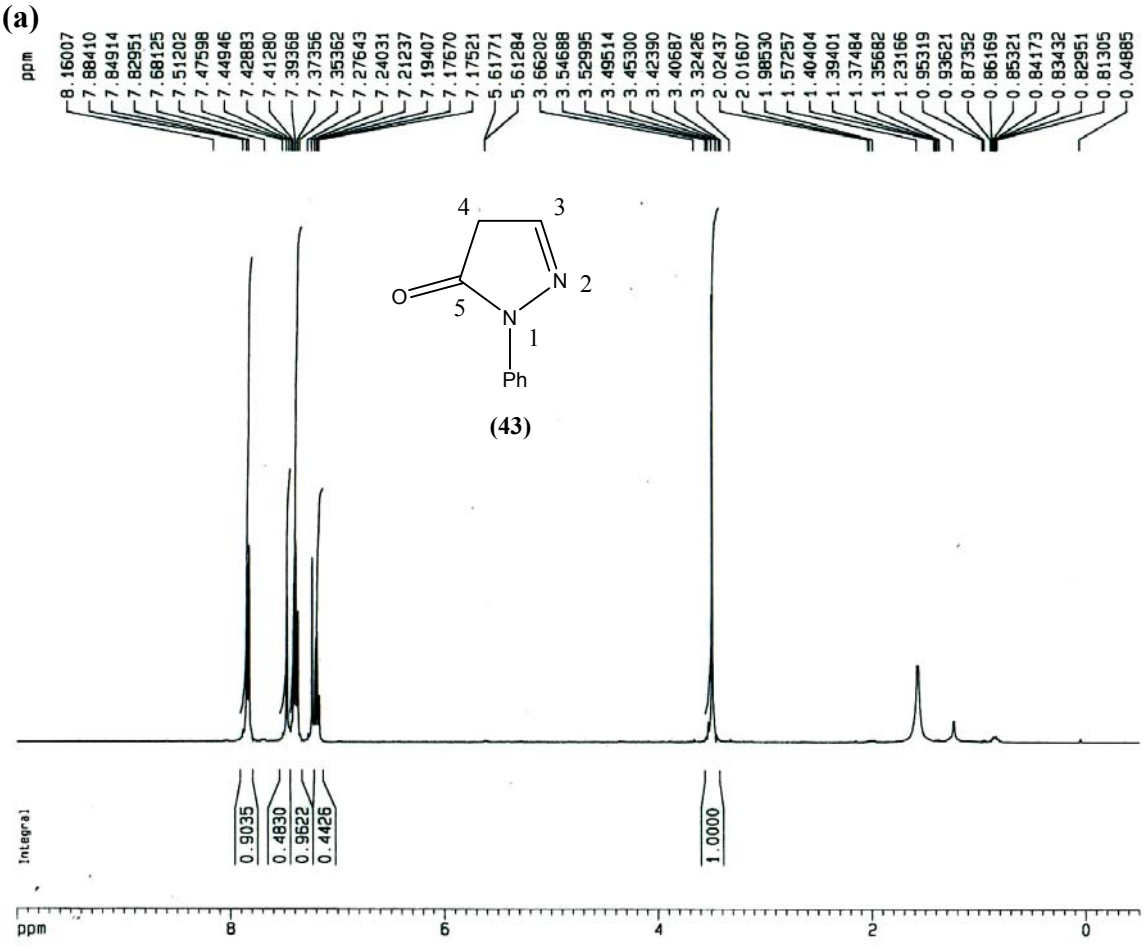
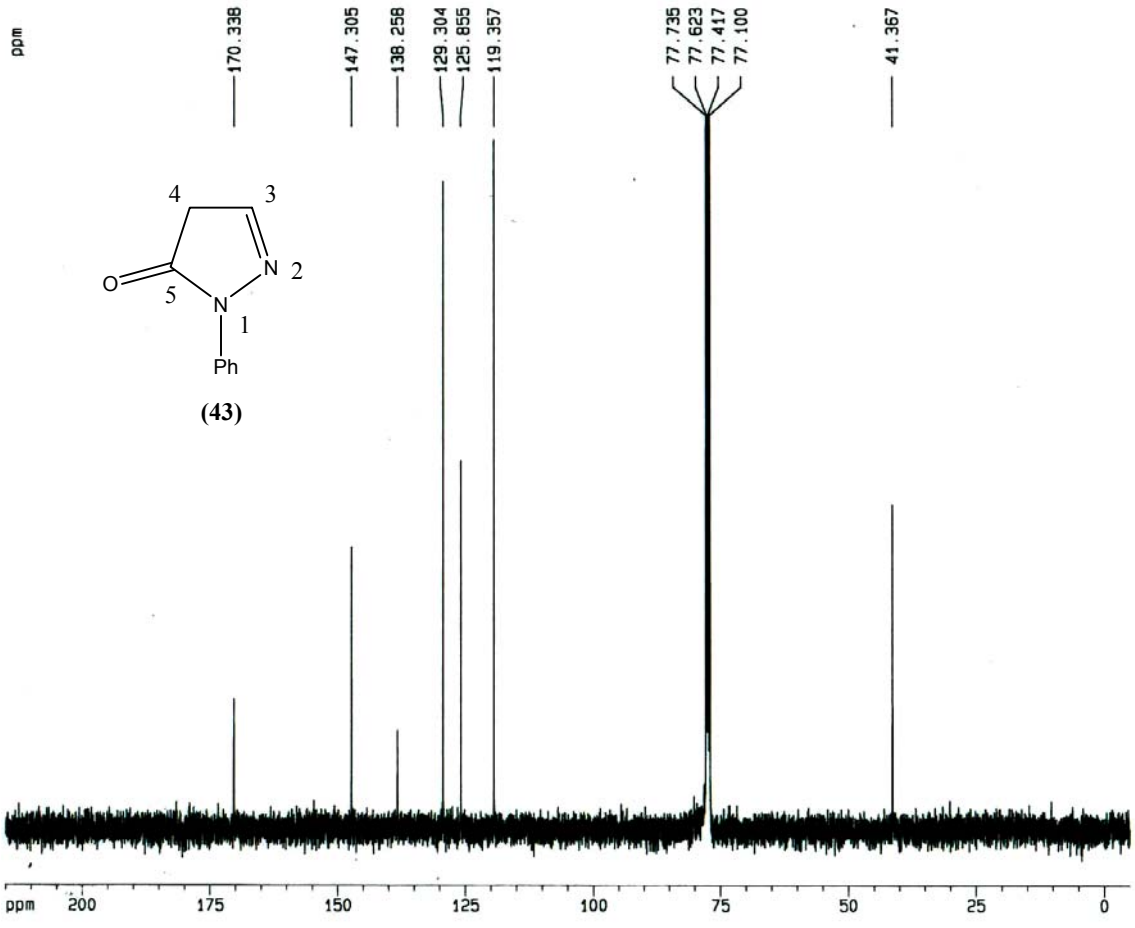


Figure 52(a) shows that the ^{1}H NMR spectrum of the white solid compound is consistent with the structure **43.** The proton at C-3 of the pyrazolone ring appears as a 1H singlet at δ 7.45, while the α-carbonyl protons of the pyrazolone ring appear as a 2H singlet at δ 3.50. Finally, the 2H doublet (J = 8.6 Hz) at δ 7.83, the two triplets at δ 7.36 (2H; J = 7.8 Hz), and 7.18 (1H; J = 7.6 Hz) are characteristic of the phenyl protons at ortho, meta, and para positions, respectively.

(b)



The ^{13}C-NMR spectrum (Figure 52(b)) is also consistent with the structure **43**. The carbonyl carbon of the pyrazolone ring absorbs the furthest downfield at δ 170.3.

Unambiguously, the sp^2 carbon at C-3 absorbs at δ 147.3, while the signal at 41.37 is due to the α-carbonyl carbon of the pyrazolone ring. Finally, the signals at δ 138.3, 129.3, 125.9, and 119.4 are due to the quaternary, meta, para, and ortho carbons of the phenyl ring, respectively.

(c)

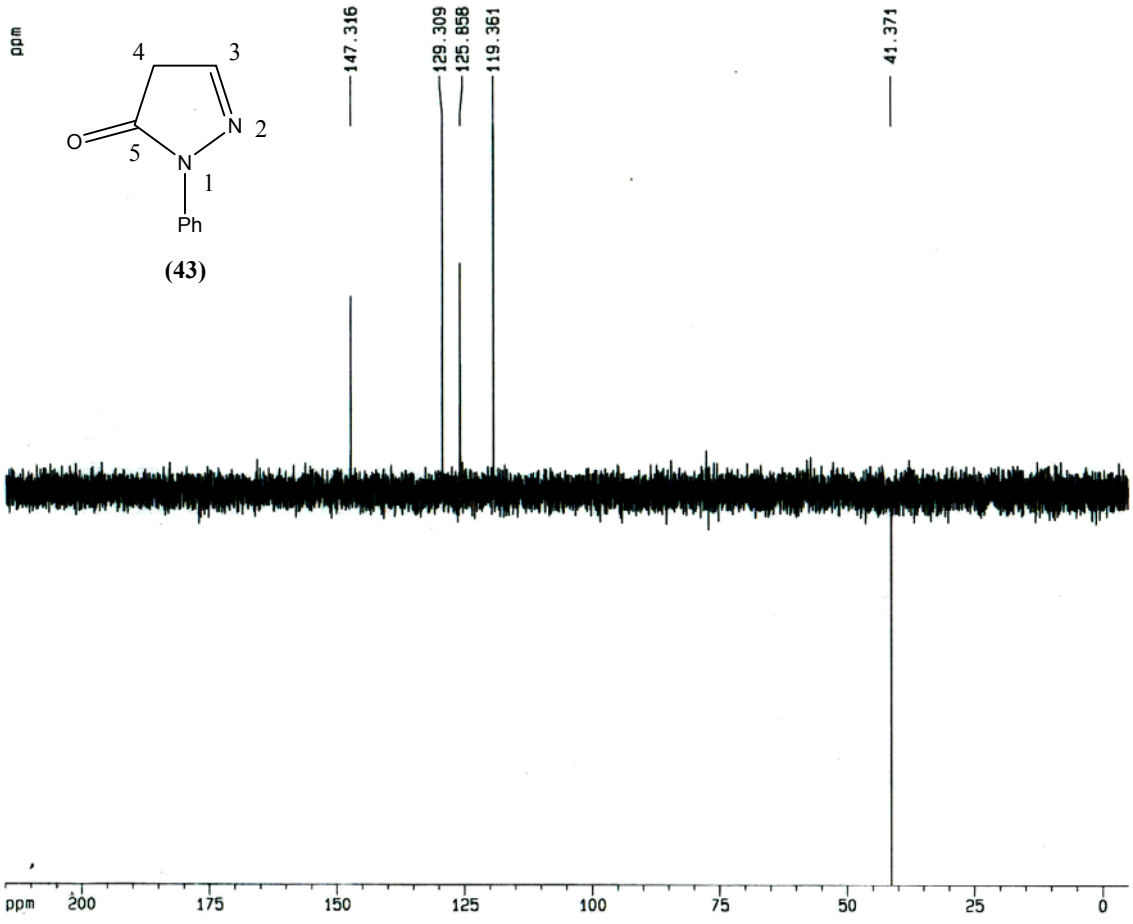
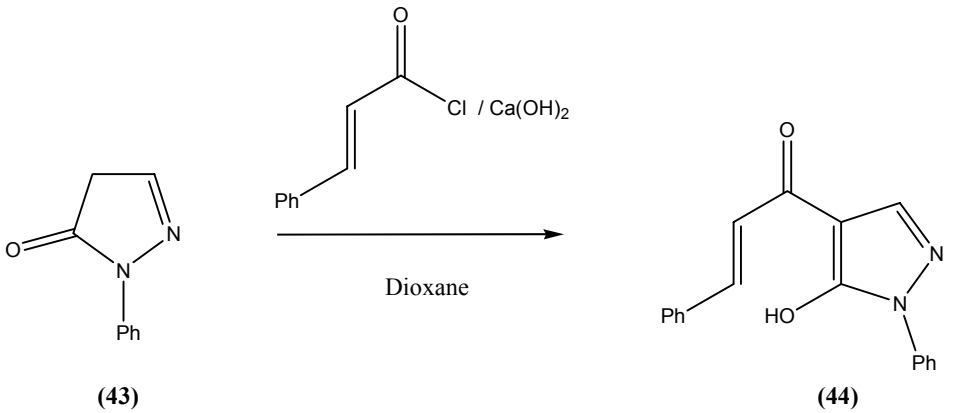


Figure 52: (a) ^{1}H-NMR of compound **43**; (b) ^{13}C-NMR of compound **43** and (c) ^{13}C-NMR DEPT 135 of compound **43**.

These assignments are consistent with the ^{13}C-DEPT 135 spectrum (Figure 52(c)). As expected, the two signals at δ 170.3 and 138.3 disappeared which is

consistent with the C-5 carbonyl carbon of the pyrazolone ring and the quaternary carbon of the phenyl ring. But, the signals at δ 147.3, 129.3, 125.9, and 119.4 still appear in the positive direction, which is consistent with the assignment to the CH type carbon of the pyrazolone ring at C-3 and the three CH type carbons of the phenyl ring. The signal at δ 41.37, however, appears in the negative direction confirming that this signal is due to a CH_2 type carbon of the pyrazolone ring at C-4.



(43) **(44)**

Scheme 46: Synthesis of (*E*)-1-(5-hydroxy-1-phenyl-1*H*-pyrazol-4-yl)-3-phenylprop-2-en-1-one **(44)**.

Based on synthetic approach by Heinisch, G. and colleagues,[4] treatment of N-phenylpyrazolone **43** with *E*-cinnamoyl chloride in a suspension of calcium hydroxide led to the orange crystalline (*E*)-1-(5-hydroxy-1-phenyl-1*H*-pyrazol-4-yl)-3-phenylprop-2-en-1-one **(44)** in a yield of 88%, mp 175-176^{o}C (Lit.[10] mp 182-183^{o}C) (Scheme 46).

(a)

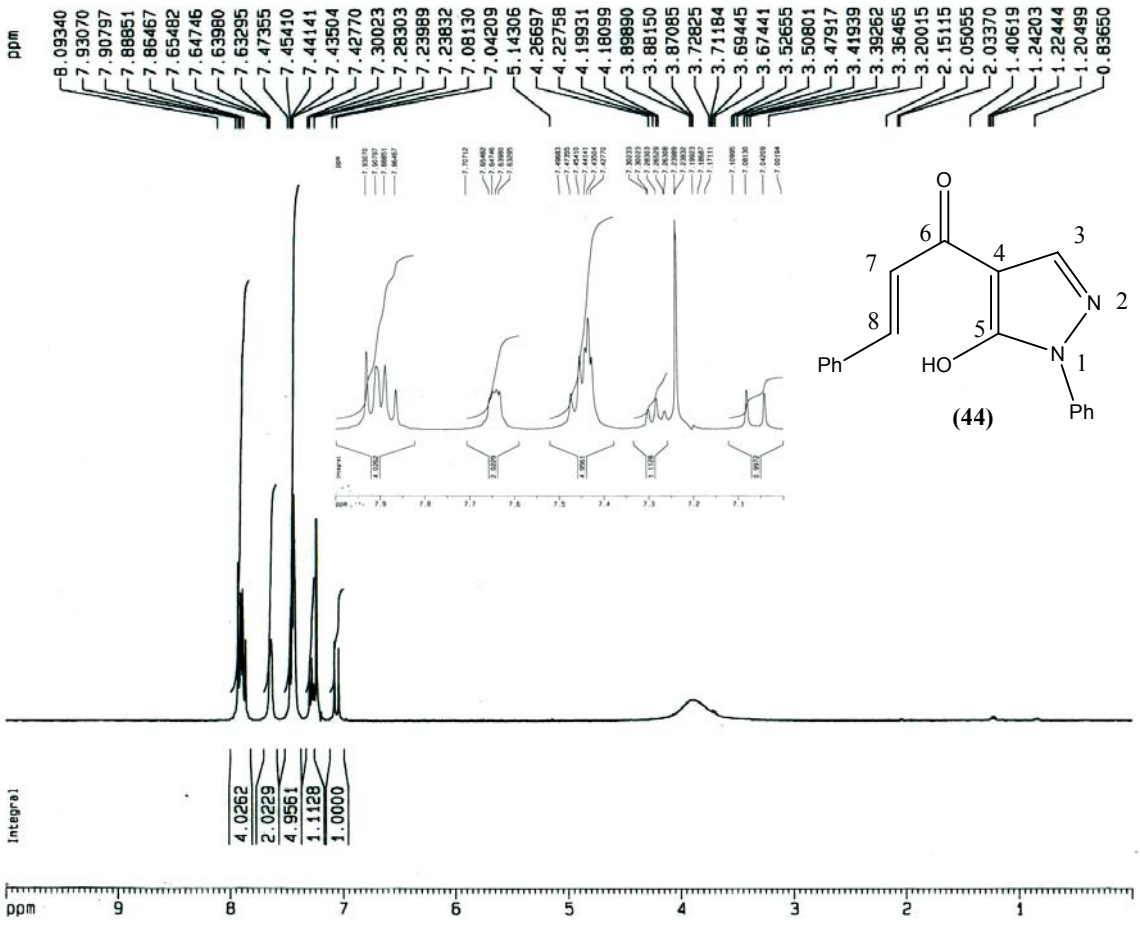
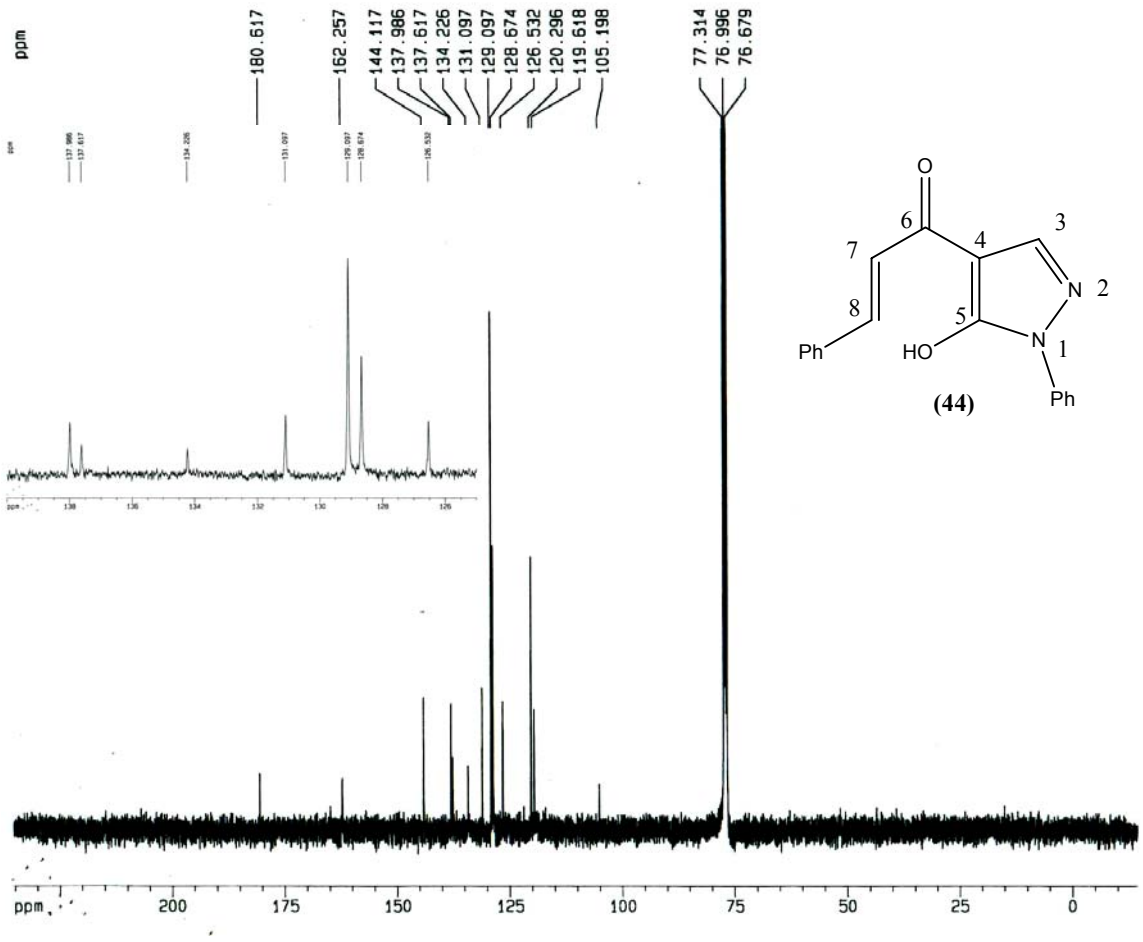


Figure 53(a) shows that the ^{1}H-NMR spectrum of the orange crystalline product is consistent with the structure **44**. The proton at C-3 of the pyrazole ring appears as a 1H singlet at δ 7.93. The protons of the α, β-unsaturated side chain appear as a pair of 1H doublets (J = 15.8 Hz) at 7.05 and 7.88 for the α and β protons, respectively due to trans isomer. The protons of the N-phenyl group are observed as 2H multiplets at δ 7.93 and 7.46 for protons at the ortho and meta positions, respectively, and a 1H multiplet at δ 7.29 for the para proton. The protons of the C-8 phenyl ring appear as a 2H multiplet at δ 7.64 for the ortho protons, while the meta and para protons appear as a 3H multiplet at δ 7.44.

(b)



The ^{13}C-NMR spectrum (Figure 53(b)) is also consistent with the structure **44**. The carbonyl carbon of the β unsaturated side chain absorbs the furthest downfield at δ 180.6, while the α and β carbons absorb at δ 119.6 and 144.1, respectively. The C-3, C-4, and C-5 carbons of the pyrazole ring were assigned to the signals at δ 137.9, 105.2, and 162.3, respectively. The N-phenyl ring carbons at the quaternary and the para positions absorb at δ 137.6 and 126.5, while the carbons at the ortho and meta positions appear as singlets at δ 120.3 and 129.1, respectively. On the other hand, the C-8 phenyl ring carbons at the quaternary and para positions absorb at δ 134.2 and 131.1, while the ortho and meta carbons absorb at δ 128.7 and 129.1, respectively.

(c)

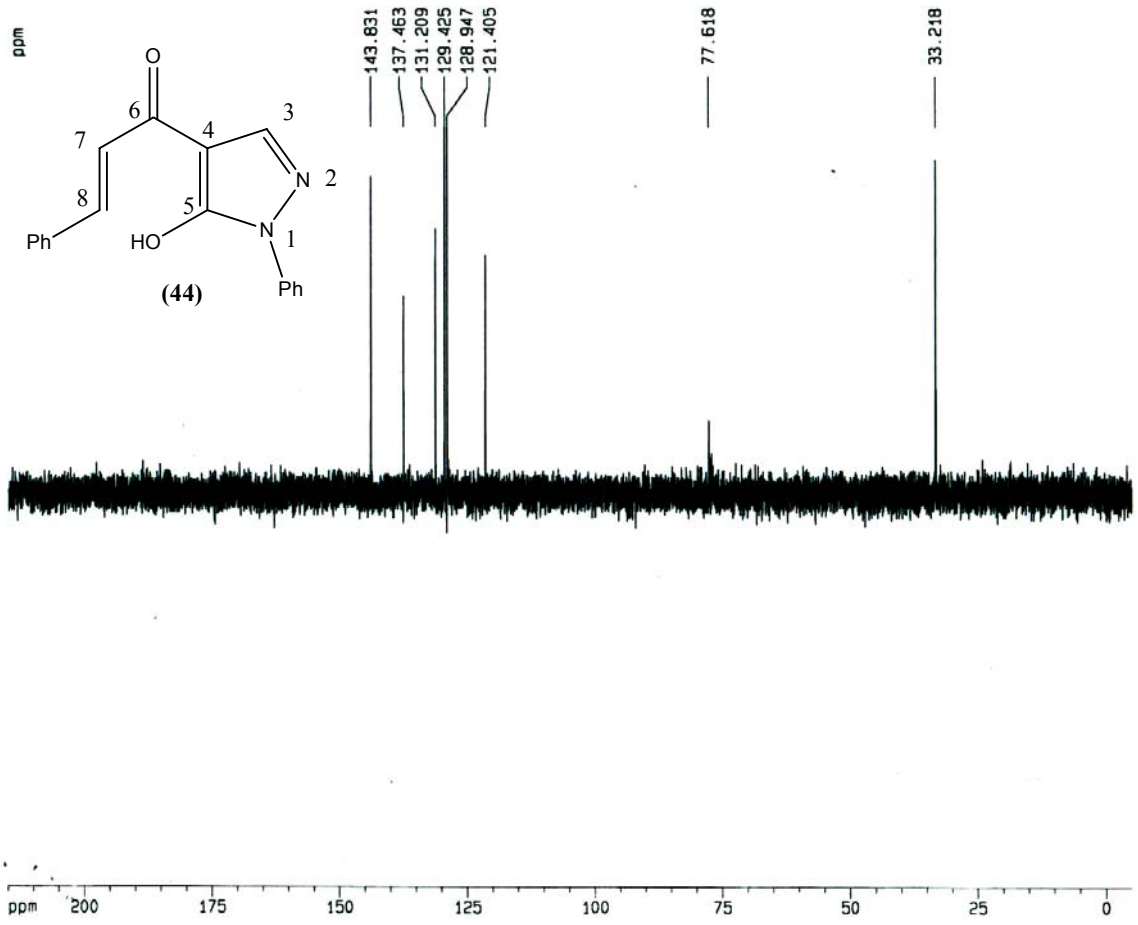
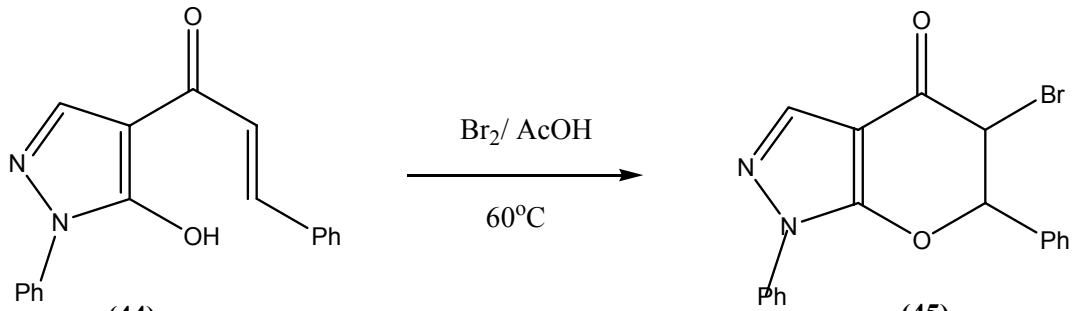


Figure 53: (a) ^{1}H-NMR of compound **44**; (b) ^{13}C-NMR of compound **44**; (c) ^{13}C-NMR DEPT 135 of compound **44**.

As expected, the ^{13}C-NMR DEPT 135 spectrum (figure 53(c)) of compound **44** shows that the five signals at δ 180.6, 162.3, 137.6, 134.2, and 105.2 disappeared which is consistent with their assignment to the quaternary carbons of **44** due to the carbonyl carbon, C-4 and C-5 carbon atoms of the pyrazole ring, and the quaternary carbons of the phenyl rings. On the other hand, the signals at δ 144.1, 137.9, 131.1, 129.1, 128.7,

126.5, 120.3, and 119.6 appear in the positive direction which is consistent with their assignment to the CH carbon on the pyrazole ring, the α and β alkene carbons, and the three CH type carbons at the ortho, meta, and para positions of each phenyl ring.

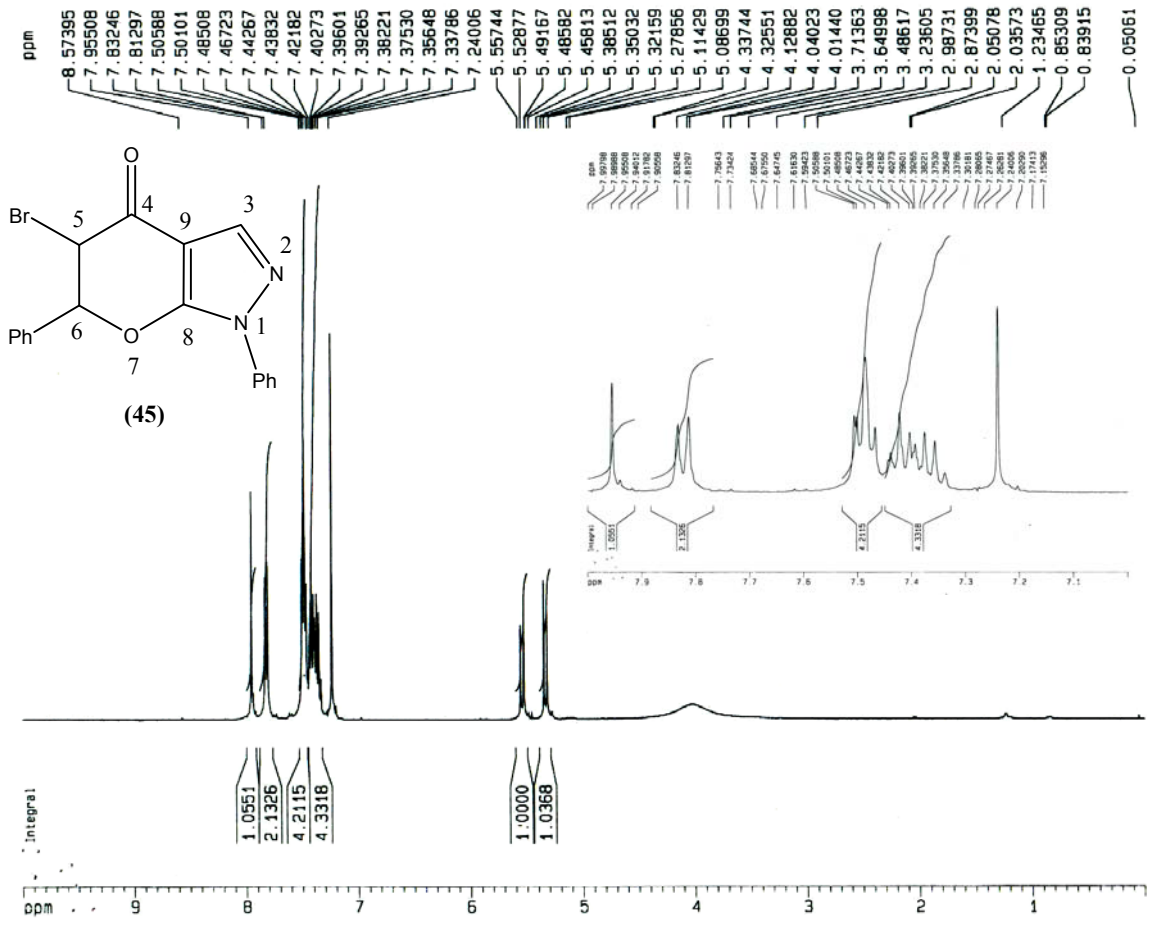


(44) **(45)**

Scheme 47: Synthesis of 5-bromo-1,6-diphenyl-5,6-dihydropyrano[2,3-*c*]pyrazol-4(1*H*)-one **(45)**.

Bromination of **44** with Br_2 in acetic acid at 60°C led to the formation of the new compound 5-bromo-1,6-diphenyl-5,6-dihydropyrano[2,3-*c*]pyrazol-4(1*H*)-one **(45)** in a yield of 47%, mp 173-175°C (Scheme 47). **45** is the key precursor of the pyranopyrazole unsubstituted at ring position 3 of the pyrazole ring.

(a)

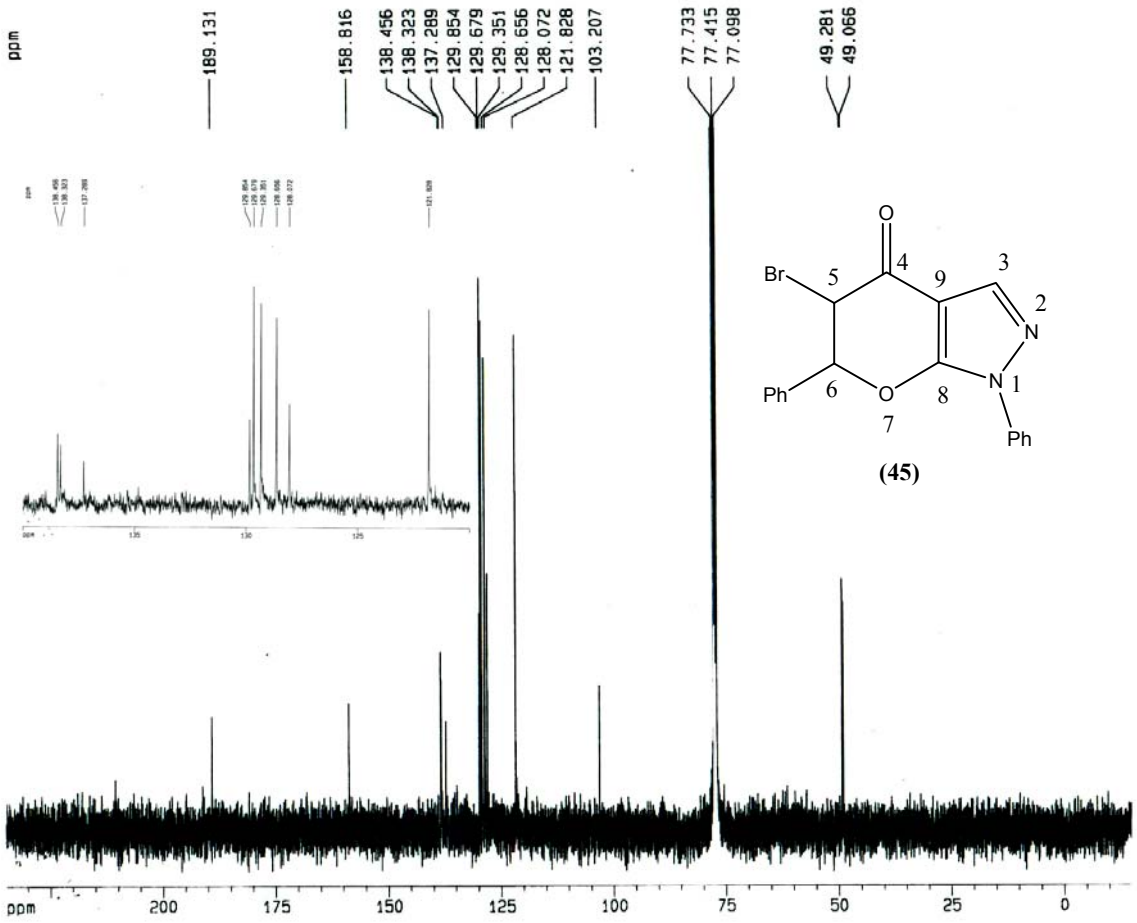


(45)

Figure 54(a) shows that the ^{1}H-NMR spectrum of the white crystals is consistent with the structure **45**. The proton at C-3 of the pyrazole ring appears as a 1H singlet at δ 7.96. The N-phenyl protons appear as a 2H doublet (J = 7.8 Hz) at δ 7.81, a 2H multiplet signal at δ 7.46 and a 1H multiplet at δ 7.35 for protons at the ortho, meta, and para positions, respectively. On the other hand, the protons of the C-6 phenyl group appear as a 3H multiplet at δ 7.37 due to absorptions of the protons at the meta and para positions, and a 2H multiplet at δ 7.46 due to the ortho protons. Finally, the C-5 and C-

6 protons appear as a pair of 1H doublets (J = 11.4 Hz) at 5.09 and 5.53, respectively, which are due to the cis isomer.

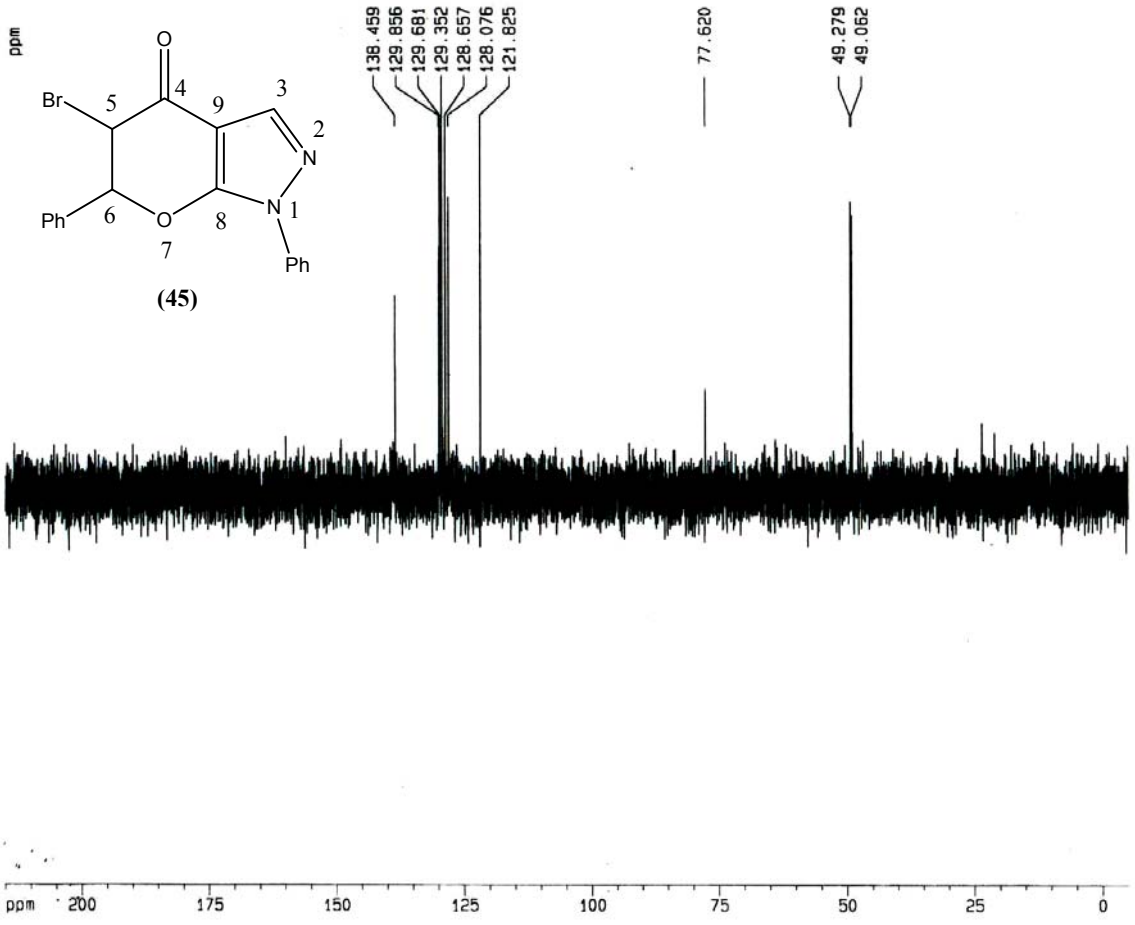
(b)



The ^{13}C-NMR spectrum (Figure 54(b)) is also consistent with the structure **45**. The carbonyl carbon of the pyrone ring absorbs the furthest downfield at δ 189.1. The signals at δ 158.8 and δ 103.2 were assigned to the bridgehead carbons at positions 8 and 9, respectively. The sp^3 carbons at positions 5 and 6 of the dihydropyrone ring appear at δ 49.07 and 49.28, respectively. The C-3 carbon of the pyrazole ring was assigned to the signal at δ 138.5. The phenyl ring carbon attached to the nitrogen atom

and at the para position absorb at δ 137.3 and 129.9 respectively, while the ortho and meta carbons in the phenyl ring appear as two singlets at δ 128.7 and 129.4, respectively. On the other hand, the quaternary and the para carbons of the N-phenyl ring absorb at δ 138.3 and 128.1, while the ortho and meta carbons of the ring appear as two singlets at δ 121.8 and 129.7, respectively.

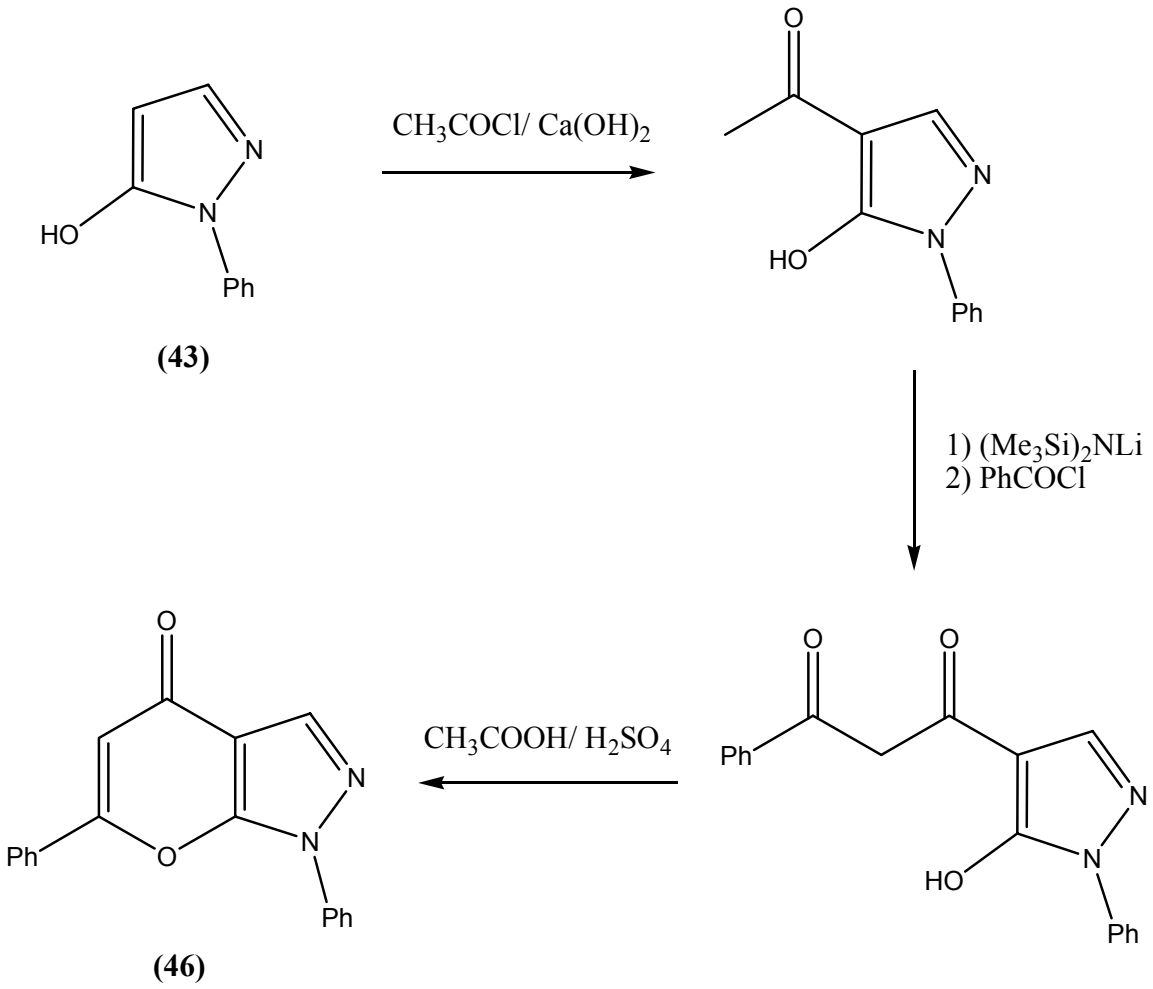
(c)



(45)

Figure 54: (a) ^{1}H NMR of compound **45**; (b) ^{13}C NMR of compound **45**; (c) ^{13}C NMR DEPT 135 of compound **45**.

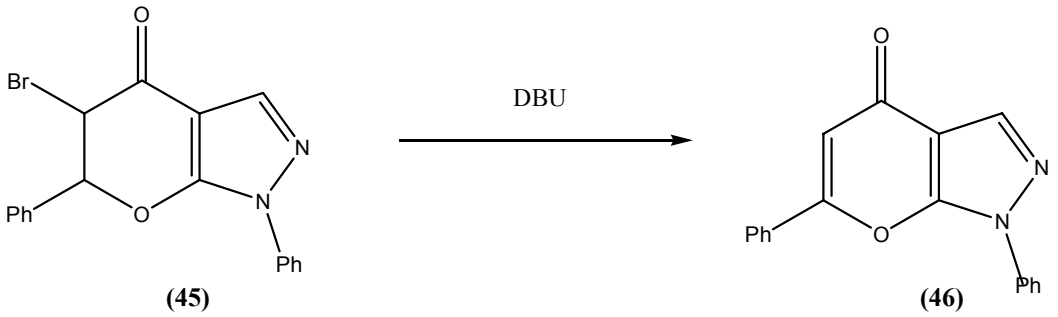
These assignments are also consistent with the ^{13}C-DEPT 135 spectrum (Figure 54(c). The five signals at δ 189.1, 158.8, 138.3, 137.3, and 103.2 disappeared which is consistent with their assignment to the five quaternary carbons in the structure. In addition, the signals at δ 138.5, 129.9, 129.7, 129.3, 128.7, 128.1, 121.8, 49.28, and 49.06 still appear in the positive direction which is consistent with their assignment to the three CH type carbons at ortho, meta, and para position of each phenyl rings, the two CH type carbons at C-5 and 6 of the pyrone, and the CH type carbon at C-3 of the pyrazole ring.



(43)

(46)

According to literature,[10] 1,6-diphenylpyrano[2,3-*c*]pyrazole-4(1*H*)-one **(46)** is a known compound,[10] which was synthesized by cyclization of β-diketone with sulfuric acid in glacial acetic acid.



(45) **(46)**

Scheme 48: Synthesis of 1,6-diphenylpyrano[2,3-*c*]pyrazole-4(1*H*)-one **(46)**.

In this work, the dehydrobromination of compound **45** to N-phenylpyranopyrazole **46** was achieved by heating **45** in dioxane containing an equivalent amount of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) at 90^{o}C to obtain **46** in a yield of 78%, mp 184-185^{o}C (Lit.[10] mp 177-180^{o}C) (Scheme 46).

(a)

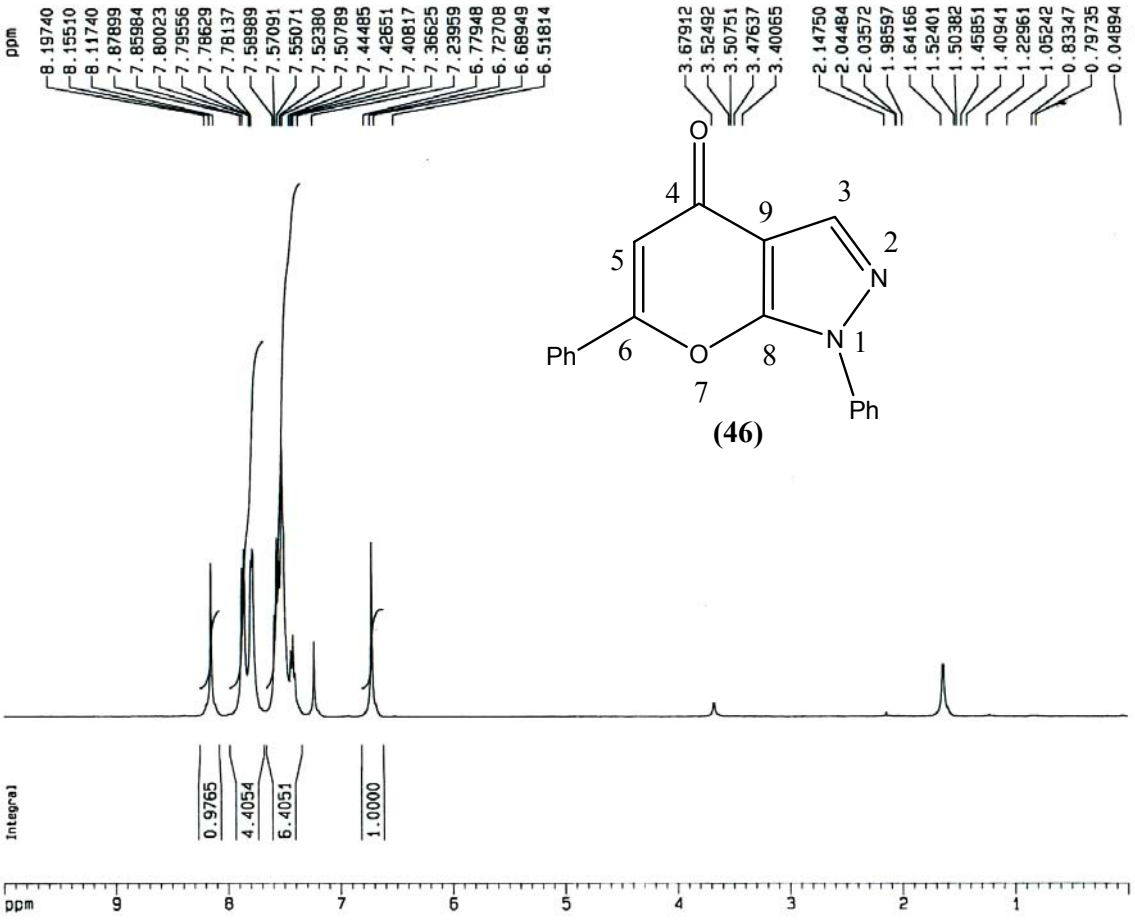
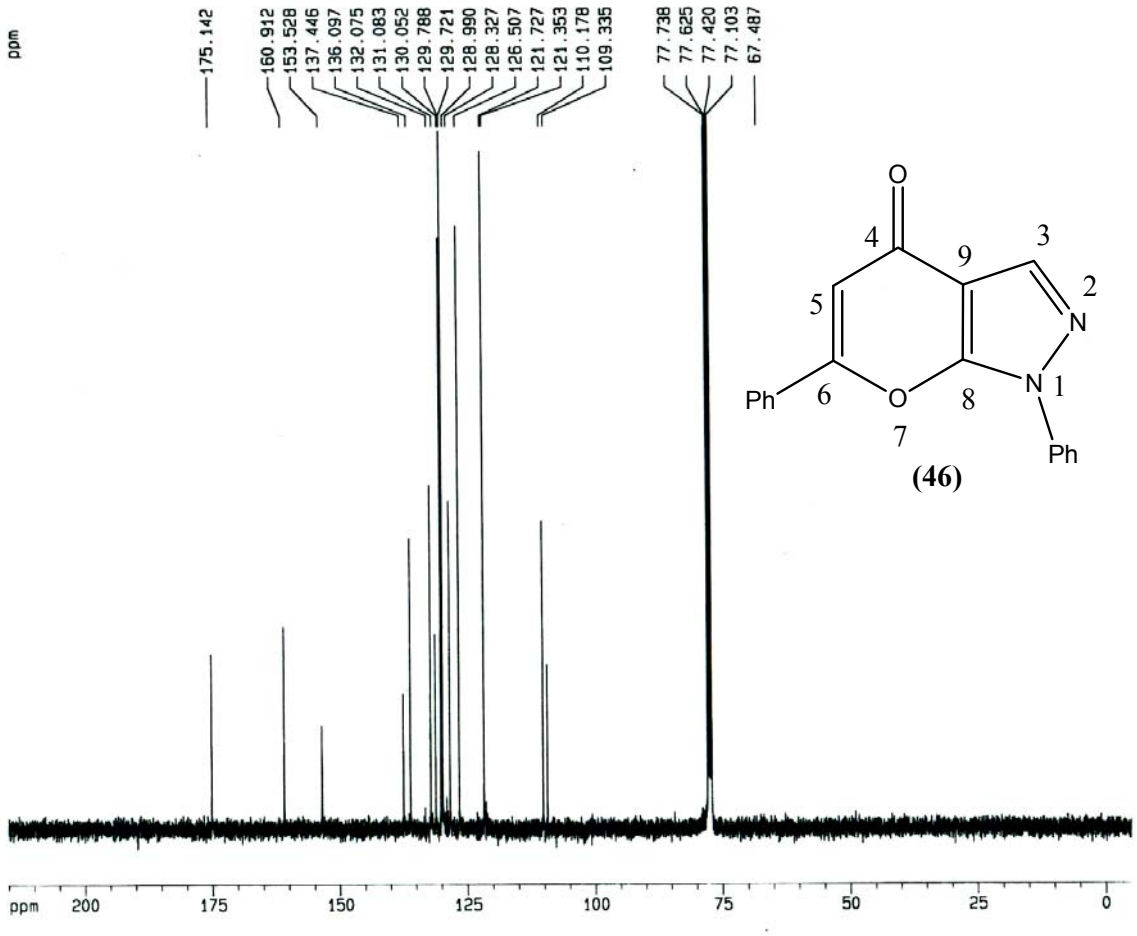


Figure 55(a) shows that the ^{1}H-NMR spectrum of the colorless crystals obtained in the previous experiment is consistent with the structure of **46**. The C-3 proton appears as a 1H singlet at δ 8.18, while the key signal due to the C-5 proton of the pyrone ring appears as a 1H singlet at δ 6.77. The protons of the C-6 phenyl group appear as a 2H multiplet at δ 7.82 due to absorption of the protons at ortho position, and a 3H multiplet at δ 7.53 is due to the protons at the meta and para positions of the phenyl ring. Finally, the protons of the N-phenyl appear as a 2H multiplet at δ 7.89 due

to the ortho protons. The 2H multiplet at δ 7.59 is due to the protons at the meta position, while the 1H multiplet at δ 7.45 is due to the para proton.

(b)



(46)

The ^{13}C-NMR spectrum (Figure 55(a)) is also consistent with the structure **46**. The carbonyl carbon of the pyrone ring absorbs the furthest downfield at δ 175.1. The signals at δ 153.5 and δ 109.3 were assigned to the bridgehead carbons at positions 8 and 9, respectively. The pyrone ring carbons in positions 5 and 6 appear at δ 110.2 and 160.9, respectively. The sp^2 carbon of the C-3 pyrazole ring was assigned to the signal at δ 136.1. The quaternary and the para carbons of the phenyl ring at C-6 absorb at δ

131.1 and 132.1 respectively, while the ortho and meta carbons in the phenyl ring appear as two singlets at δ 126.5 and 129.8, respectively. On the other hands, the quaternary and para carbons of the N-phenyl ring appear at δ 137.4 and 128.9, respectively, while the signal at δ 130.1 and 121.7 were assigned to the meta and ortho carbons, respectively.

(c)

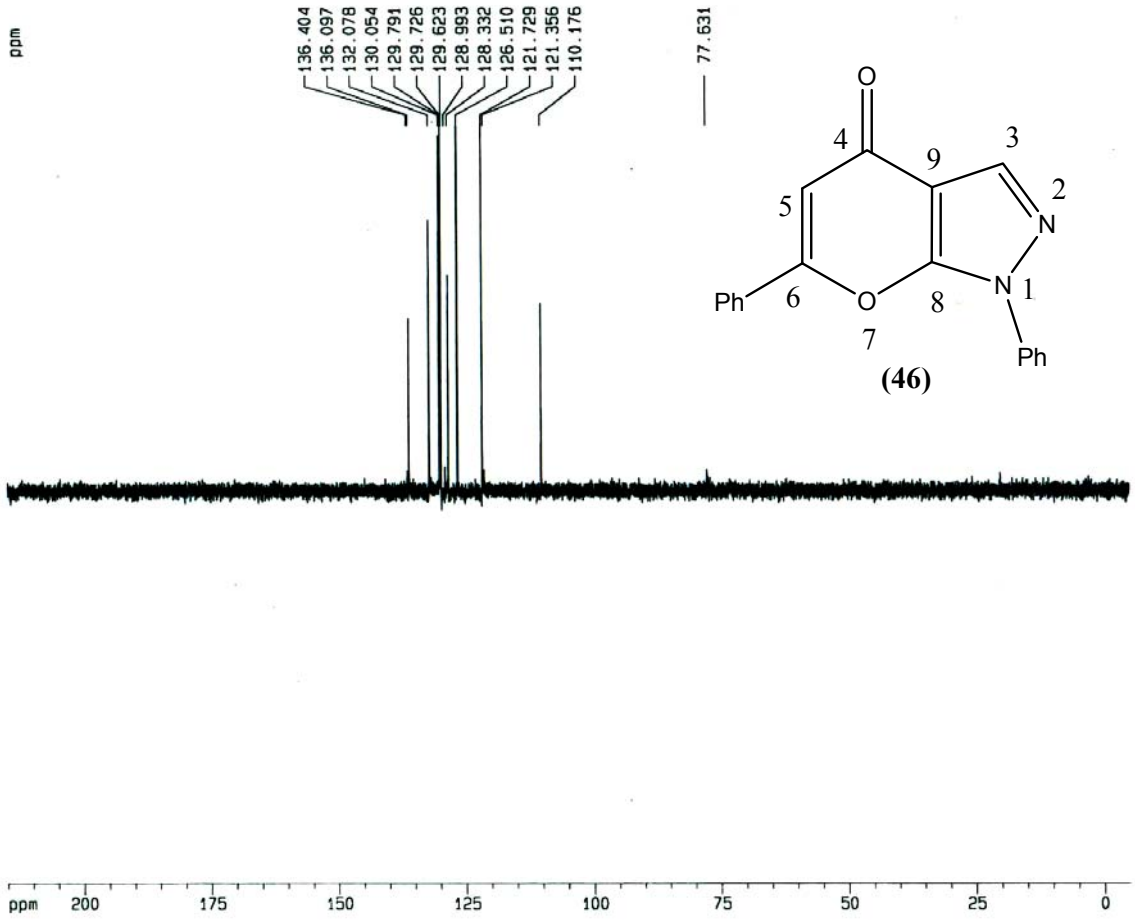


Figure 55: (a) ^{1}H-NMR of compound **46**; (b) ^{13}C-NMR of compound **46**; (c) ^{13}C-NMR DEPT 135 of compound **46**.

These assignments are consistent with the ^{13}C-DEPT 135 spectrum (Figure 55(c)). The six signals at δ 175.1, 160.9, 153.5, 137.4, 131.1, and 109.3 disappeared which is compatible with their assignment to the six quaternary carbons. In addition, the signals at δ 136.1, 132.1, 131.1, 130.1, 129.8, 128.9, 126.5, 121.7, and 110.2 still appear in the positive direction which is consistent with their assignment to the three CH type carbons of each the phenyl rings, and the CH type carbons at C-3 of the pyrazole ring and C-5 of the pyrone ring.

Photochemistry of 1,3,6-trimethyl-[2,3-*c*]pyrazole-4(1*H*)-one

Figure 56 shows the UV-absorption spectrum of an 8.0×10^{-5} M solution of **7** in acetonitrile (ACN) solution. The spectrum exhibits λ_{max} at 250.8 nm and 206.0 nm with extinction coefficients of 9,068 and 14,764 L mol^{-1} cm^{-1}, respectively. Considering the magnitude of these extinction coefficients, these two absorptions have been assigned to S_0 to S_1 (π,π^*) and S_0 to S_2 (π,π^*) transitions.

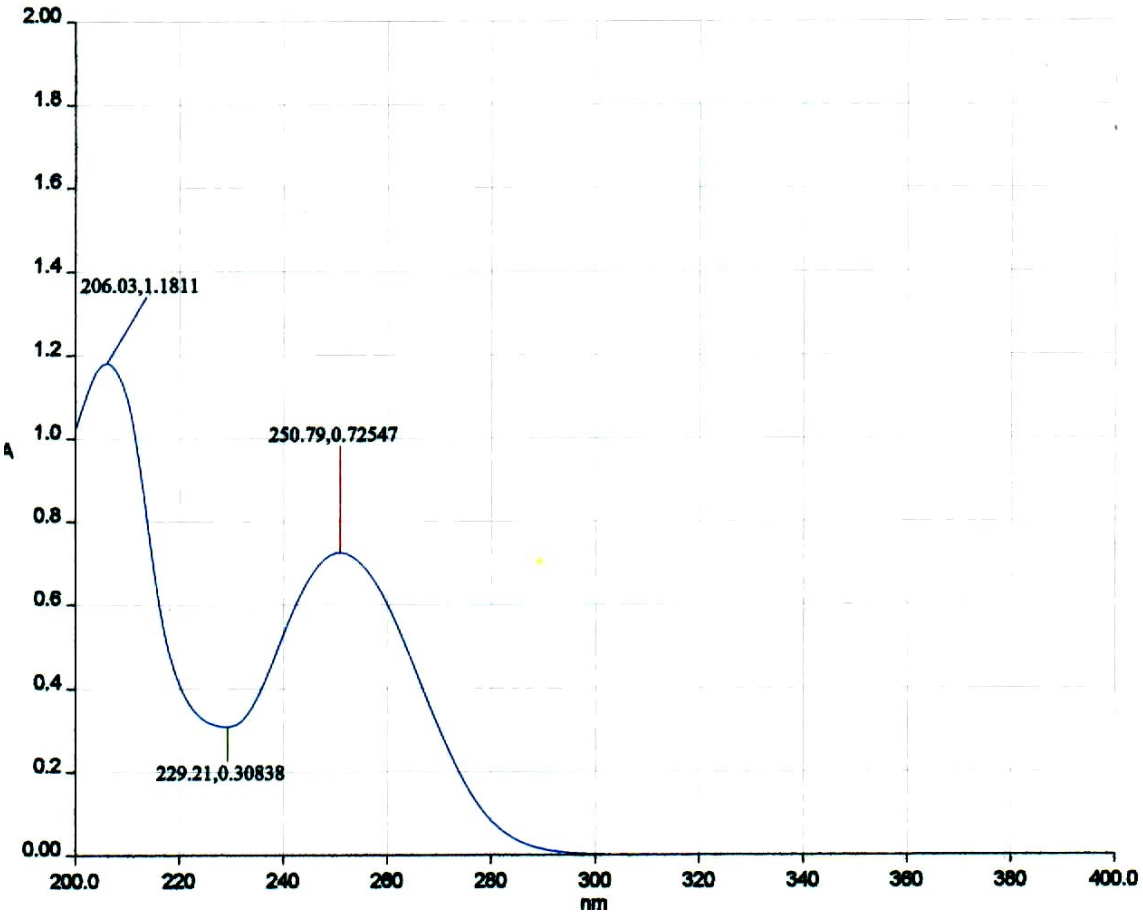


Figure 56: UV-absorption spectrum of **7** in acetonitrile (8.0×10^{-5} M).

Figure 57 shows the UV-absorption spectrum of the same solution before and after six consecutive 5 seconds irradiations at 254 nm. As the figure shows, irradiation

is accompanied by a decrease in the absorbance of the band at 250.8 nm from 0.73 to 0.61 and a shift from 250.8 to 251.1 nm. The absorption band at 206.0 nm decreases from 1.18 to 1.00.

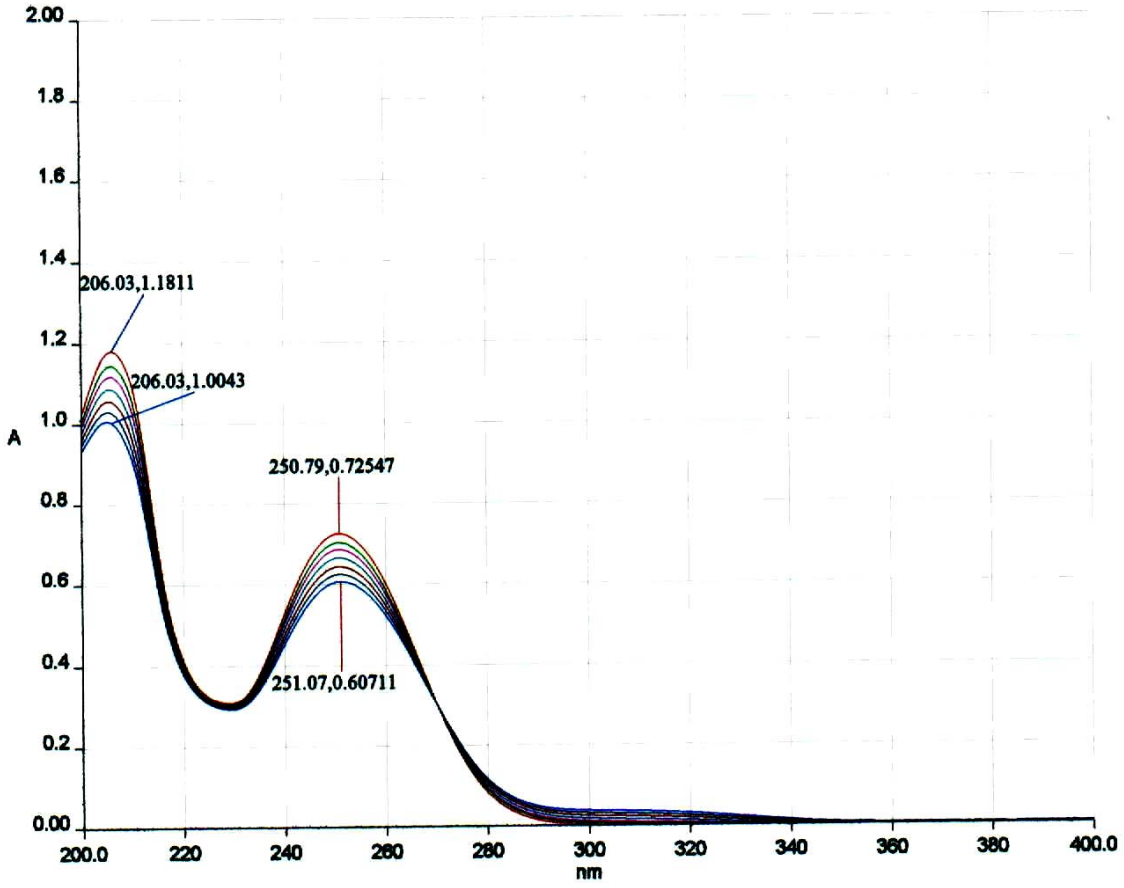


Figure 57: UV-overlay spectrum of the photolysis of **7** in acetonitrile (8.0×10^{-5}M).

The photochemical reaction of **7** was also monitored by HPLC. Figure 58 shows the HPLC trace of **7** (2.0×10^{-2} M) in ACN (methanol 75 : water 25; flow rate = 0.50 ml/ min; detector at 250 nm). The trace shows only one peak due to **7** with a retention of 7.26 minutes. The solution of **7** (2.0×10^{-2} M) in ACN was placed in a quartz tube (20 cm long × 0.7 cm id). The tube was sealed with a rubber septum, purged with

helium for 15 minutes, and irradiated at 254 nm with thirteen lamps. Aliquots were removed for HPLC analysis after 5, 10, 30, 45, 60, and 90 minutes of irradiation. Figure 59 shows the HPLC trace after 10 minutes of irradiation and reveals the formation of a product peak with a retention of 6.7 minutes.

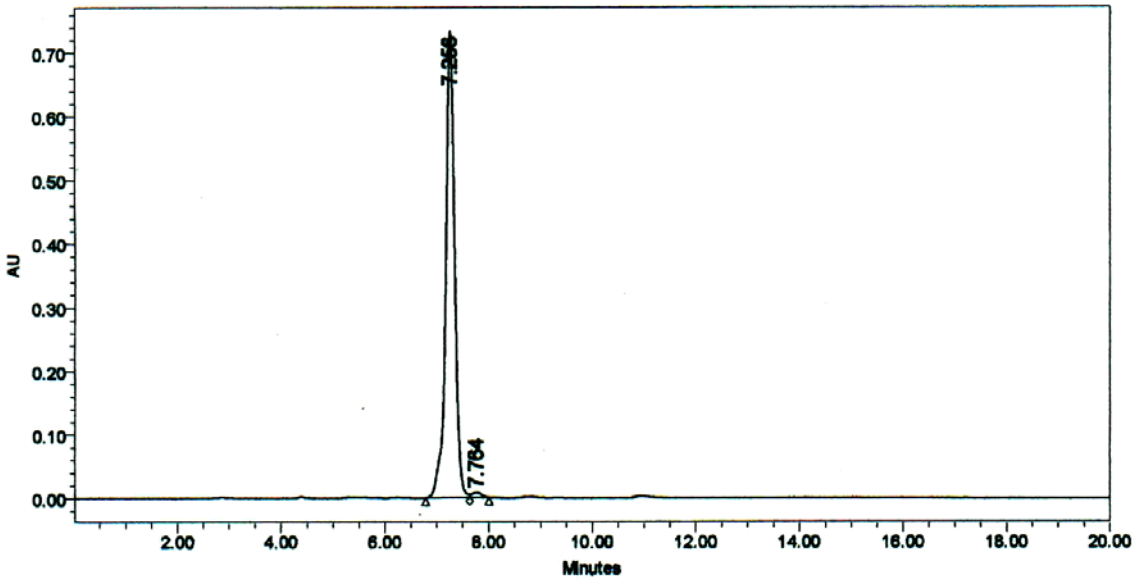


Figure 58: HPLC-trace of the solution **7** before irradiation.

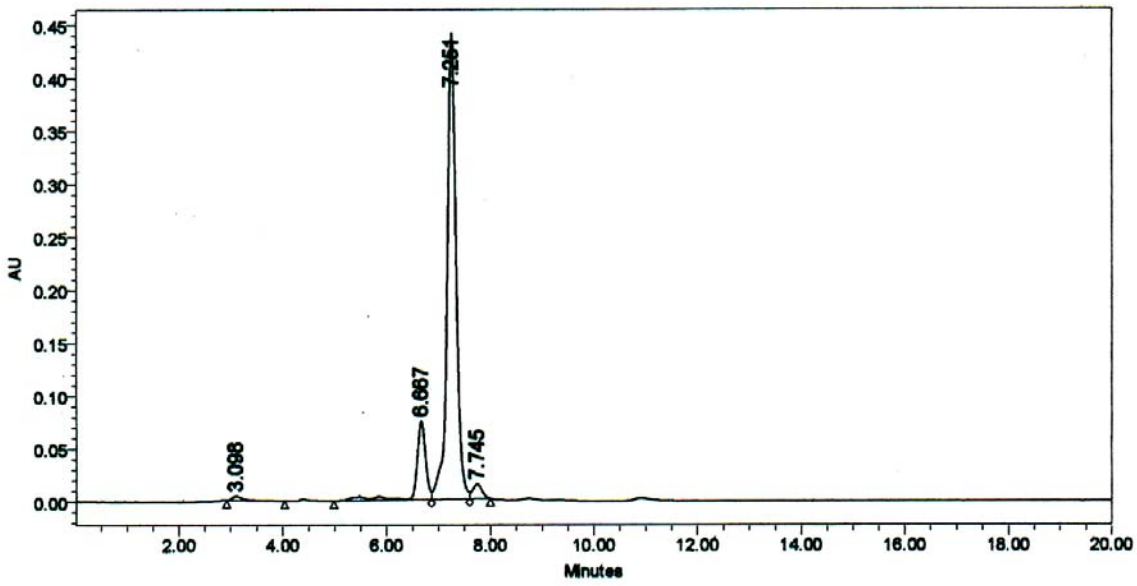


Figure 59: HPLC report of the solution of **7** after 10 minutes of irradiation.

Figure 60 shows how these peak areas changed during the irradiation time. The figure shows a continuous decrease in the peak area of the reactant indicating continuous consumption of the reactant during the 90 minutes of irradiation.

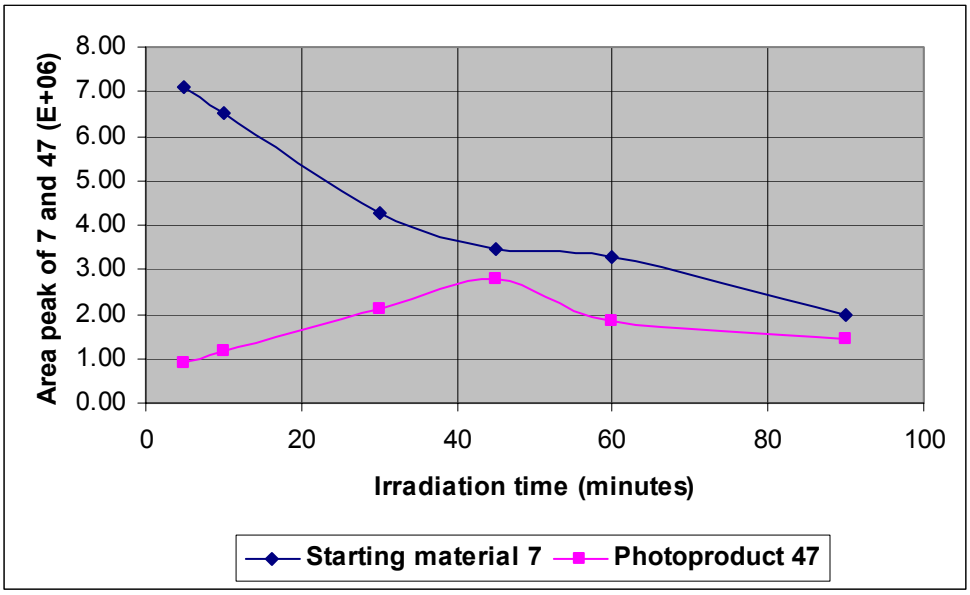


Figure 60: The correlation between the irradiation time of **7** and Area peak of **7** and **47**.

As shown in the graph, however, there is a change in the slope at approximately 45 minutes of irradiation indicating that after that time there was a decrease in the rate of reactant consumption. The figure shows that the peak area due to the product increases during the first 45 minutes of irradiation and then slowly decreases upon longer irradiation time. This indicates that after 45 minutes of irradiation the product competes with the reactant for the incident light and begins to be consumed in a secondary photoreaction.

In order to isolate the photoproduct, a second solution of **7** (2.0×10^{-2}M) in ACN was irradiated until HPLC analysis indicated maximum formation of the photoproduct. Preparative-layer chromatography of the resulting solution revealed a band at $R_f = 0.40$ due to the unconsumed reactant **7** and three additional bands at $R_f =$ 0.65, 0.25, and 0. Although extraction of the bands at $R_f = 0.65$ and 0 resulted in negligible recovery of any material, extraction of the band at $R_f = 0.25$ provided a white crystalline product, mp 229-230°C.

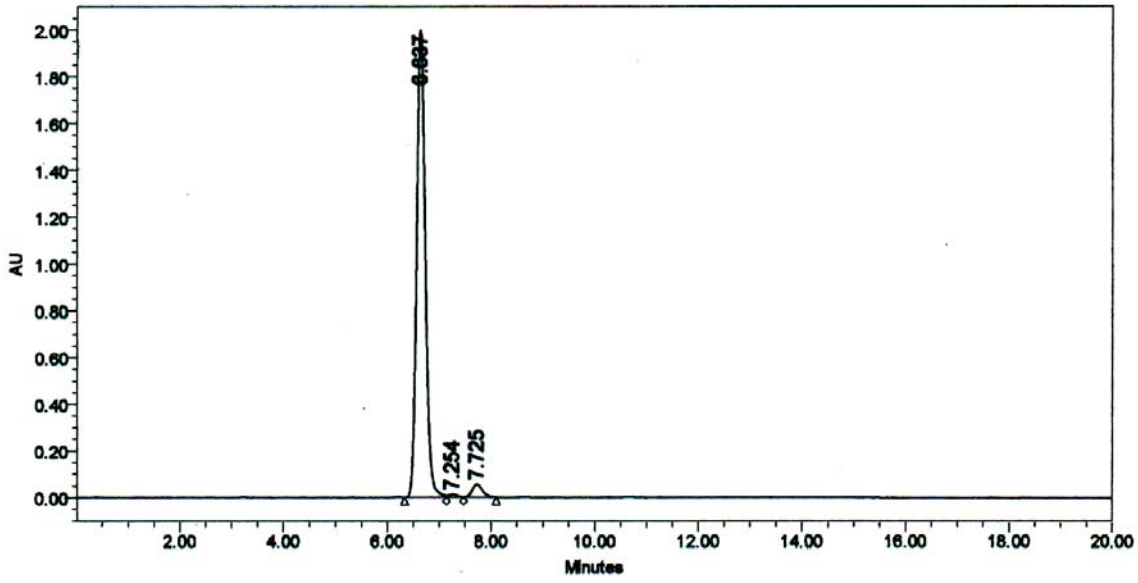


Figure 61: HPLC-trace of an isolated product of **47**

HPLC analysis of an ACN solution of this material in Figure 61 showed a single peak with a retention time identical to the retention time of the product peak shown in Figure 59. This confirms that the isolated white crystalline compound is the photoproduct observed by HPLC.

This photoproduct was also analyzed by gas chromatography-mass spectrometer. Figure 62 shows the gas chromatogram which exhibits a single peak with a retention of 6.8 minutes. The mass spectrum of the material at this retention time is shown in Figure 63 and reveals a molecular ion at m/z = 356 with major fragments at m/z 218, 139, and 80.

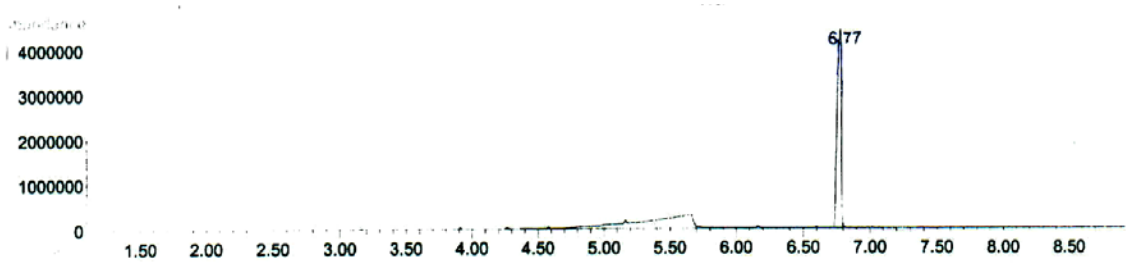


Figure 62: GC-trace of photoproduct **47**

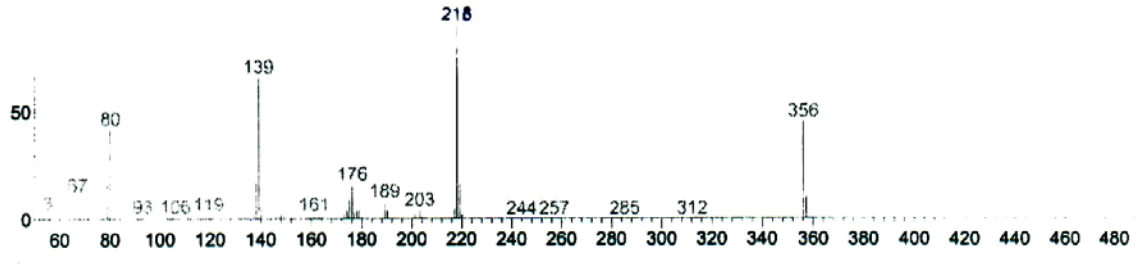
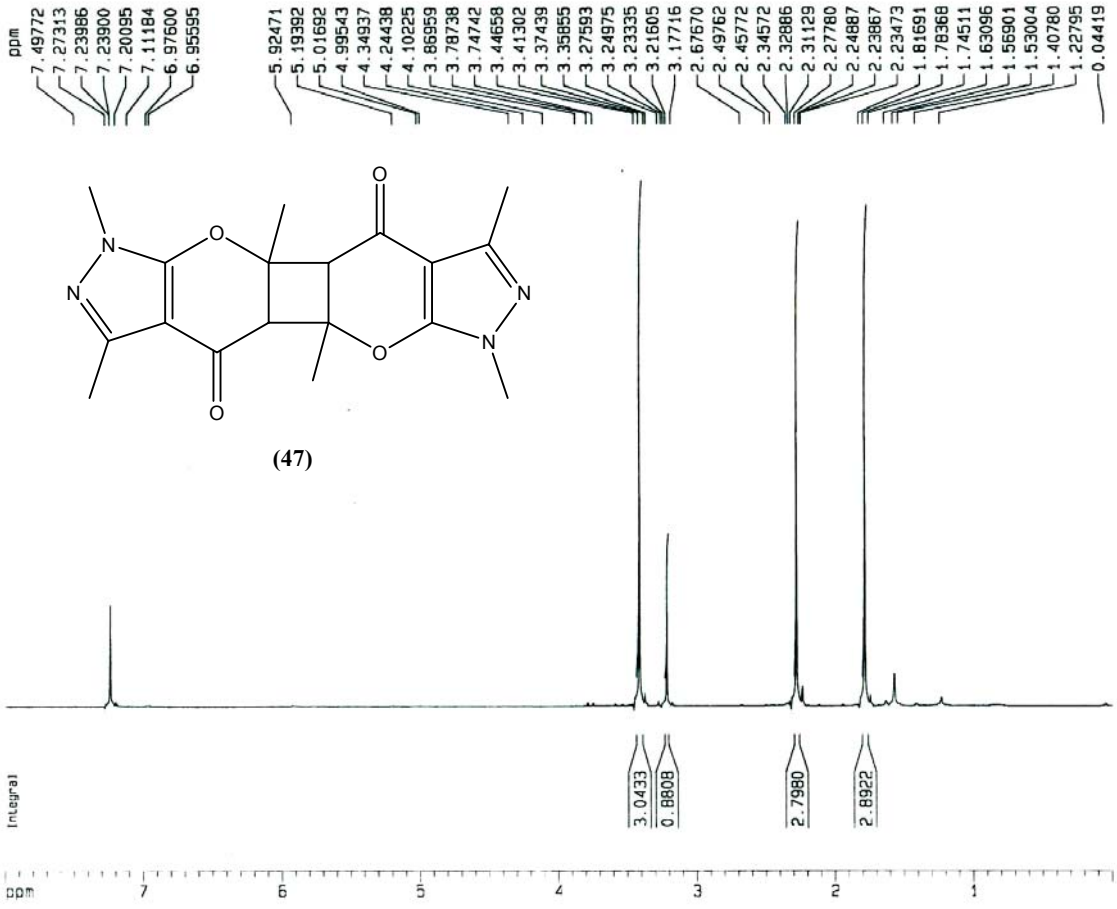


Figure 63: Mass spectrum of the photoproduct **47**

The molecular ion at m/z 356 is exactly twice the mass of the reactant which has a molecular weight of 178. The mass spectrum thus shows that the photoproduct is a dimer of the reactant. Elemental analysis of the photoproduct showed 60.60 % carbon,

5.56 % hydrogen, and 15.52 % nitrogen which is consistent with the molecular formula of $C_{18}H_{20}N_4O_4$, the correct formula of a dimer.

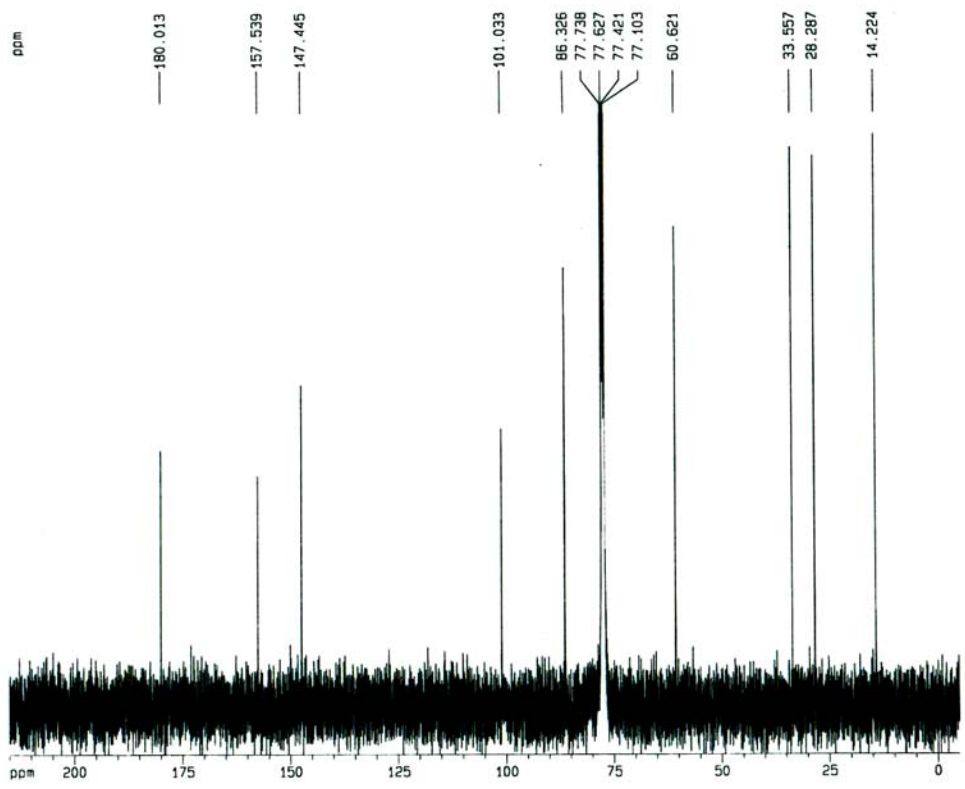
(a)



(47)

The ^{1}H-NMR spectrum of the photoproduct (Figure 64 (a)) shows signals at δ 1.78, 2.28, 3.41, and 3.22 with an integrated ratio of 3:3:3:1. Thus, although the molecular formula is consistent with the presence of six methyl groups, the ^{1}H-NMR shows the presence of these different sets of methyl groups. This means that each set contains two methyl groups.

(b)


ppm
180.013
157.539
147.445
101.033
86.326
77.738
77.627
77.421
77.103
60.621
33.557
28.287
14.224
ppm 200 175 150 125 100 75 50 25 0

(c)

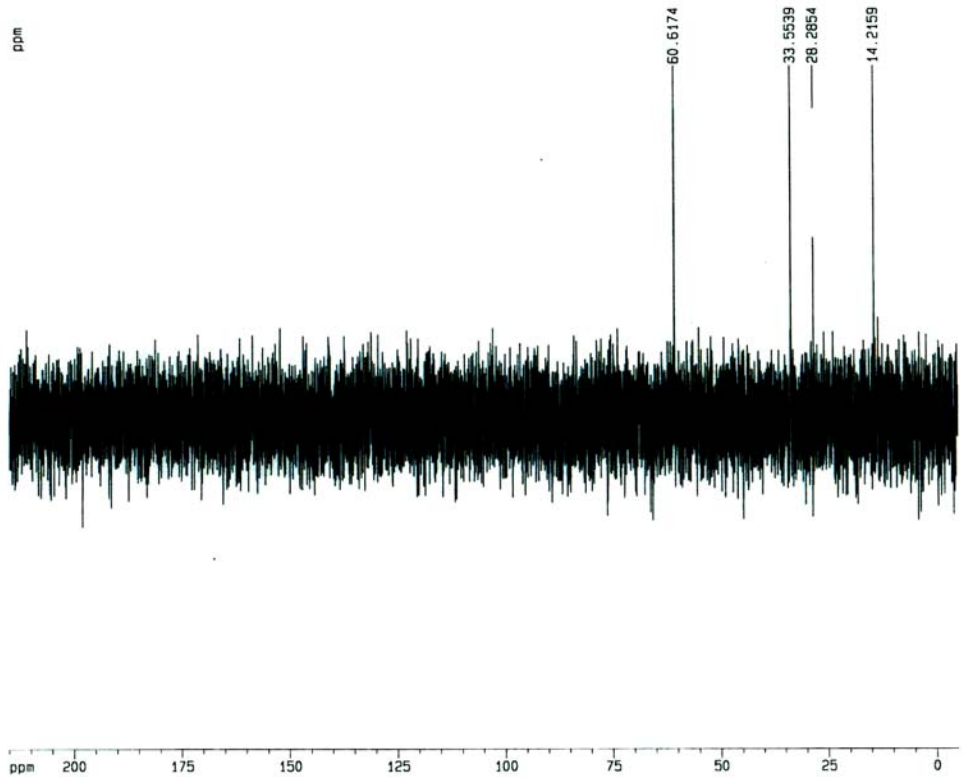
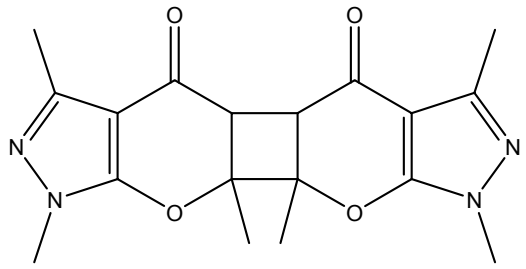
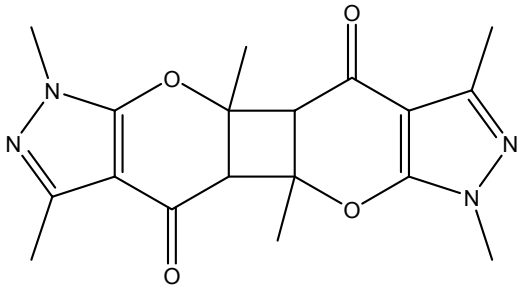

ppm
60.6174
33.5539
28.2854
14.2159
ppm 200 175 150 125 100 75 50 25 0

Figure 64: (a) ^{1}H-NMR of compound **47**; (b) ^{13}C-NMR of compound **47** and (c) ^{13}C-NMR DEPT 135 of compound **47**

The ^{13}C-NMR spectrum in Figure 64 (b) shows the presence of nine different sets of carbon atoms and the ^{13}C-NMR DEPT 135 spectrum in Figure 64 (c) shows the presence of four different sets of positive carbon atoms. Since the molecular formula shows that the photoproduct contains 18 carbon atoms, each set must contain two identical carbon atoms. The ^{1}H and ^{13}C spectra indicate that the dimer must have a very symmetric structure with each half identical to the other. Structures consistent with this molecule include the cis or trans-head-to-head **(A)** or head-to-tail **(B)** [2+2] cycloaddition adducts shown below.

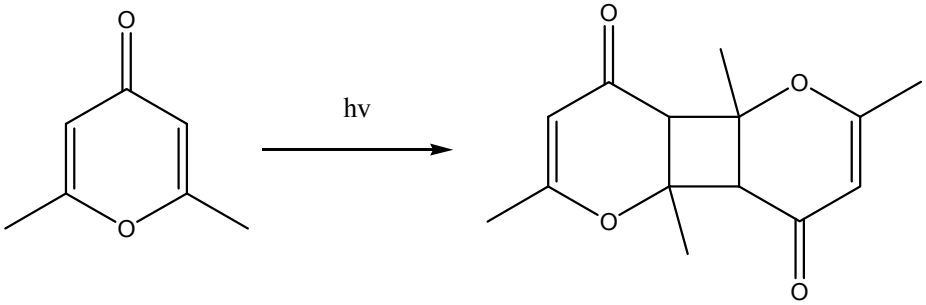


(A)



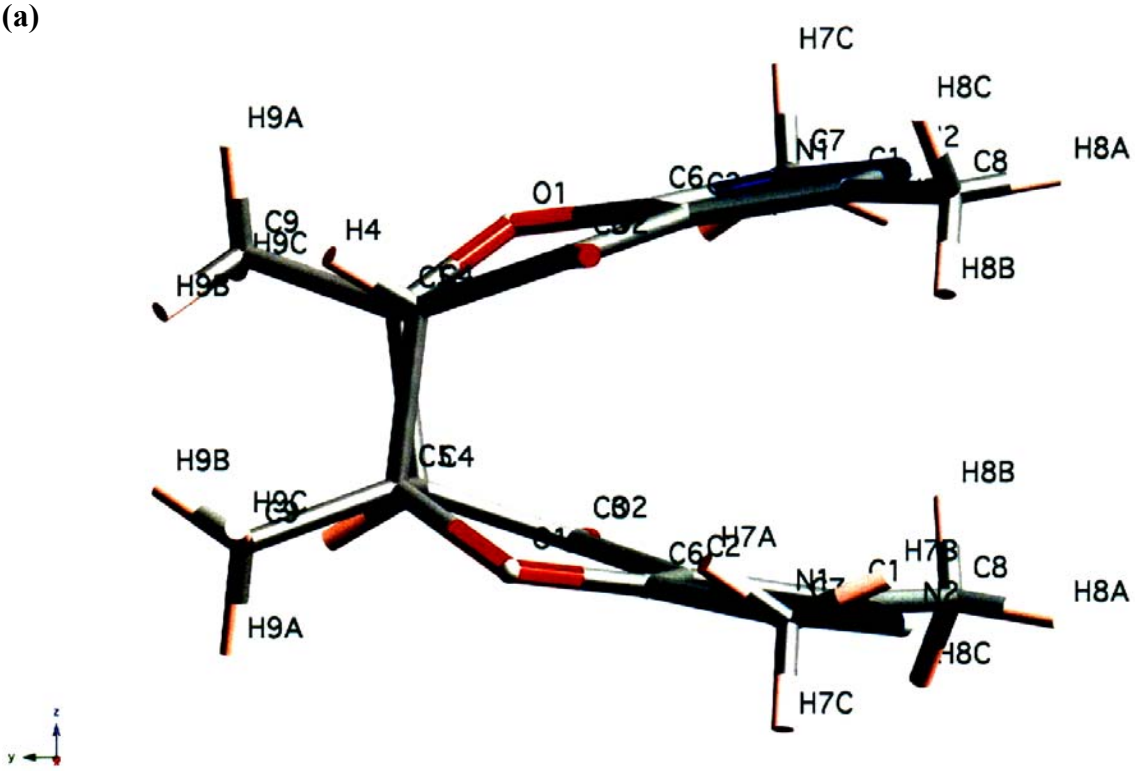
(B)

These suggested structures are consistent with the known head-to-tail [2+2] dimer obtained from the photodimerization of 2,6-dimethyl-4-pyrone shown below.[12]



Since ^{1}H and ^{13}C-NMR cannot distinguish among the possible dimeric structures shown above, the compound was therefore analyzed by single crystal x-ray diffraction. The structure is shown in Figure 65 (a) which confirms that the photoproduct is the cis head-to-tail [2+2] cycloaddition dimer.

(a)



(b)

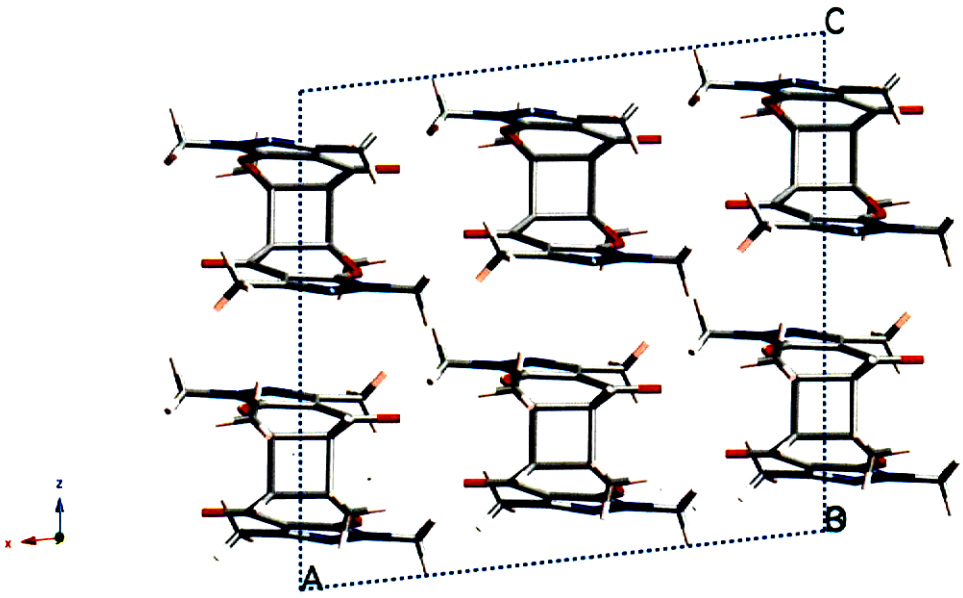


Figure 65: (a) Molecular structure showing the numbering scheme; (b) Packing diagram. Selected geometrical parameters for compound **47** (see Appendix)

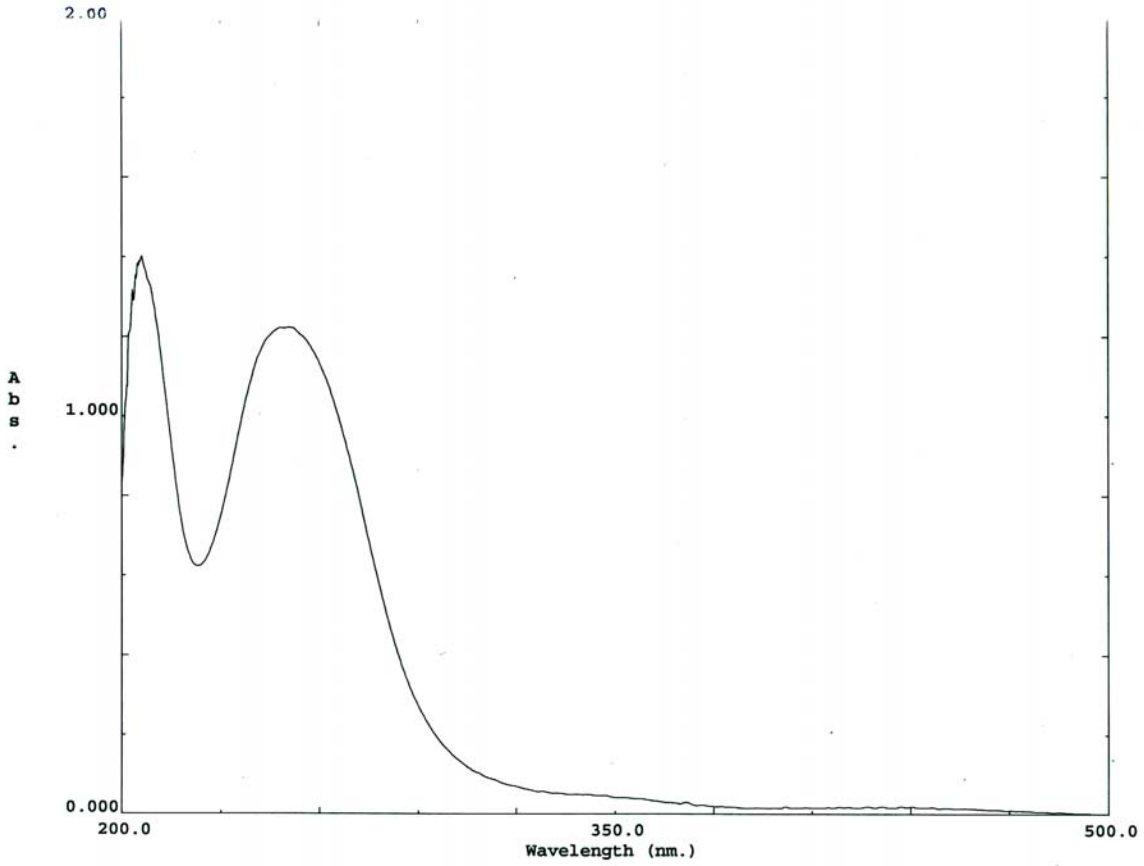


Figure 66: UV-absorption spectrum of the photoproduct **47** in ethanol (9.0×10^{-5} M).

Figure 66 shows the UV-absorption spectrum of a 9.0×10^{-5} M solution of **47** in ethanol solution. The spectrum exhibits λ_{max} at 251.0 nm and 206.0 nm with extinction coefficients of 13,600 and 15,600 L mol^{-1} cm^{-1}, respectively. These absorption maxima are identical to the absorption maxima of the photoproduct shown in Figure 66.

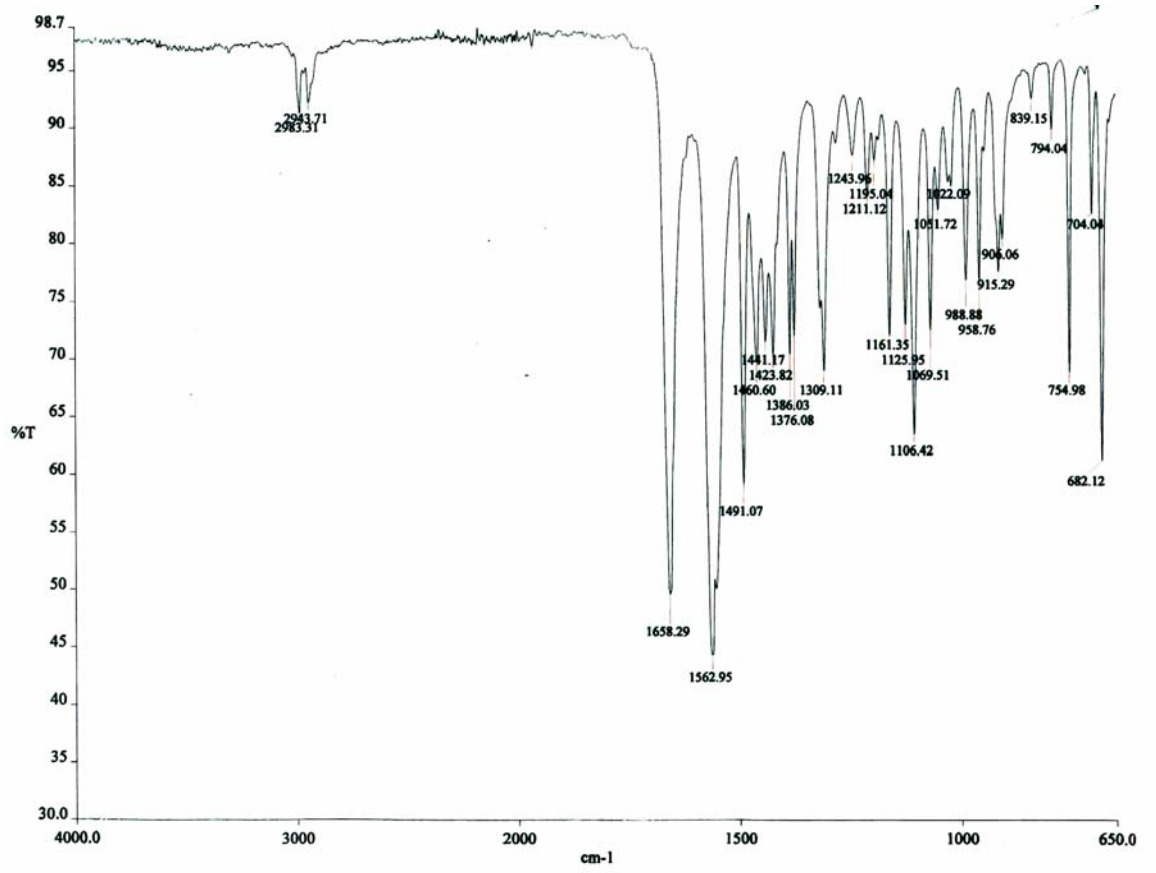


Figure 67: IR spectrum of the photoproduct **47**

Figure 67 shows the IR spectrum of the dimeric product **47** which is consistent with the structure. The C-H stretching peaks of the aliphatic chain absorbs at 2983.31 and 2943.71 cm^{-1}. The intense absorption of 1,658.29 cm^{-1} is due to the carbonyl (C=O) stretching of the ketone group. The strong signal of 1,526.95 cm^{-1} is compatible with C=C stretching of the pyrazole ring.

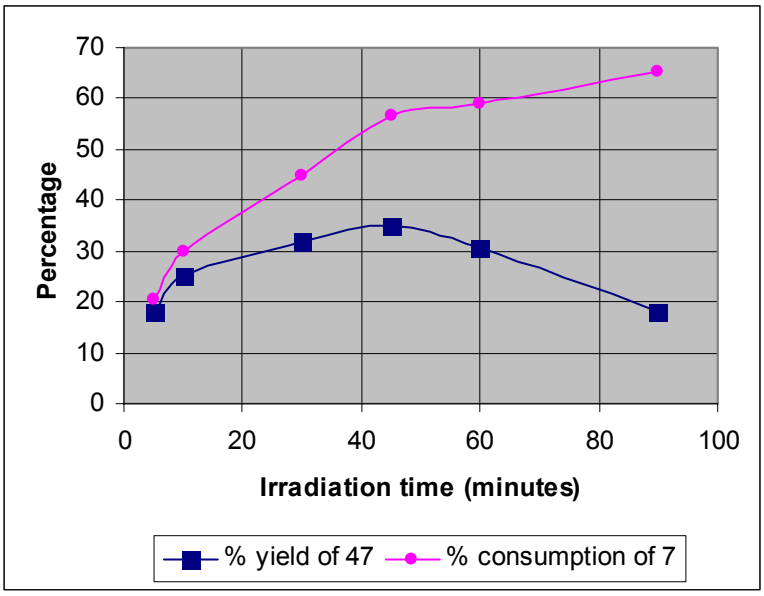


Figure 68: The correlation between the irradiation time of **7** and % consumption of **7** and % yield of **47**.

Based on the results in Figure 60, the results of the HPLC analyses are summarized in Figure 68 where the percent consumption of the reactant **7** and the percent yield of the photoproduct **47** are plotted as a function of irradiation time and were determined by the peak area relative to standard curve. The figure is also consistent with Figure 68 that shows the consumption of the reactant **7** with a decrease in the slope at 45 minutes indicating a decrease in the rate of consumption of **7** after that time. The figure also shows a steady increase in the yield of the photoproduct **47** until a maximum yield of 35 % was reached at 45 minutes of irradiation. HPLC analysis showed that the yield of **47** decreased upon more prolonged irradiation indicating that after 45 minutes of irradiation it was being consumed faster that it was being form.

The photochemistry of pyranopyrazole **7** was also investigated in ethanol solution. Figure 69 shows the UV-absorption spectrum of an (8.0×10^{-5} M) solution of **7** in ethanol. The spectrum exhibits λ_{max} at 252.7 nm and 206.0 nm with extinction coefficients of 12,047 and 18,392 and L mol^{-1} cm^{-1}, respectively. Considering the magnitude of these extinction coefficients, these two absorptions have been assigned to S_0 to S_1 (π,π^*) and S_0 to S_2 (π,π^*) transitions.

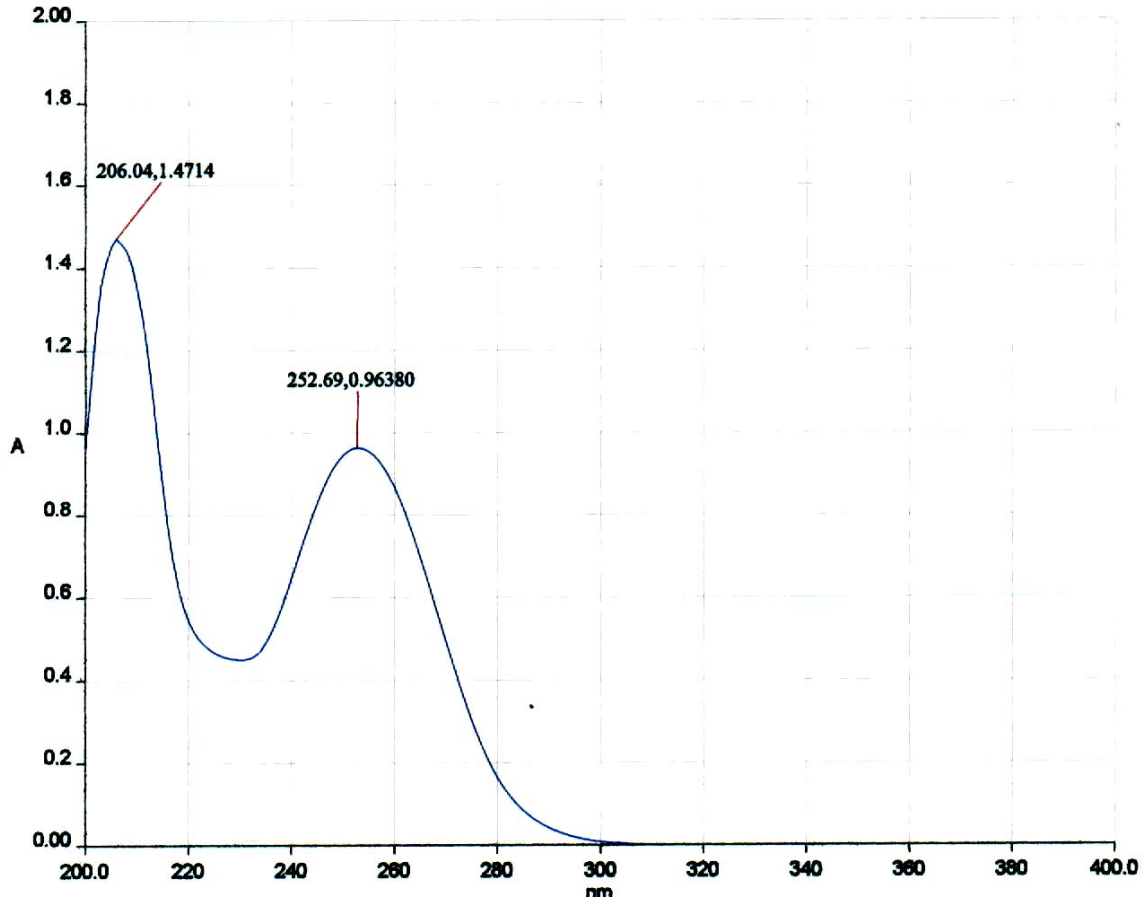


Figure 69: UV-absorption spectrum of **7** in ethanol (8.0×10^{-5} M)

Figure 70 shows the UV-absorption spectrum of the same solution before and after five consecutive 5 seconds irradiation at 254 nm. As the figure shows, irradiation

is accompanied by a decrease in the absorbance of the band at 252.7 nm from 0.96 to 0.68 and a shift from 252.7 nm to 251.8 nm. The absorption band at 206.0 nm decreases from 1.47 to 1.01 and a shift from 206.0 to 203.9 nm.

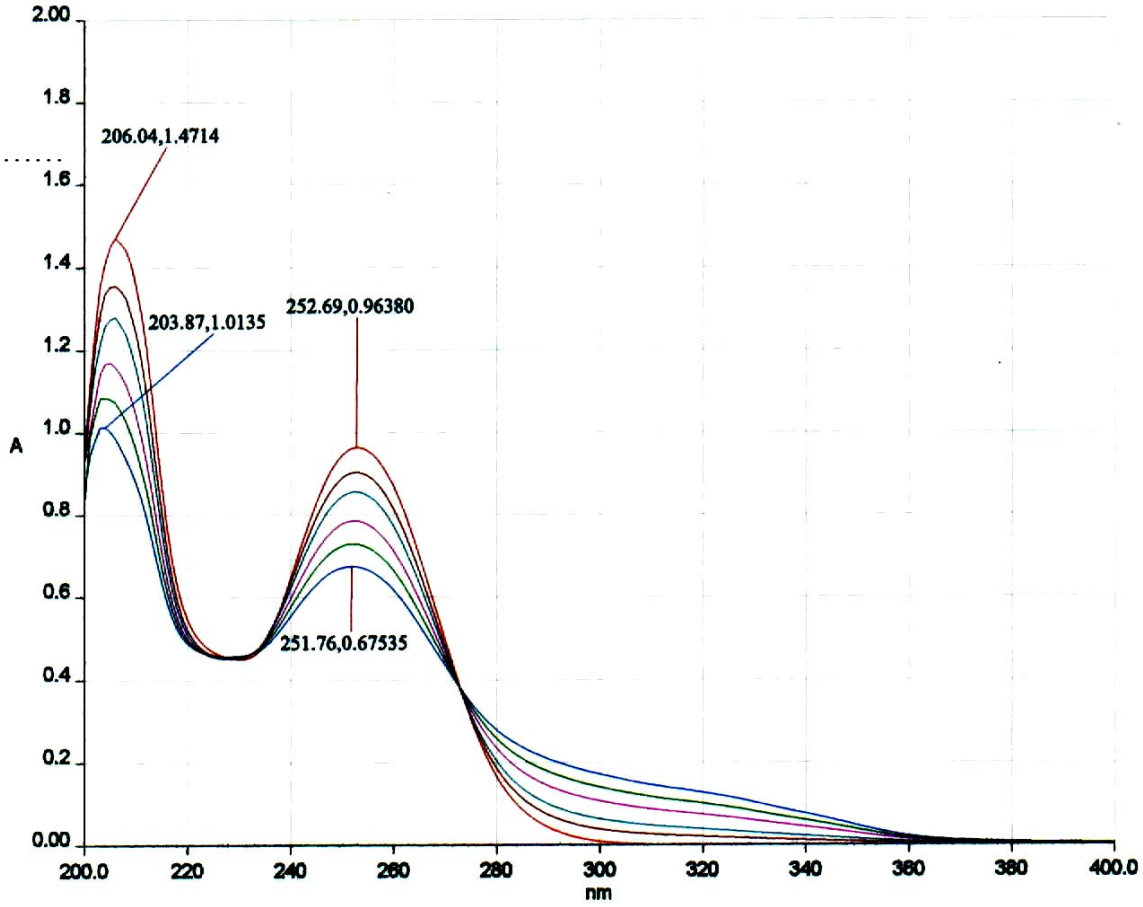


Figure 70: UV-overlay spectrum of the photolysis of **7** in ethanol (8.0×10^{-5} M)

The photochemical reaction of **7** was also monitored by HPLC. Figure 71 shows the HPLC trace of **7** (2.0×10^{-2} M) in ethanol (methanol 75 : water 25; flow rate = 0.50 ml/ min; detector at 250 nm). The trace shows only one peak due to **7** with a retention of 7.26 minutes. The solution of **7** (2.0×10^{-2} M) in ethanol was placed in a quartz tube (20 cm long × 0.7 cm id). The tube was sealed with a rubber septum, purged with

helium for 15 minutes, and irradiated at 254 nm with thirteen lamps. Aliquots were removed for HPLC analysis after 10, 20, 30, 45, 60, 90, and 120 minutes of irradiation. Figure 72 shows the HPLC trace after 10 minutes of irradiation and reveals the formation of the photodimer **47** with a retention of 6.7 minutes.

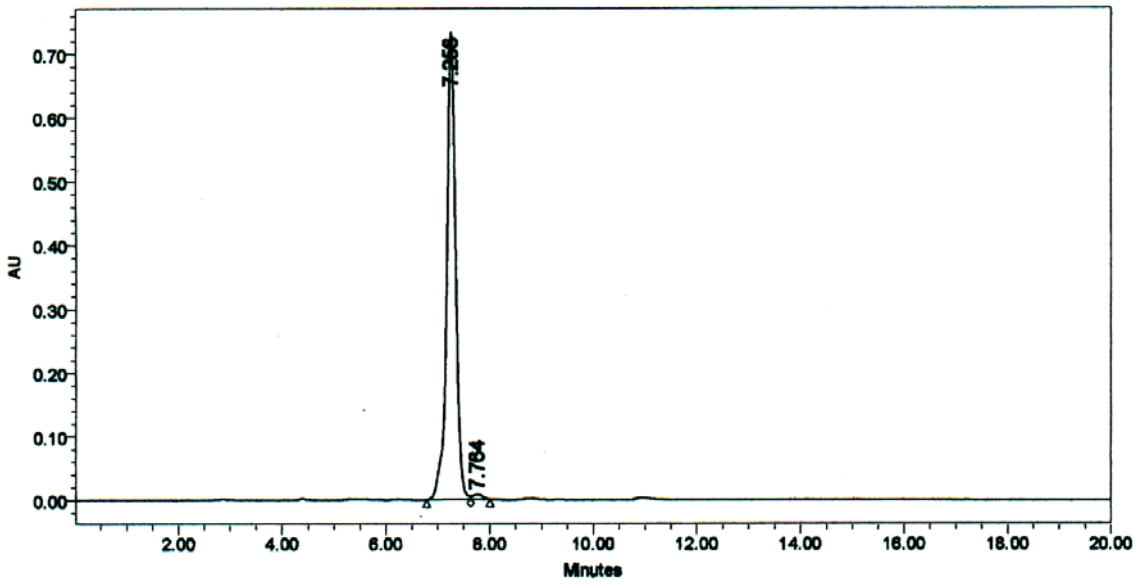


Figure 71: HPLC-trace of the solution **7** before irradiation

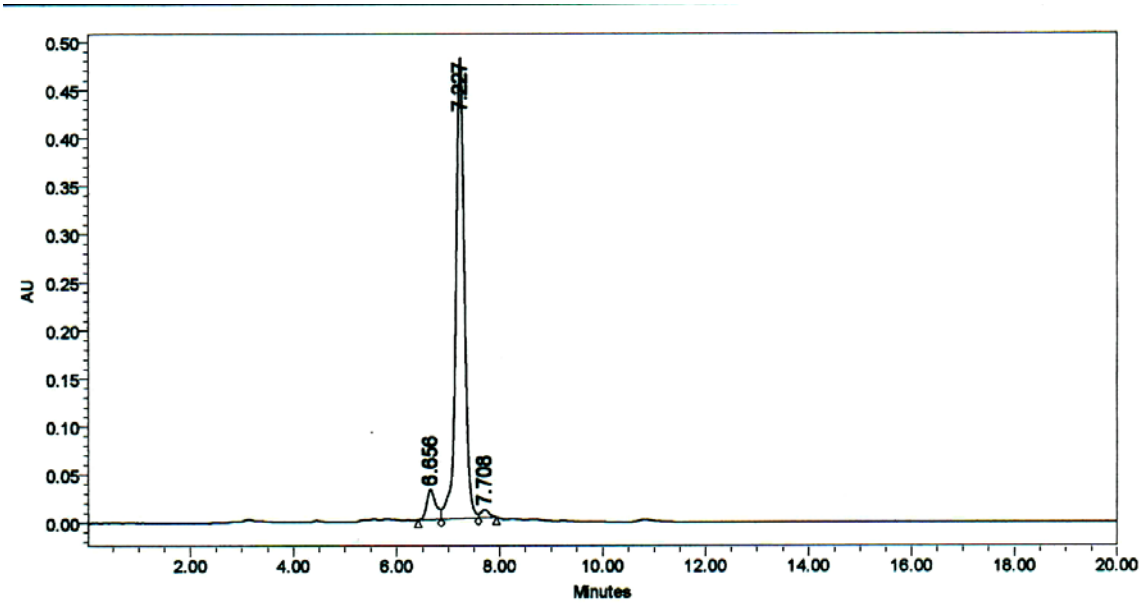


Figure 72: HPLC report of the solution of **7** after 10 minutes of irradiation

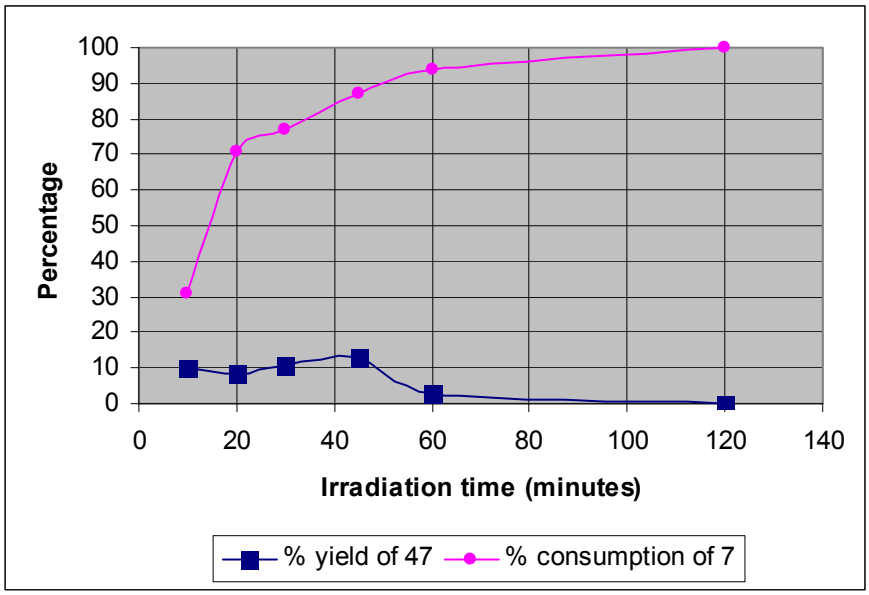


Figure 73: The correlation between the irradiation time of **7** and % consumption of **7** and % yield of **47**.

Figure 73 shows how the consumption of the reactant **7** and the yield of the photodimer **47** changed as a function of irradiation time. Comparison of Figure 73 with Figure 68 shows that **7** is more rapidly consumed upon irradiation in ethanol solution then when **7** was irradiated in ACN solution. Thus while approximately 38 % of **7** was consumed after 20 minutes of irradiation in ACN solution, 70 % of **7** was consumed after irradiation of **7** for 20 minutes in ethanol solution. Comparison of the two figures also shows that the yield of the photodimer is much less upon irradiation in ethanol than upon irradiation in ACN. Thus, whereas in ACN the yield of **47** reaches a maximum of 35 % after 45 minutes of irradiation, in ethanol the maximum yield of **47** is only 12 % after the same irradiation time. Furthermore, after 60 minutes of irradiation in ethanol essentially all **47** has been consumed.

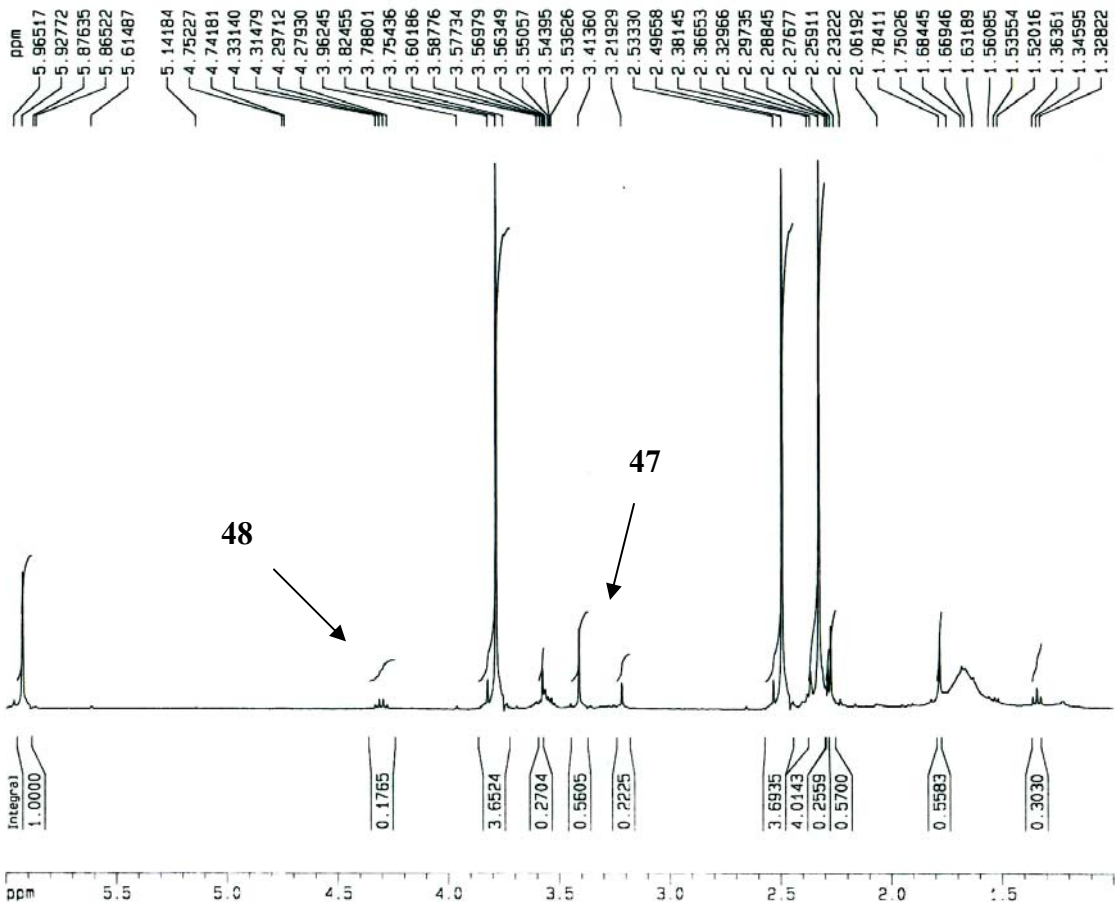


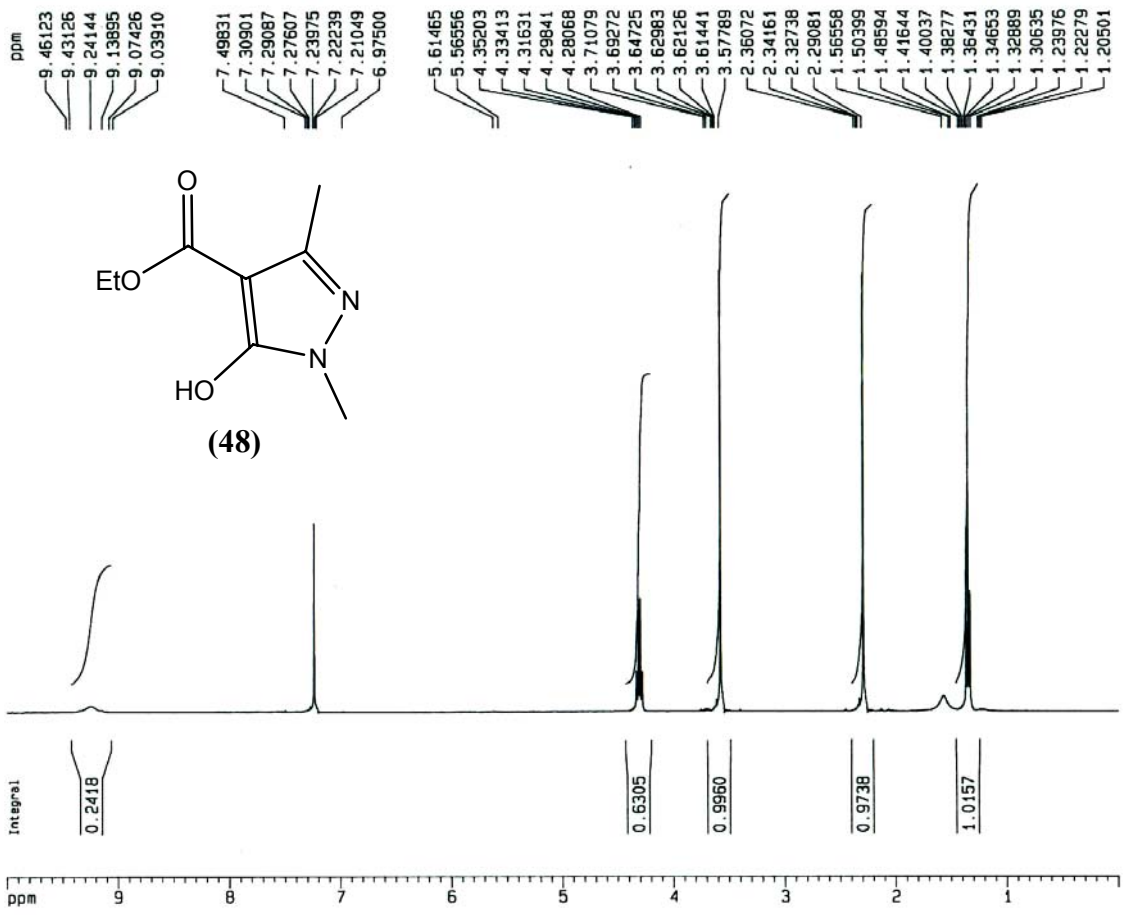
Figure 74: ^{1}H-NMR of the crude product after 10 minutes of irradiation

Surprisingly, the ^{1}H-NMR spectra of the crude product mixture after 10 minutes of irradiation shows the formation of the photodimer **47**, and the formation of a second product **48** which was not detected by 250 nm lamp of the HPLC detector. That means the absorption coefficient of the photoproduct **48** might be low at 250 nm.

In order to isolate the photoproduct, a second solution of **7** (2.0×10^{-2}M) in ethanol was irradiated until HPLC analysis indicated maximum formation of the photoproduct. Preparative-layer chromatography of the resulting solution revealed a band at $R_f = 0.40$ due to the unconsumed reactant **7** and four additional bands at $R_f =$

0.65, 0.30, 0.25, and 0. Although extraction of the bands at R_f = 0.65 and 0 resulted in negligible recovery of any material, extraction of the band at R_f = 0.25 provided a white crystalline product, mp 229-230°C indicating to dimer, and extraction of the band at R_f = 0.30 provided a white crystalline product, mp 124-125°C indicating to a new photoproduct **48**.

(a)



(48)

The ^{1}H-NMR spectrum of the new photoproduct **48** is shown in Figure 75 (a). The spectrum reveals a 2H quartet (J = 7.1 Hz) at δ 4.28 and a 3H triplet (J = 7.1 Hz) at δ 1.24. Thus, it appears that a molecule of ethanol has been incorporated into the

photoproduct. The spectrum also shows a 3H singlet at δ 3.58, consistent with an N-CH_3 group, and a 3H singlet at δ 2.29, consistent with an allylic methyl group. Significantly, although the reactant had three methyl groups, the product has only two. One methyl group has been lost. In addition, the 1H singlet due to the C-5 proton in the pyrone ring of the reactant, is not observed in the product. This suggests that the α and β carbons of the pyrone ring has been lost during photoreaction. Finally, the ^{1}H-NMR spectrum exhibits a broad peak at δ 9.24 (D_2O exchangeable) due to the presence of a hydroxyl proton in the structure.

(b)

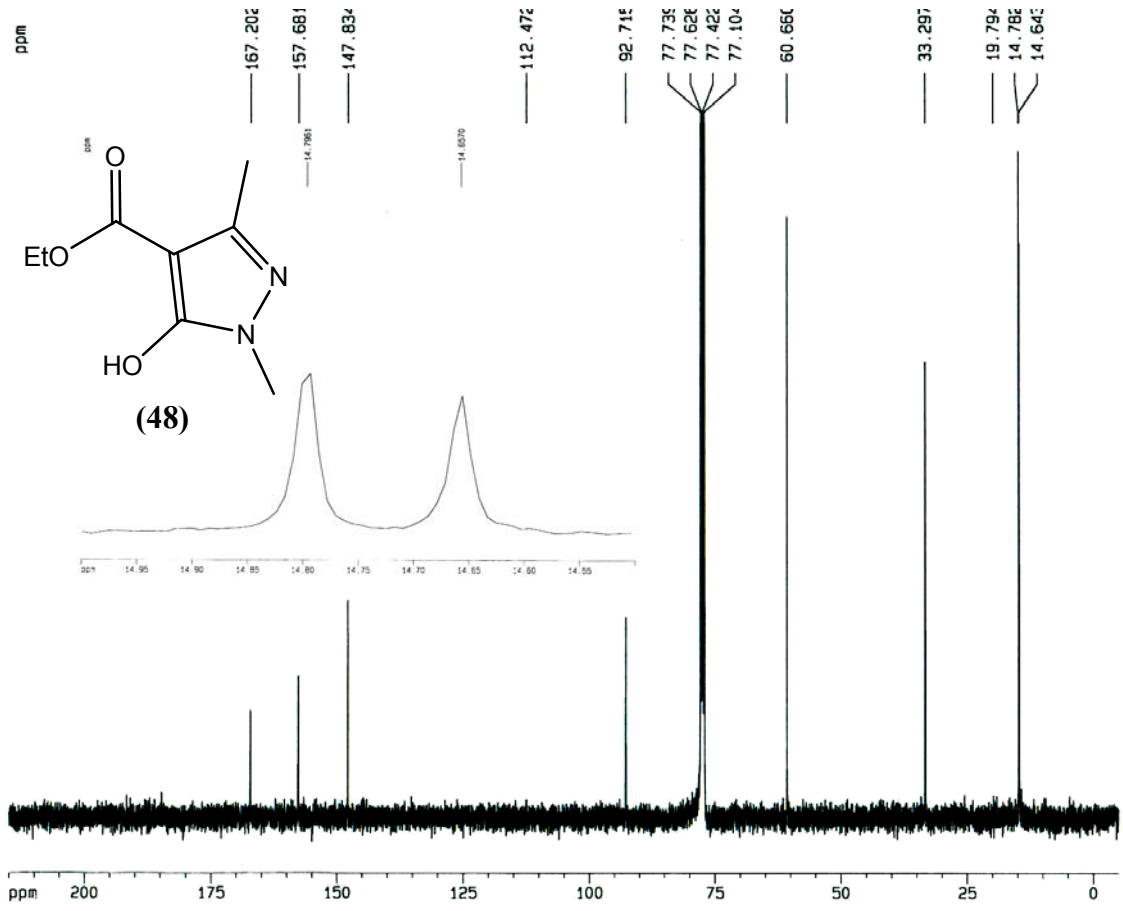
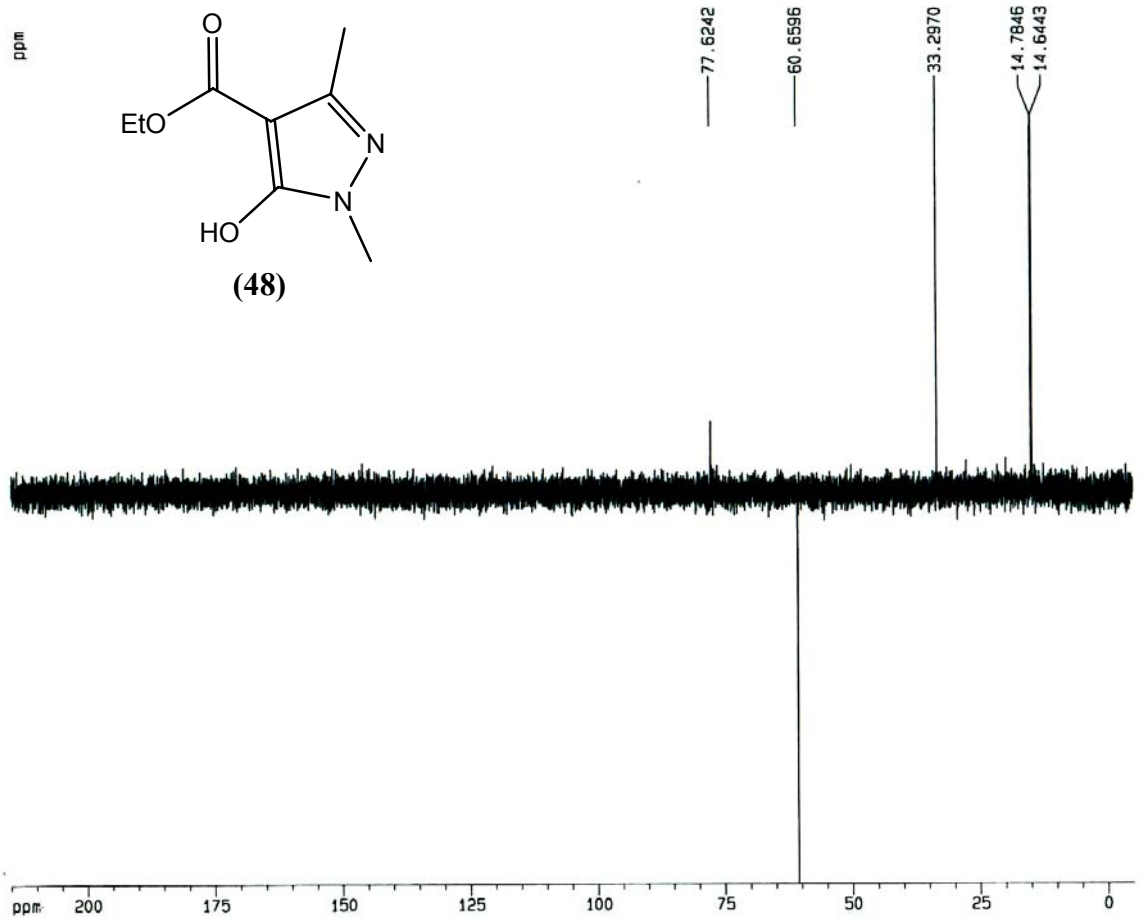


Figure 75 (b) shows the ^{13}C-NMR spectrum of the photoproduct. The spectrum shows the presence of eight sets of carbon. These include the three methyl groups absorbing at δ 14.64, 14.78, and 33.29 and the methylene carbon of the ethoxy group at δ 60.66. These groups were suggested by the ^{1}H-NMR spectrum. Significantly, the ^{13}C-NMR spectrum also exhibits at signal at δ 167.2, consistent with an ester carbonyl carbon, and signals at δ 157.7, 147.8, and 92.72, consistent with the C-3, C-5, and C-4 carbon atoms of a pyrazole ring.

(c)



(48)

Figure 75: (a) ^{1}H-NMR of compound **48**; (b) ^{13}C-NMR of compound **48**; (c) ^{13}C-NMR DEPT 135 of compound **48**.

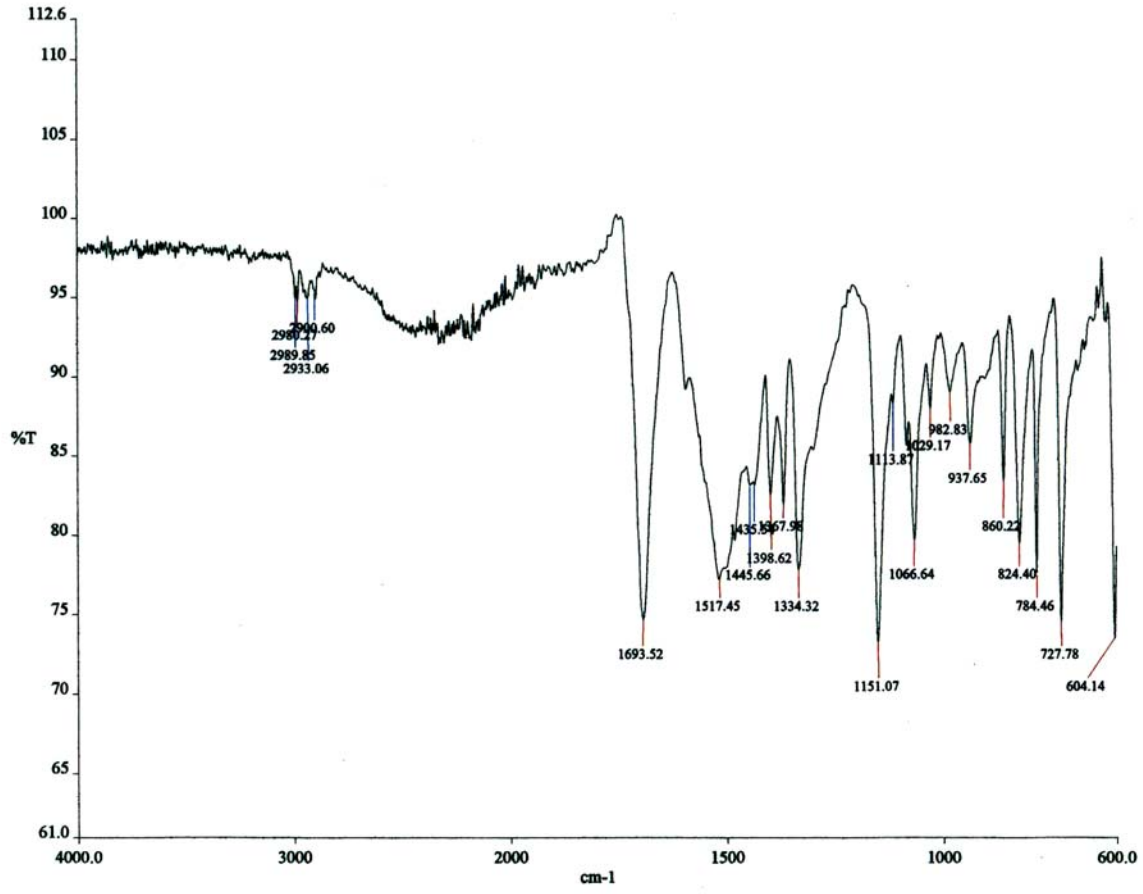


Figure 76: IR spectrum of the photoproduct **48**

Figure 76 shows the IR spectrum of the photoproduct **48** in which the functional group might be suggested. The C-H stretching peaks of the aliphatic chain absorbs at 2,989.8 and 2,980.3 cm^{-1}. The intense absorption of 1,693.3 cm^{-1} is due to the carbonyl (C=O) stretching of the ester group. The strong signal of 1,517.4 cm^{-1} is consistent with C=C stretching of the pyrazole ring.

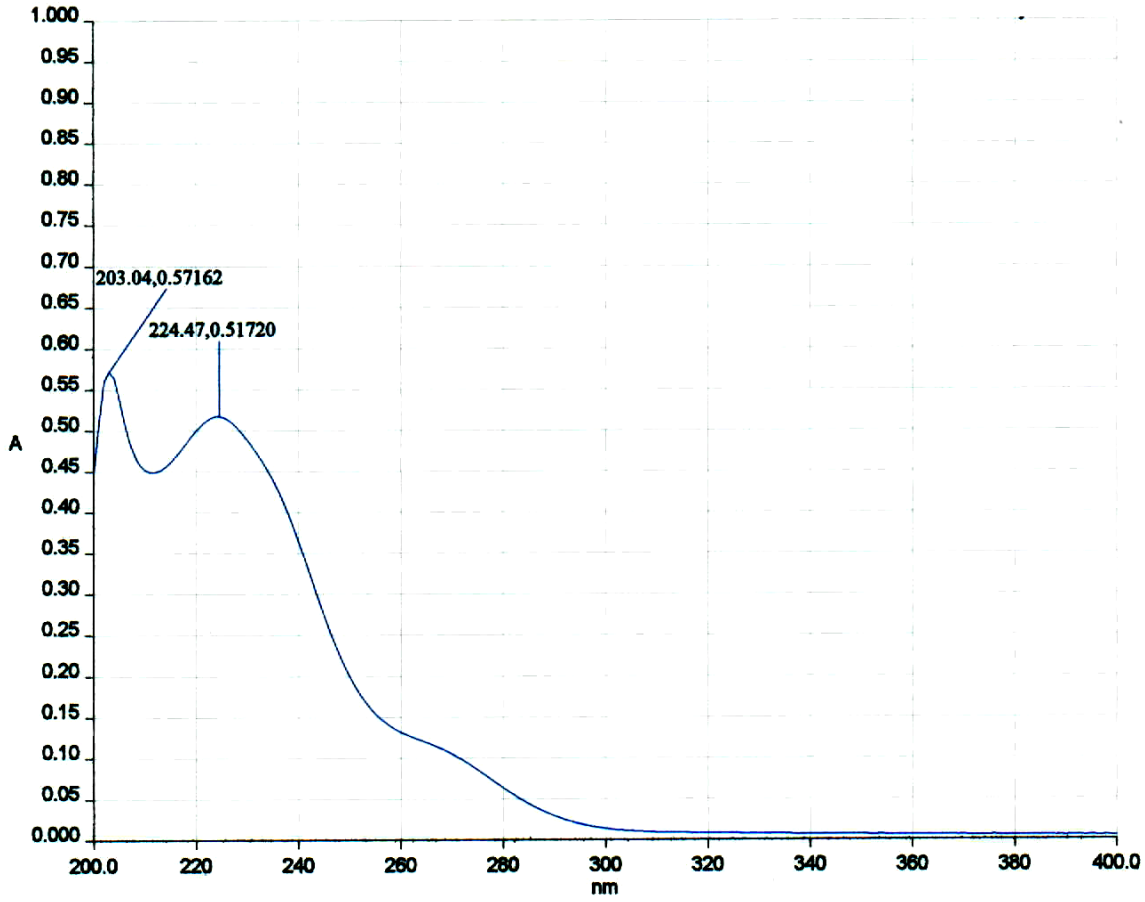
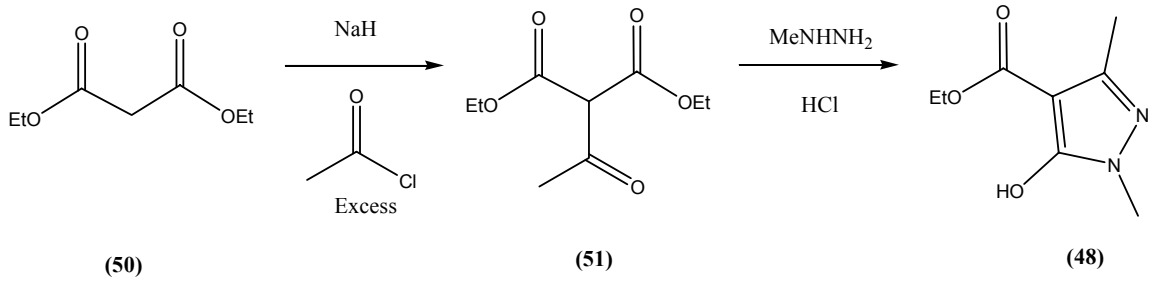


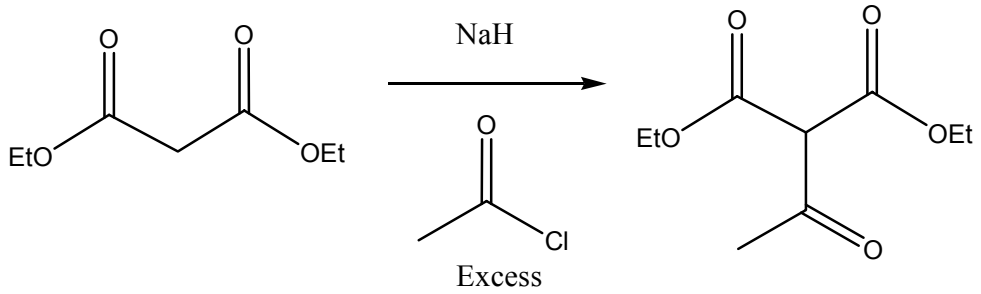
Figure 77: UV-absorption spectrum of the photoproduct **48** in ethanol

Figure 77 shows the UV-absorption spectrum of a 4.0×10^{-5} M solution of **48** in ethanol solution. The spectrum exhibits λ_{max} at 224.5 nm and 203.0 nm with extinction coefficients of 12,930 and 14,290 L mol^{-1} cm^{-1}, respectively.



(50) **(51)** **(48)**

Taken together, these spectroscopic data suggest that the photoproduct **48** is ethyl 5-hydroxy-1,3-dimethylpyrazole-4-carboxylate. The structure of the photoproduct was confirmed by synthesis of **48** according to the pathway shown above.



(50) **(51)**

Scheme 49: Synthesis of diethyl 2-acetylmalonate **(51)**.

Although, diethyl 2-acetylmalonate **(51)** is a known compound,[13] a new methodology for preparing **51** was developed by allowing diethyl malonate **50** to react with excess acetyl chloride in the presence of sodium hydride. This gave **51** in a yield of 60%, (Scheme 49).

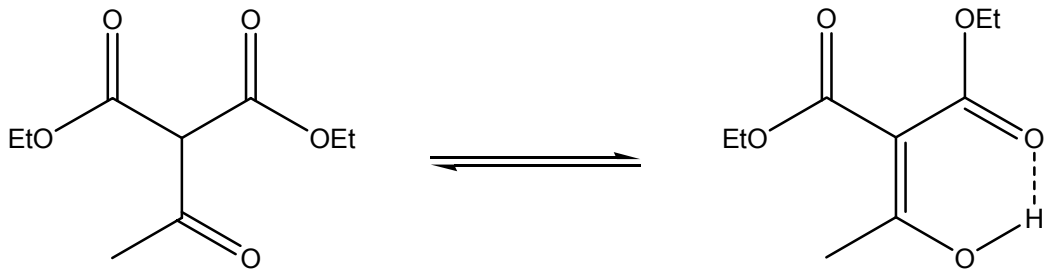
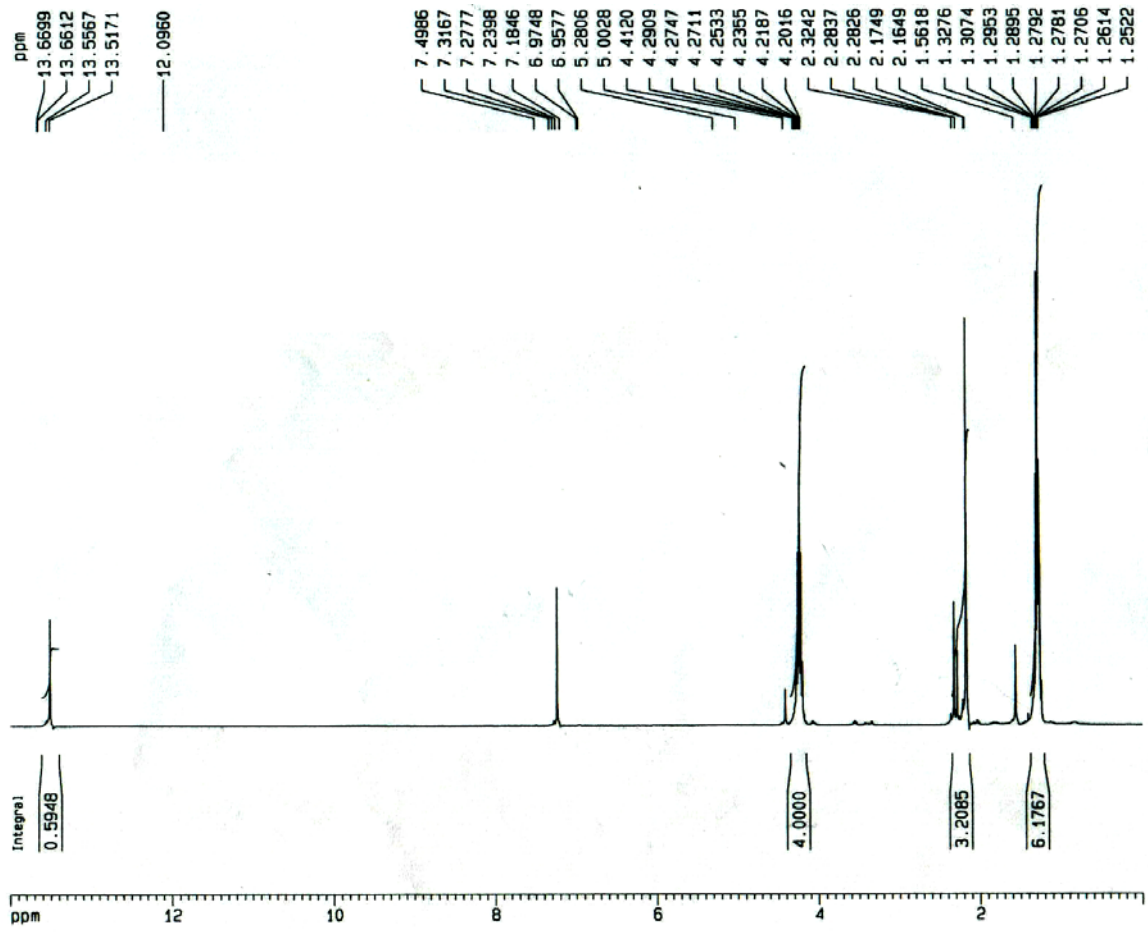


Figure 78: Equilibrial tautomerization of compound **51**

(a)

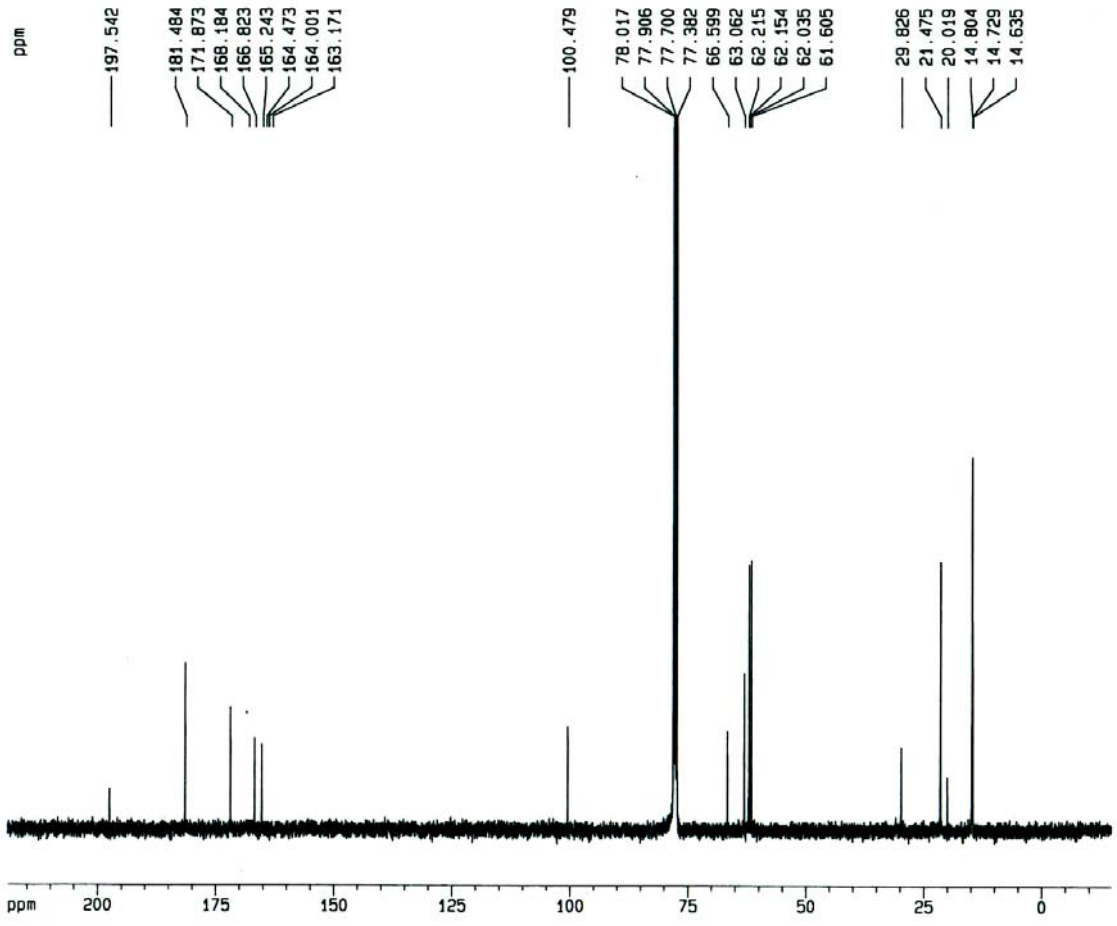


The ^{1}H-NMR spectrum (Figure 79 (a)) shows that **51** is an equilibrium mixture of conformers A and B. The equilibrium between keto form A and OH-stabilized by an

intramolecular hydrogen bonding enol form B is expected to be slow on the NMR time scale so that both forms are expected to be detected as distinct species.

The strongly H-chelated due to enol form is observed as a 1H singlet at δ 13.67, while the α-proton of diketo ester and ketone due to keto form appear as a 1H singlet at δ 4.41. In addition, the diethyl protons appear as a 4H multiplet at δ 4.20-4.29 and a 6H multiplet at δ 1.25-1.32, while the acetyl protons are observed as two 3H singlets at δ 2.17 and 2.32 due to both tautomers.

(b)



The ^{13}C-NMR spectrum (figure 79 (b)) in $CDCl_3$ solution of compound **51** gives rise to two conformers for all the carbon atoms. The characteristic ^{13}C-NMR spectrum

of keto form, the signal at δ 197.5 is due to the acyl carbonyl, while the signal at δ 165.2 was assigned to diester carbonyls. The α-carbon of diketo ester and α-methyl carbon appear at δ 66.59 and 29.82, respectively, while the ethyl carbons are due to δ 63.26 and 14.64. On the other hand, the B conformer is observed in more intense spectrum of ^{13}C-NMR spectrum. The signal at δ 181.5 is due to enol carbon, while the chelated carbonyl and free carbonyl of non-equivalent ester side appear as two signals at δ 171.9 and 166.8, respectively. Thus, the two sets of non-equivalent diethyl carbons are observed at δ 62.15 and 14.80, and δ 61.60 and 14.73 due to the chelated ethyl side and free ethyl side, respectively. The signal at δ 101.5 is due to a **C**=CH in α-carbon of the dicarbonyl groups, while the α-methyl carbon of hydroxyl group appears at δ 21.47.

(c)

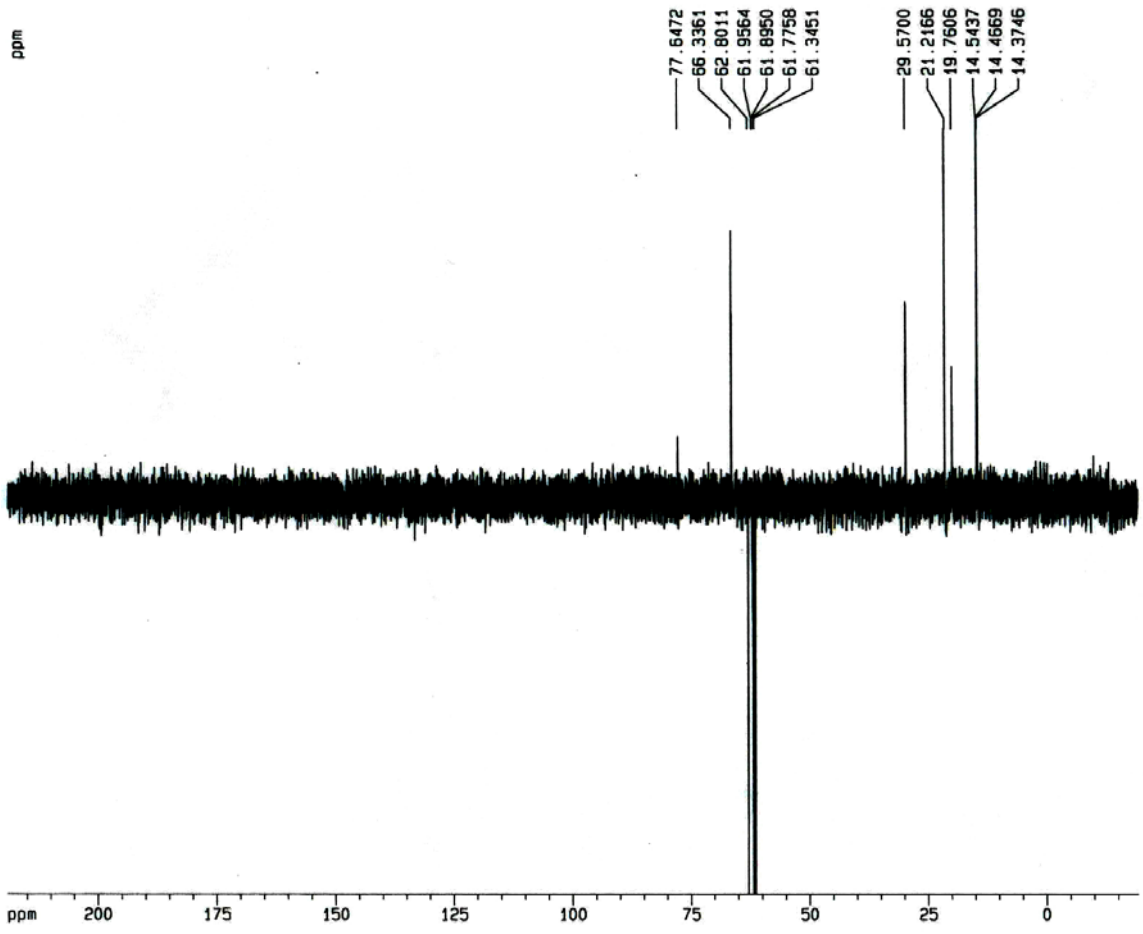
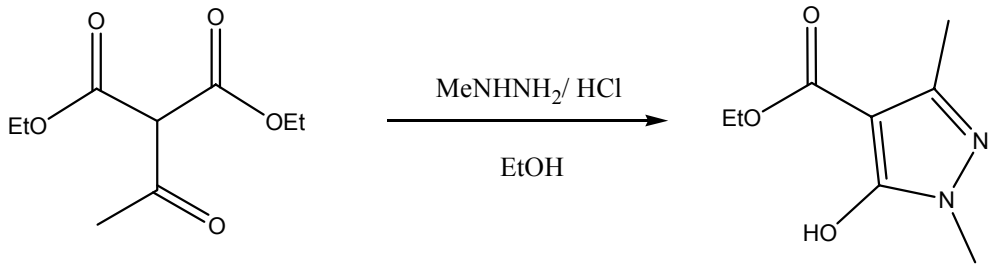


Figure 79: (a) ^{1}H NMR of compound **51**; (b) ^{13}C NMR of compound **51**; (c) ^{13}C NMR DEPT 135 of compound **51**.

As expected, the ^{13}C-NMR DEPT 135 (figure 79 (c)) of compound **51** shows that the six signals at δ 197.5, 181.5, 171.9, 166.8, 165.2, and 100.5 disappeared which are consistent with the two sets of the quaternary signal of A and B conformers. However, the consistently positive signals at δ 66.33, 29.57, 19.76, and 14.37 are due to CH type carbon and methyl carbons of keto form, while the positives signals at δ 21.22, 14.5, and 14.47 were assigned to the methyl carbons of enol form. In addition the negative signal due to CH_2 type carbon of keto form appears as a singlet at 62.80, while the two negative signals at δ 61.78 and 61.35 are due to two non-equivalent CH_2 type carbons of enol form.



(51) **(48)**

Scheme 50: Synthesis of ethyl 5-hydroxy-1,3-dimethyl-1*H*-pyrazole-4-carboxylate **(48)**.

Based on the literature condition,[13] the synthesis of ethyl 5-hydroxy-1,3-dimethyl-1*H*-pyrazole-4-carboxylate **(48)** was accomplished by treatment of **51** with

methylhydrazine in acid condition to give **48** in 62% yield; mp 124-125°C (Lit.[14] 142-143°C) (Scheme 50). Direct comparison of their spectroscopic properties showed that the photoproduct is identical to this synthetic compound confirming that the photoproduct is ethyl 5-hydroxy-1,3-dimethyl-1*H*-pyrazole-4-carboxylate **(48)**.

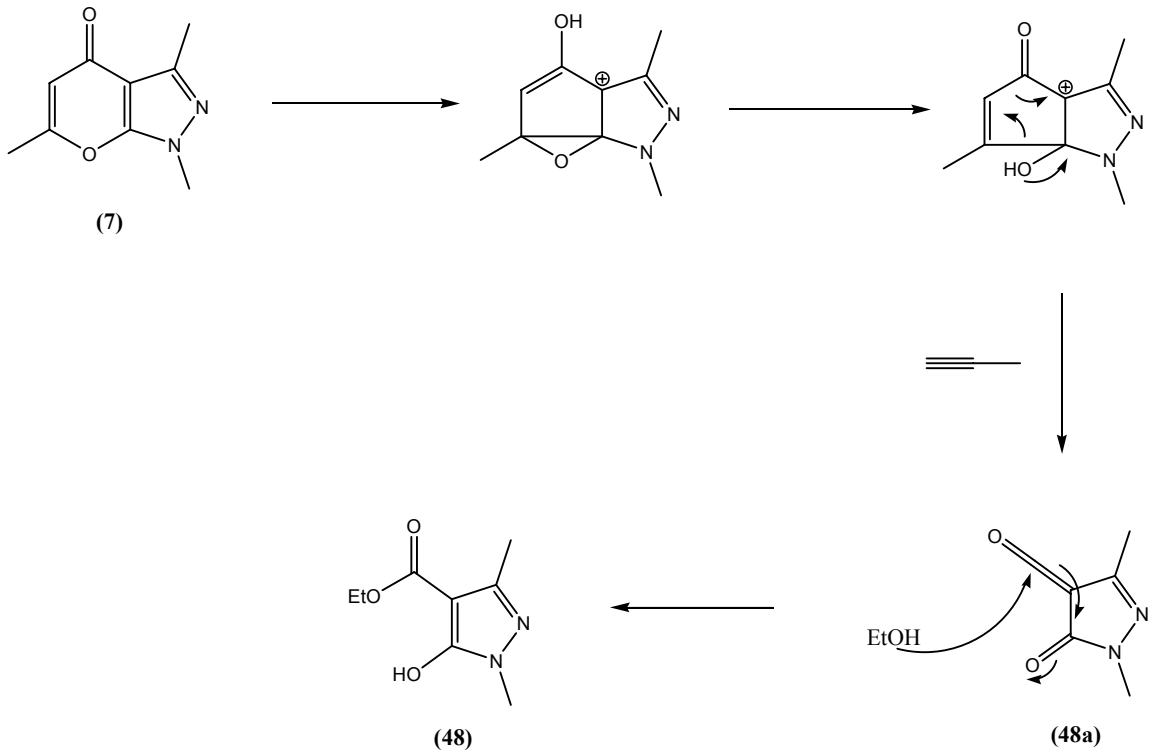


Figure 80: The mechanism of the formation of the photo fragmentation **48**.

Mechanistically, it is suggested that pyranopyrazole **7** undergoes photofragmentation to yield ketene **48a** which is trapped by the nucleophilic solvent ethanol to yield **48**. In order to investigate this further, the photochemistry of **7** in other nucleophilic solvents was studied.

Figure 81 shows the UV-absorption spectrum of an (8.0×10^{-5} M) solution of **7** in methanol. The spectrum exhibits λ_{max} at 253.3 nm and 206.3 nm with extinction coefficients of 11,051 and 16,281 L mol^{-1} cm^{-1}, respectively. Considering the magnitude of these extinction coefficients, these two absorptions have been assigned to S_0 to S_1 (π,π^*) and S_0 to S_2 (π,π^*) transitions.

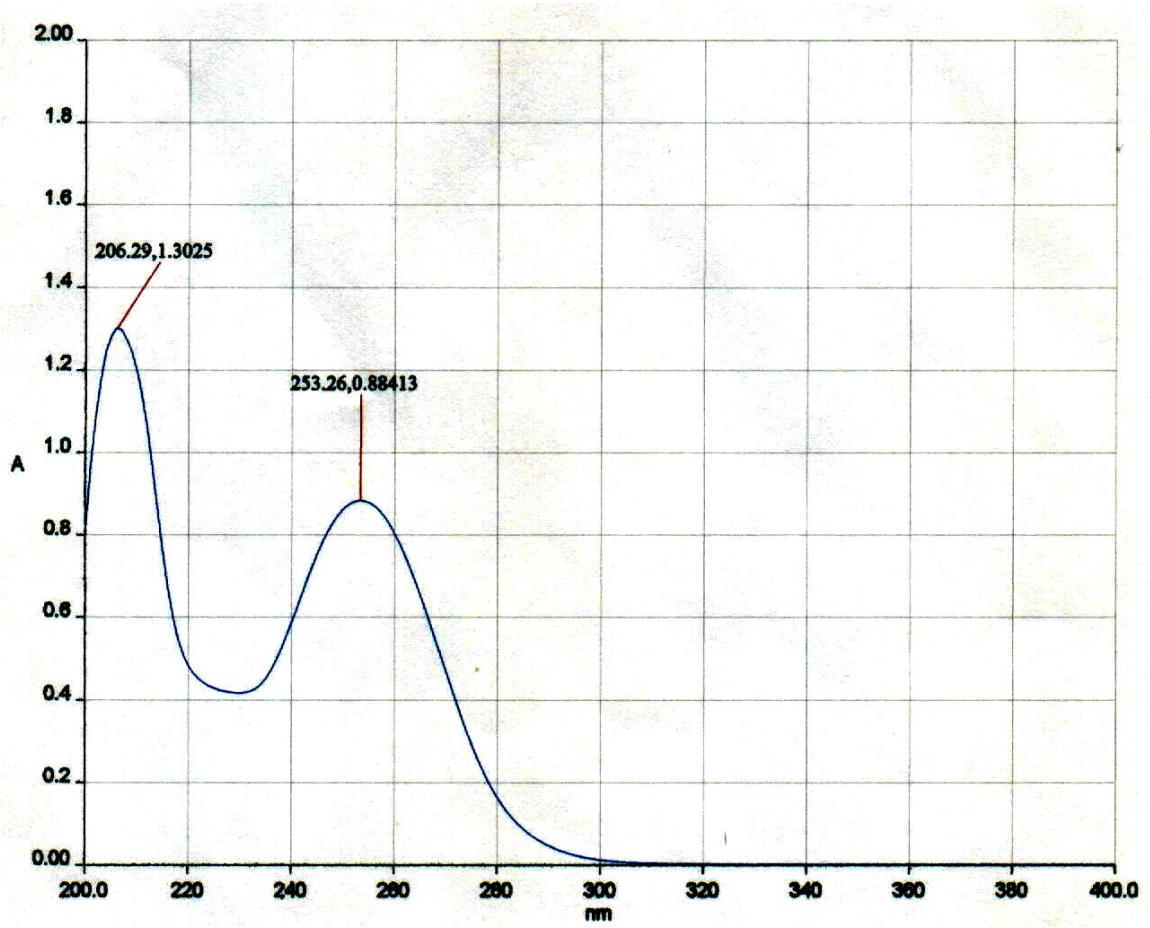


Figure 81: UV-absorption spectrum of **7** in methanol (8.0×10^{-5} M).

Figure 82 shows the UV-absorption spectrum of the same solution before and after five consecutive 5 seconds irradiation at 254 nm. As the figure shows, irradiation is accompanied by a decrease in the absorbance of the band at 253.3 nm from 0.88 to

0.77 and a shift from 253.3 nm to 253.8 nm. The absorption band at 206.3 nm decreases from 1.30 to 1.16 and a shift from 206.3 to 205.9 nm.

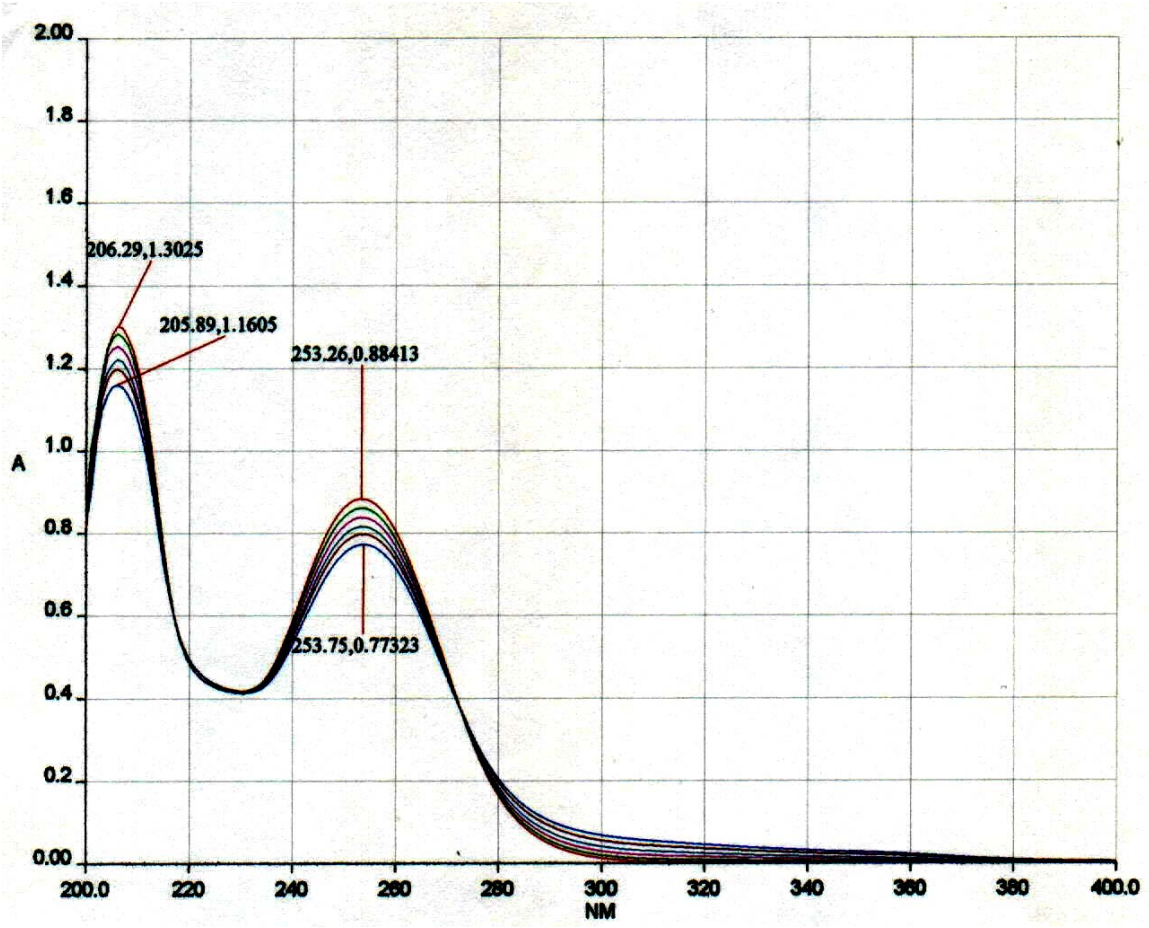


Figure 82: UV-overlay spectrum of the photolysis of **7** in methanol (8.0×10^{-5} M).

The photochemical reaction of **7** was also monitored by HPLC. Figure 83 shows the HPLC trace of **7** (2.0×10^{-2} M) in methanol (methanol 75 : water 25; flow rate = 0.50 ml/ min; detector at 250 nm). The trace shows only one peak due to **7** with a retention of 7.26 minutes. The solution of **7** (2.0×10^{-2} M) in methanol was placed in a quartz tube (20 cm long × 0.7 cm id). The tube was sealed with a rubber septum,

purged with helium for 15 minutes, and irradiated at 254 nm with thirteen lamps. Aliquots were removed for HPLC analysis after 10, 30, 45, 60, 75, 90, and 120 minutes of irradiation. Figure 84 shows the HPLC trace after 30 minutes of irradiation and reveals the formation of photodimer **47** with a retention of 6.6 minutes.

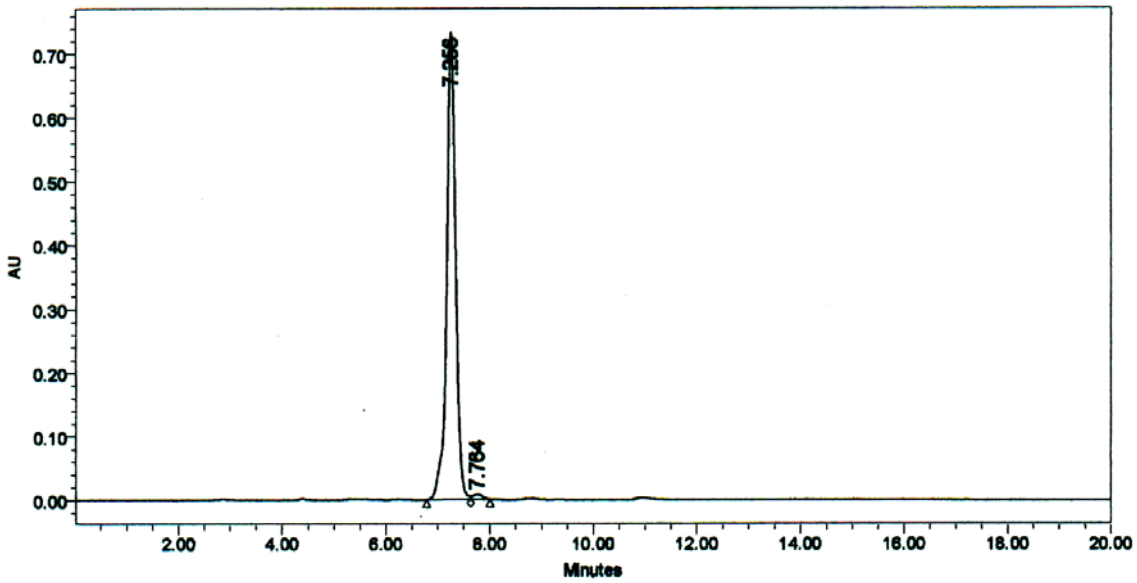


Figure 83: HPLC-trace of the solution **7** before irradiation

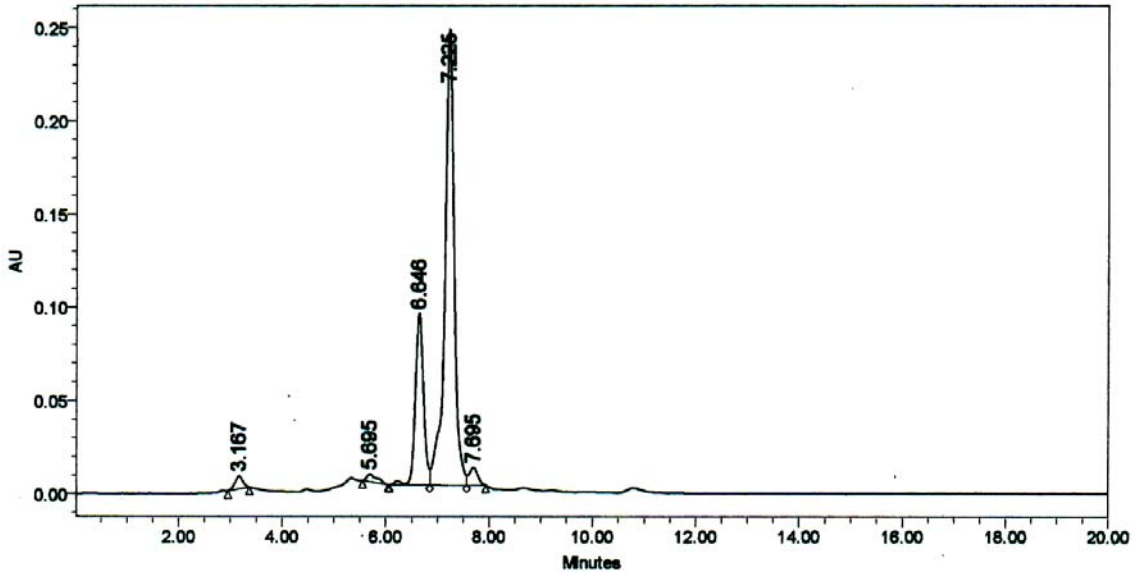


Figure 84: HPLC report of the solution of **7** after 30 minutes of irradiation

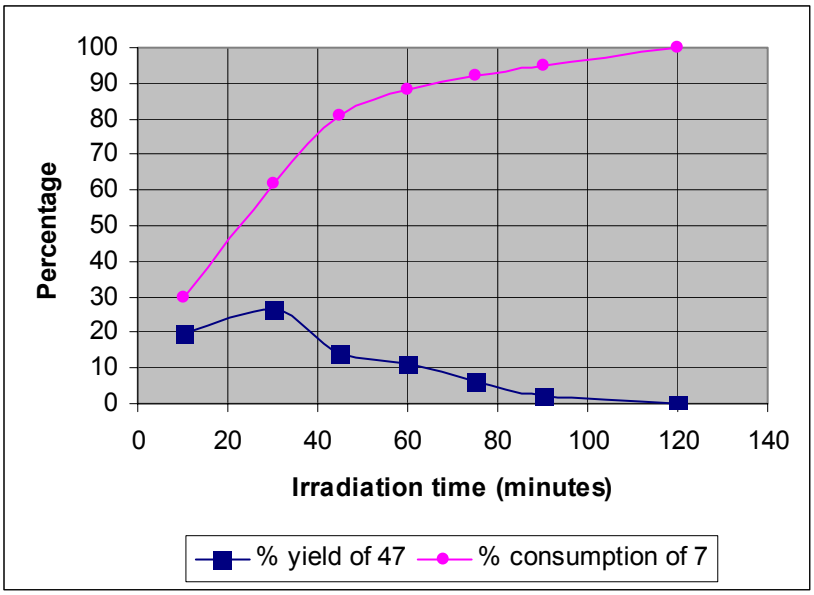


Figure 85: The correlation between the irradiation time of **7** and % consumption of **7** and % yield of **47**.

Figure 85 shows the rapid consumption of the reactant **7** during the first 40 minutes of irradiation after which approximately 75% of the reactant was consumed. Comparison of Figure 73 with Figure 85 shows that **7** is more rapidly consumed upon irradiation in ethanol solution then when **7** was irradiated in methanol solution. After approximately 45 minutes of irradiation, the figure shows a decrease in the slope of the consumption curve indicating a decrease in the rate of consumption of **7** after that time until after 120 minutes of irradiation the consumption of **7** is complete. The figure also shows an increase in the formation of photodimer **47** until it reaches a maximum yield of approximately 28% after 30 minutes of irradiation. Continuing irradiation results in the consumption of **47** until it is completely consumed after 120 minutes of irradiation.

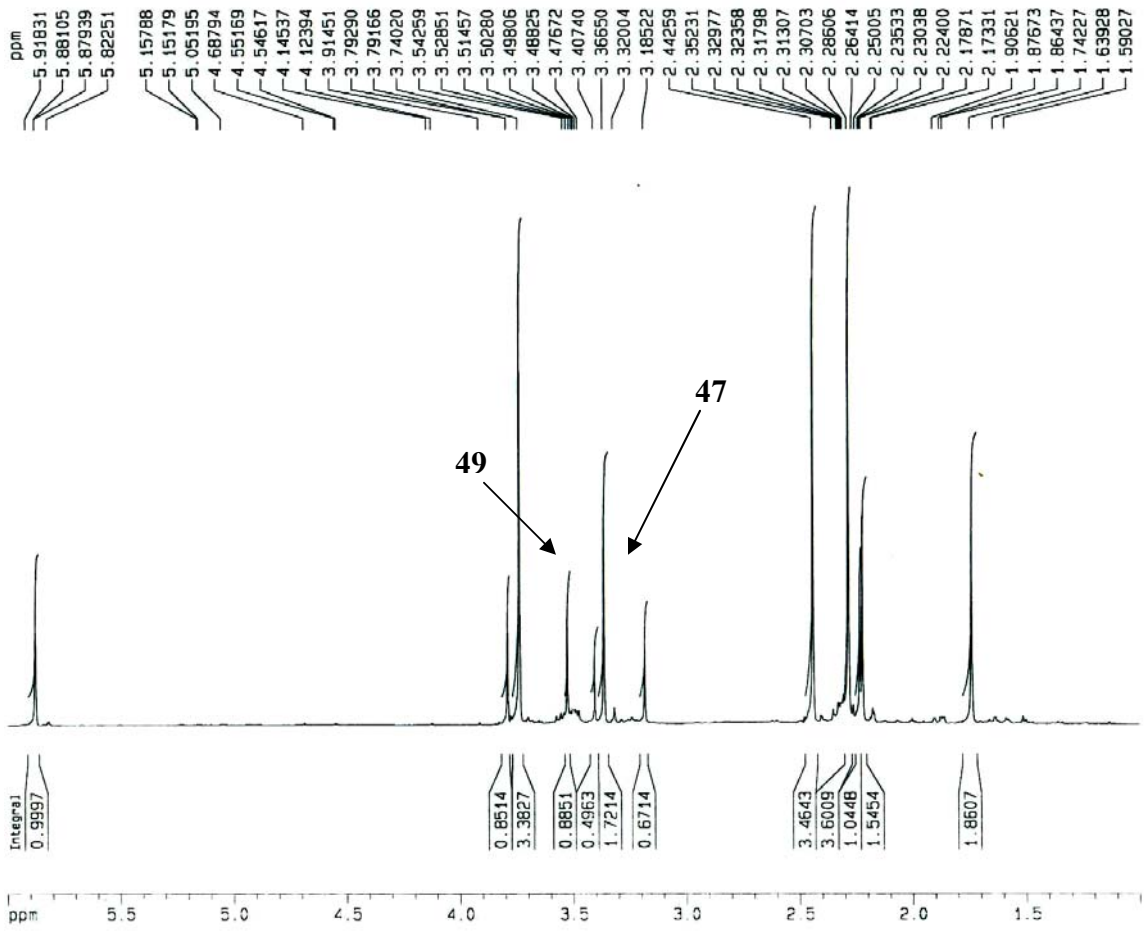


Figure 86: ^{1}H NMR of the crude product after 30 minutes of irradiation

As with the irradiation of **7** in methanol solution, the ^{1}H-NMR spectra of the crude product after 30 minutes of irradiation shows the presence of the photodimer **47** and an unknown product **49**.

In order to isolate the photoproduct, a second solution of **7** (2.0×10^{-2}M) in methanol was irradiated until HPLC analysis indicated maximum formation of the photoproduct. Preparative-layer chromatography of the resulting solution revealed a band at $R_f = 0.40$ due to the unconsumed reactant **7** and four additional bands at $R_f =$ 0.65, 0.25, 0.10, and 0. Although extraction of the bands at $R_f = 0.65$ and 0 resulted in

negligible recovery of any material, extraction of the band at R_f = 0.25 provided photodimer **47** as a white crystalline product, mp 229-230°C, and extraction of the band at R_f = 0.10 provided a photoproduct **49** as a white crystalline product, mp 119-120°C.

(a)

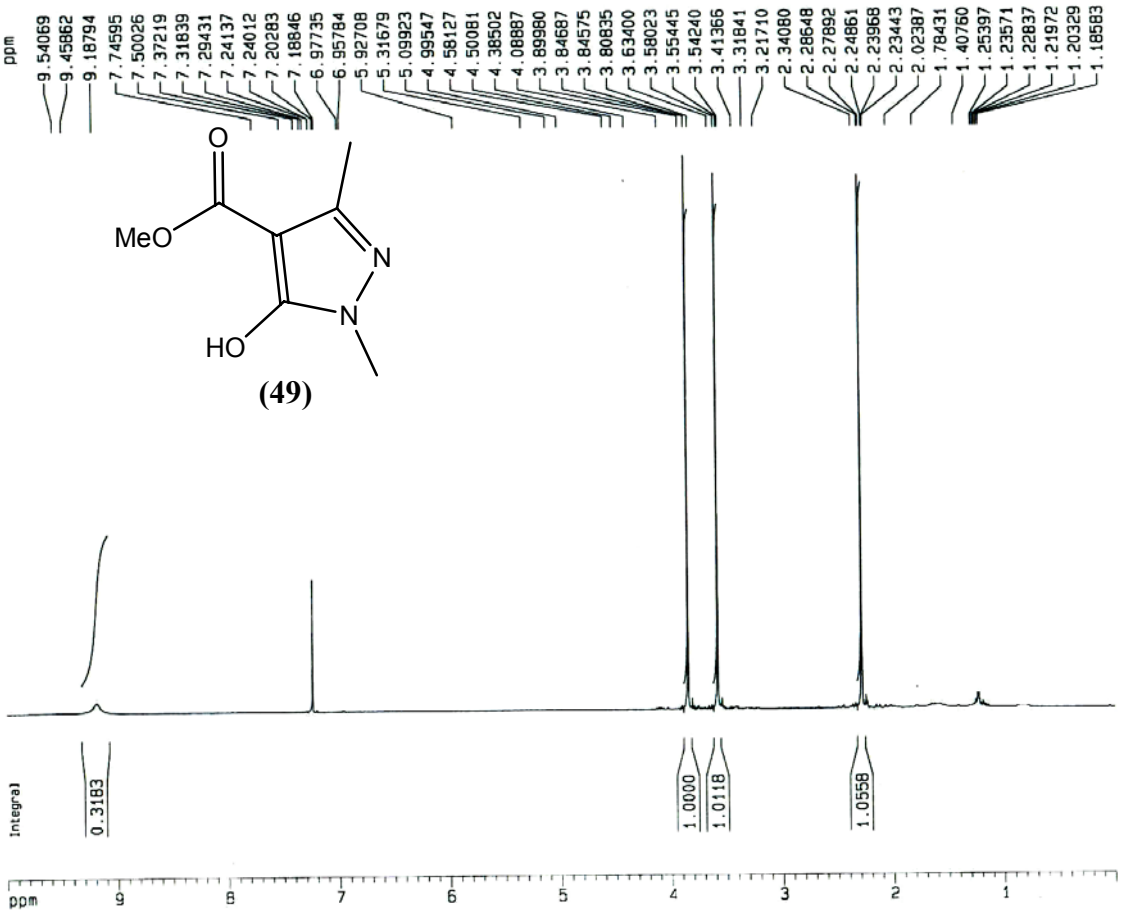
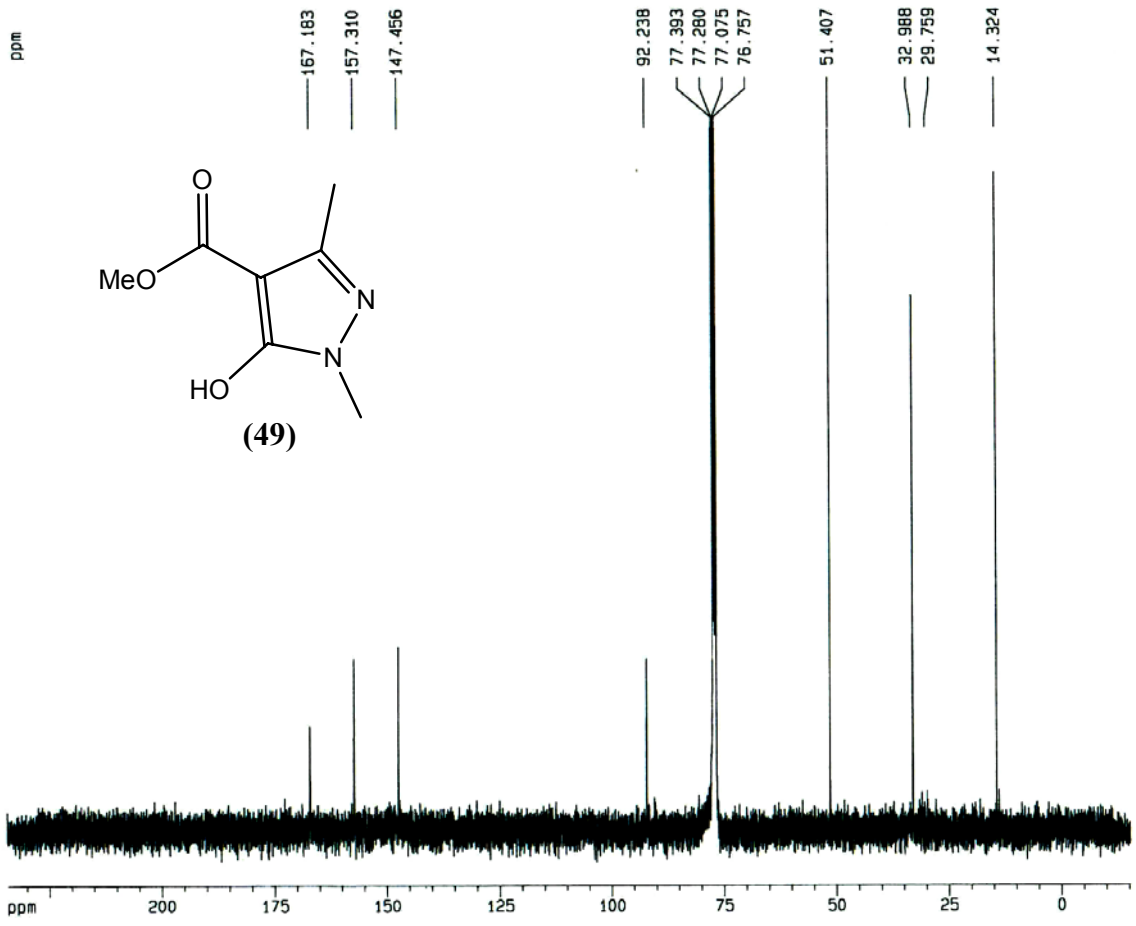


Figure 87 (a) shows the ^{1}H-NMR spectrum of the white crystalline photoproduct **49**. By comparison with the ^{1}H-NMR spectrum of the photoproduct formed upon irradiation of **7** in ethanol, the spectrum in Figure 87 (a) suggest that photoproduct **49** is methyl 5-hydroxy-1,3-dimethylpyrazole-4-carboxylate. Thus, the spectrum shows three 3H singlets at δ 3.85, 3.58, and 2.28 consistent with CH_3O,

CH_3N, and allylmethyl groups and a broad signal at δ 9.19 (D_2O exchangeable) consistent with an OH proton.

(b)



(49)

The ^{13}C-NMR spectrum (Figure 87 (b)) is also compatible with the structure **49**. The ester carbonyl carbon absorbs the furthest downfield at δ 167.2, while the signal at δ 157.3, 147.5, and 92.24 are consistent with the carbons at C-5, C-3, and C-4 of the pyrazole ring. In addition, the signals at δ 32.99 and 14.32 are due to the methyl carbons of the pyrazole ring at nitrogen atom and C-3, respectively, while the O-methyl carbon appears the signals at δ 51.41.

(c)

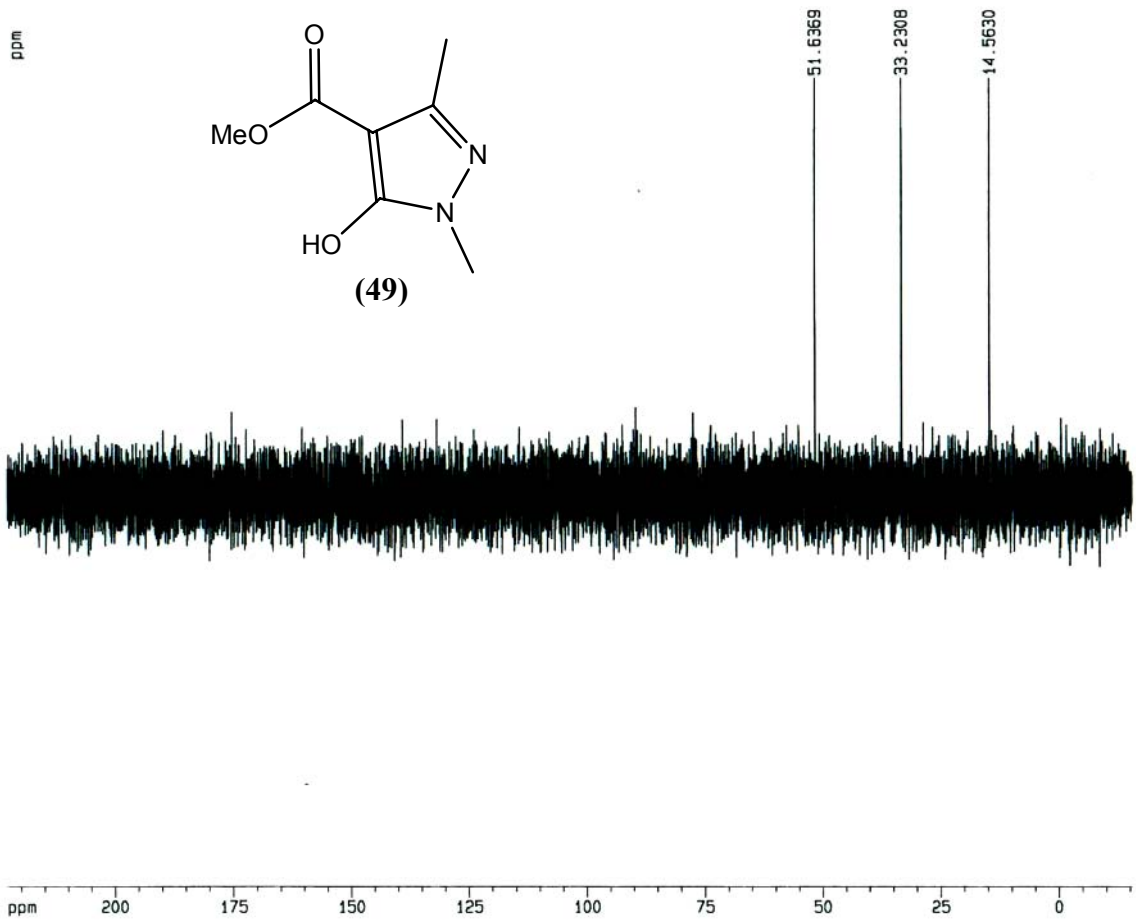


Figure 87: (a) ^{1}H NMR of compound **49**; (b) ^{13}C NMR of compound **49**; (c) ^{13}C NMR DEPT 135 of compound **49**.

As expected, the four signals at δ 167.2, 157.7, 147.6, and 92.71 disappeared in the ^{13}C-DEPT 135 spectrum (Figure 87 (c)) which is consistent with their assignment to the carbonyl carbon and three quaternary carbons of the pyrazole ring. In addition, the signals at δ 51.64, 33.23, and 14.56 still appear in the positive directions which are consistent with their assignment to the three methyl carbons.

Also, figure 88 shows the UV-absorption spectrum of an (4.0×10^{-5} M) solution in water. The spectrum exhibits λ_{max} at 256.5 nm and 203.5 nm with an extinction coefficient of 11,175 and 15,275 L mol^{-1} cm^{-1}. Considering the magnitude of these extinction coefficients, these two absorptions have been assigned to S_0 to S_1 (π,π^*) and S_0 to S_2 (π,π^*) transitions.

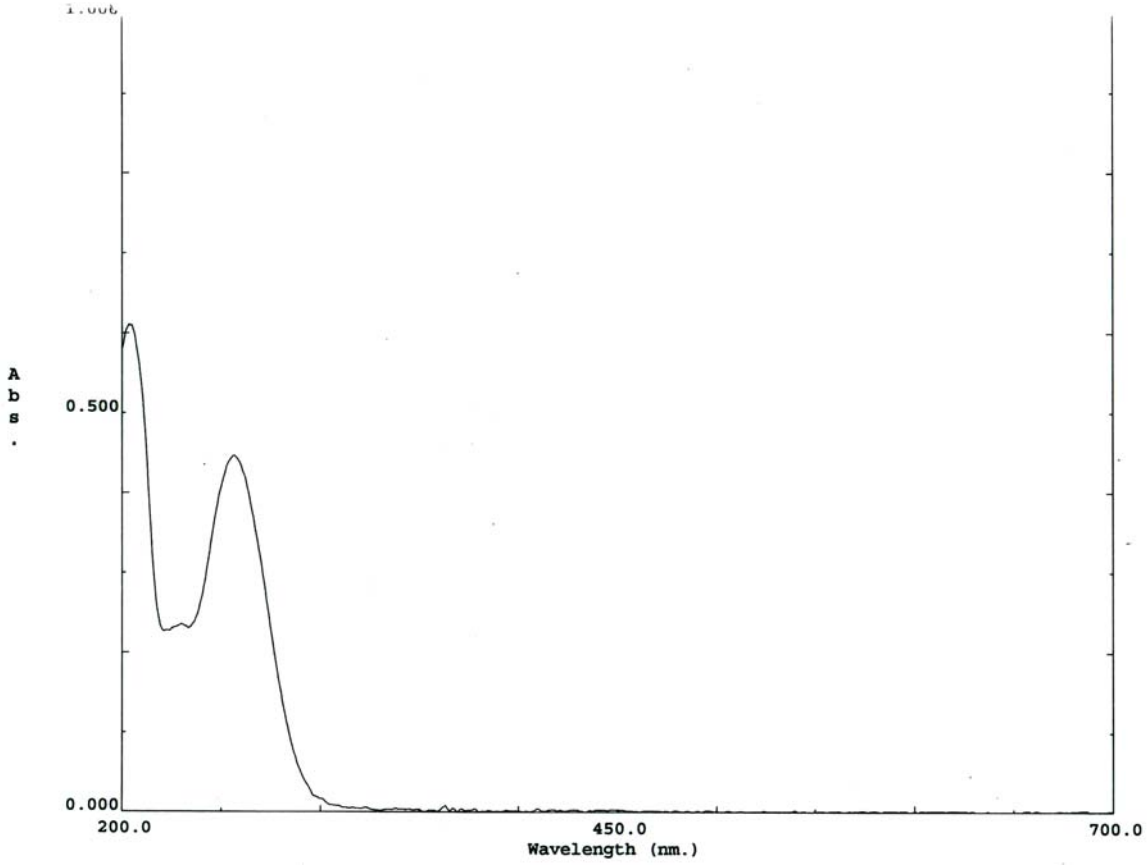


Figure 88: UV-absorption spectrum of **7** in water (4.0×10^{-5} M)

Figure 89 shows the UV-absorption spectrum of the same solution before and after 7 minutes of irradiation at 254 nm. As the figure shows, irradiation is accompanied by a decrease in the absorbance of the band at 256.5 nm from 0.447 to

0.293 and a shift from 256.5 nm to 257.0 nm. The absorption band at 203.5 nm decreases from 0.611 to 0.457 and a shift from 203.5 nm to 203.0 nm.

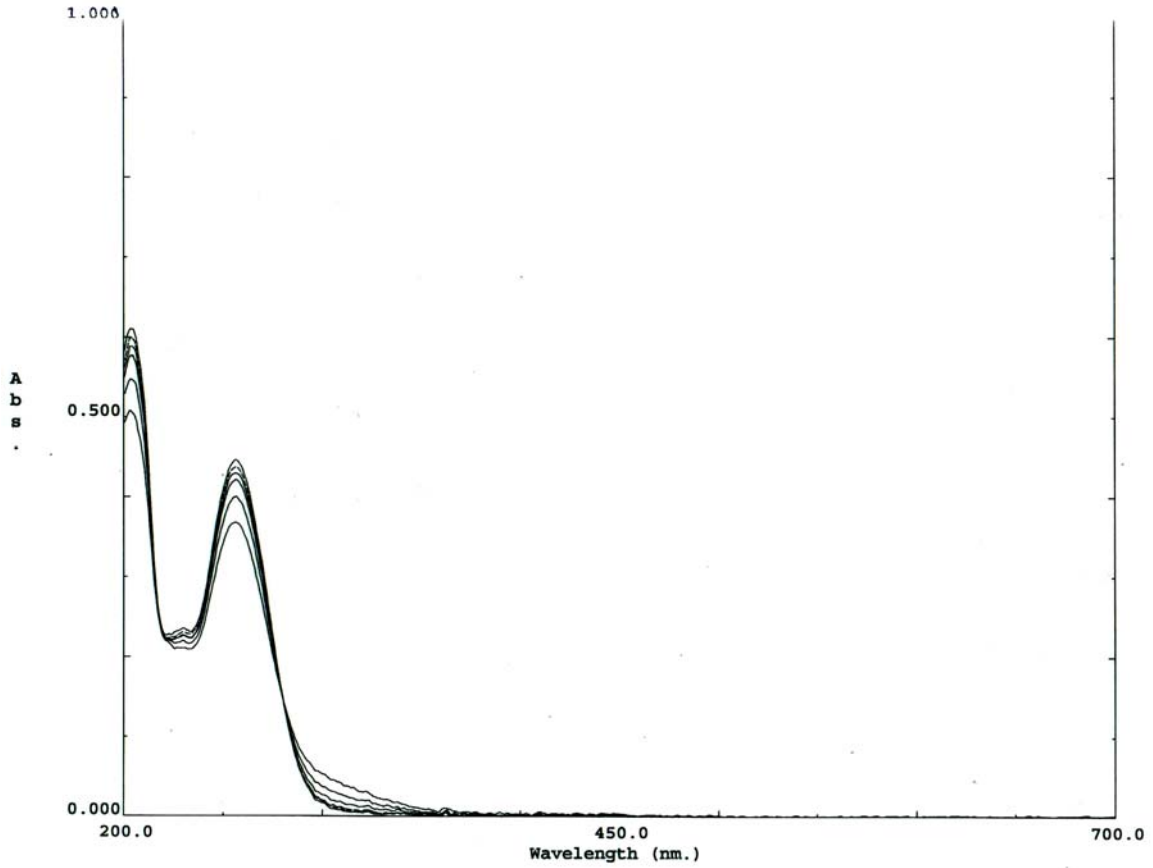


Figure 89: UV-overlay spectrum of the photolysis of **7** in water (4.0×10^{-5} M)

The photochemical reaction of **7** was also monitored by HPLC. Figure 90 shows the HPLC trace of **7** (2.0×10^{-2} M) in water (methanol 70 : water 30; flow rate = 0.50 ml/ min; detector at 250 nm). The trace shows only one peak due to **7** with a retention of 9.94 minutes. The solution of **7** (2.0×10^{-2} M) in water was placed in a quartz tube (20 cm long × 0.7 cm id). The tube was sealed with a rubber septum, purged with helium for 15 minutes, and irradiated at 254 nm with thirteen lamps. Aliquots were

removed for HPLC analysis after 10, 30, 45, 60, 120, 180, and 240 minutes of irradiation. Figure 91 shows the HPLC trace after 10 minutes of irradiation and reveals the formation of photodimer **47** with a retention of 9.2 minutes.

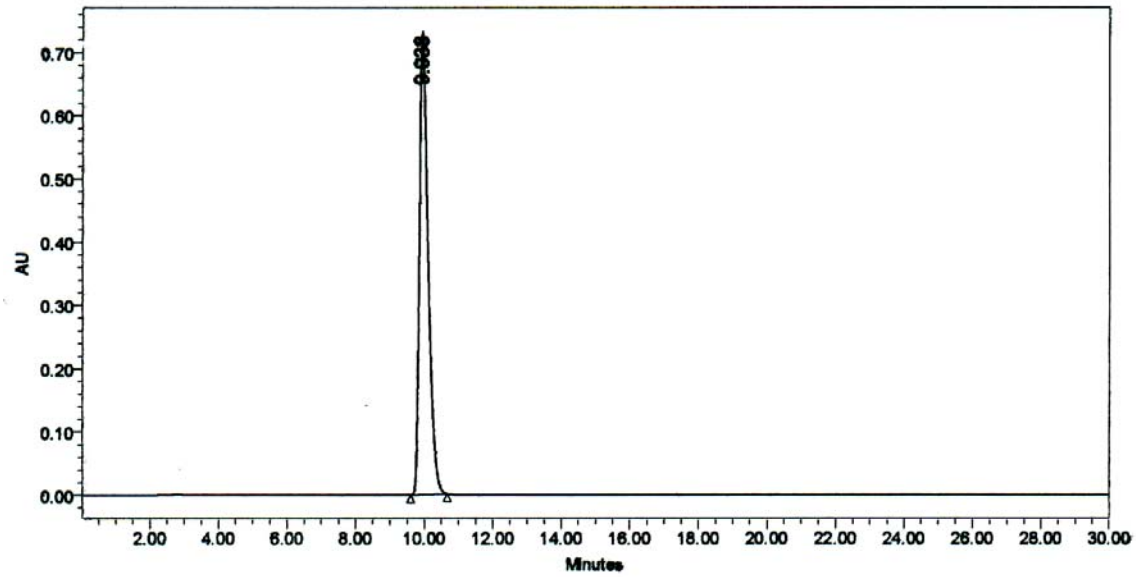


Figure 90: HPLC-trace of the solution **7** before irradiation

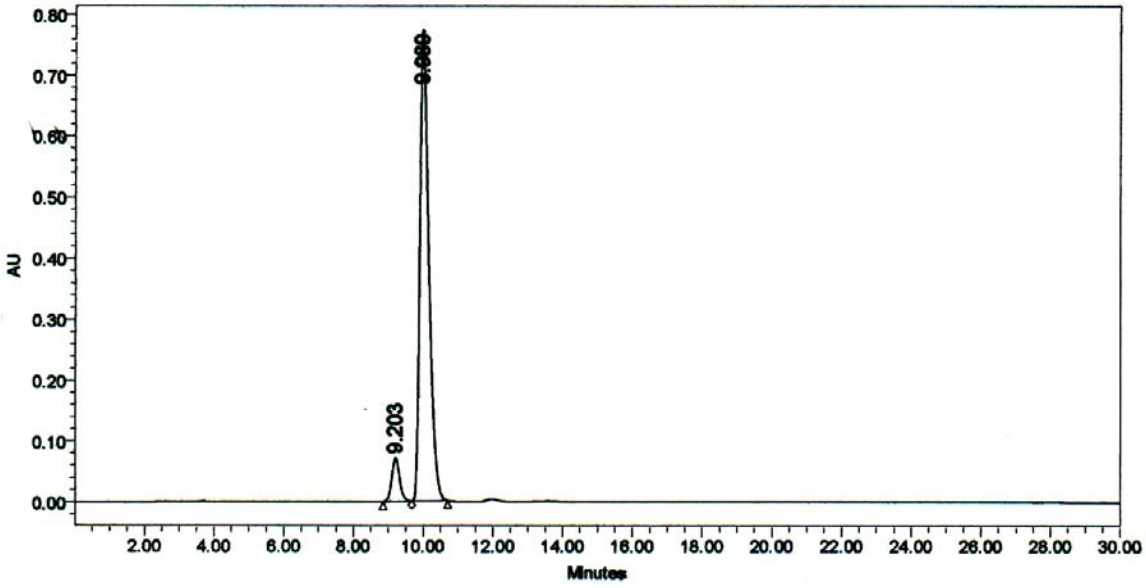


Figure 91: HPLC report of the solution of **7** after 10 minutes of irradiation

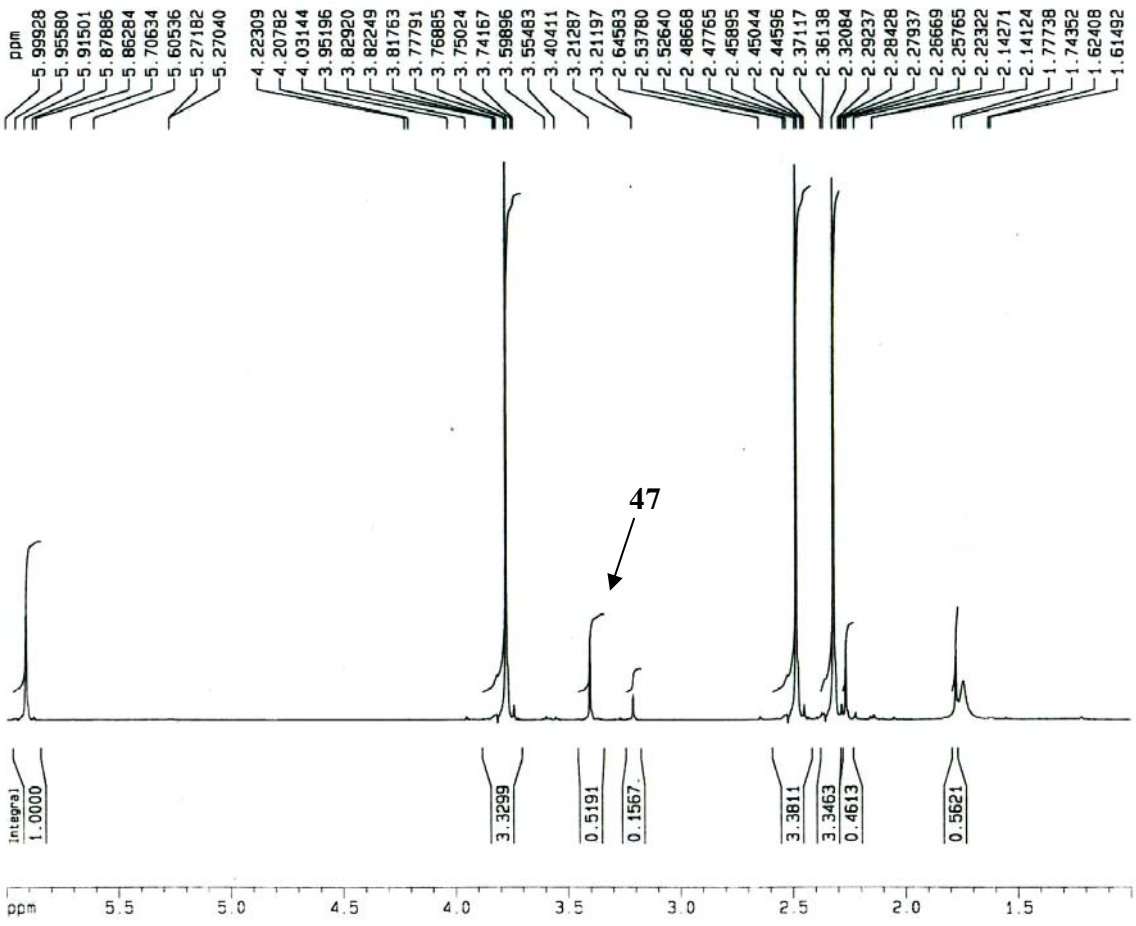


Figure 92: ^{1}H-NMR of the crude product after 10 minutes of irradiation

As with the irradiation of **7** in water solution, the ^{1}H-NMR spectra of the crude product after 10 minutes of irradiation shows only the presence of the photodimer **47**.

In order to isolate the photoproduct, a second solution of **7** (2.0×10^{-2}M) in water was irradiated until HPLC analysis indicated maximum formation of the photoproduct. Preparative-layer chromatography of the resulting solution revealed a band at $R_f = 0.40$ due to the unconsumed reactant **7** and three additional bands at $R_f =$ 0.55, 0.25, and 0. Although extraction of the bands at $R_f = 0.55$ and 0 resulted in negligible recovery of any material, extraction of the band at $R_f = 0.25$ provided a dimeric product **47**.

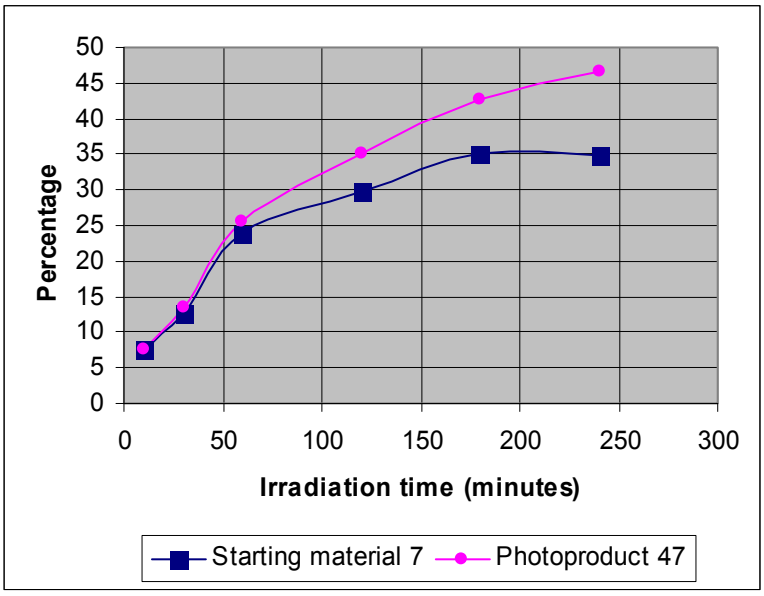


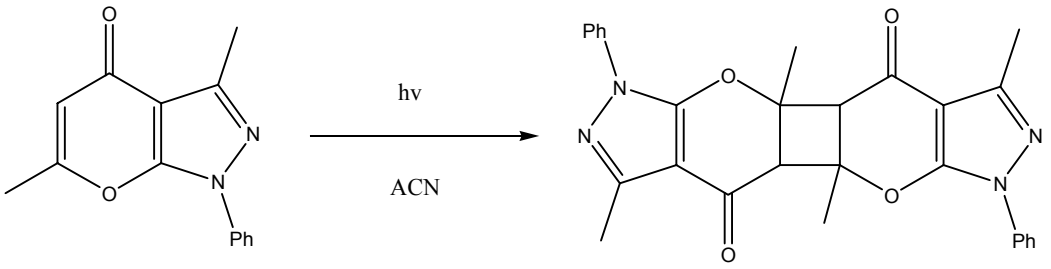
Figure 93: The correlation between the irradiation time of **7** and % consumption of **7** and %yield of **47**.

Figure 93 shows how the consumption of the reactant **7** and the yield of the photodimer **47** changed as a function of irradiation time. Comparison of Figure 93 with Figure 68 shows that **7** is more slowly consumed upon irradiation in water solution then

when **7** was irradiated in ACN. Thus while approximately 60 % of **7** was consumed after 60 minutes of irradiation in ACN solution, 26 % of **7** was consumed after irradiation of **7** for 60 minutes in water solution. Comparison of the two figures also shows that the yield of the photodimer is much less upon irradiation in ACN than upon irradiation in water. Thus, whereas in ACN the yield of **47** reaches a maximum of 35 % after 45 minutes of irradiation, in water the maximum yield of **47** is only 18 % after the same irradiation time. Furthermore, after 180 minutes of irradiation in water the yield of **47** reaches a maximum of 36 %.

Photochemistry of 3,6-dimethyl-1-phenyl[2,3-*c*]pyrazole-4(1*H*)-one

The photolysis of the N-phenylpyranopyrazole **4** gave the same results as N-methylpyranopyrazole 7 in both acetonitrle and ethanol solvents. 3,6-dimethyl-1-phenyl[2,3-*c*]pyrazole-4(1*H*)-one **(4)** in acetonitrile was observed to undergo the [2+2] cycloaddition reaction as shown below.



(4) **(52)**

Figure 94 shows the UV-absorption spectrum of a 4.0×10^{-5} M solution of **4** in acetonitrile (ACN) solution. The spectrum exhibits λ_{max} at 242.5 nm with extinction coefficients of 24,646 L mol^{-1} cm^{-1}, respectively. Considering the magnitude of this extinction coefficient, this absorption has been assigned to S_0 to S_1 (π,π^*) transition.

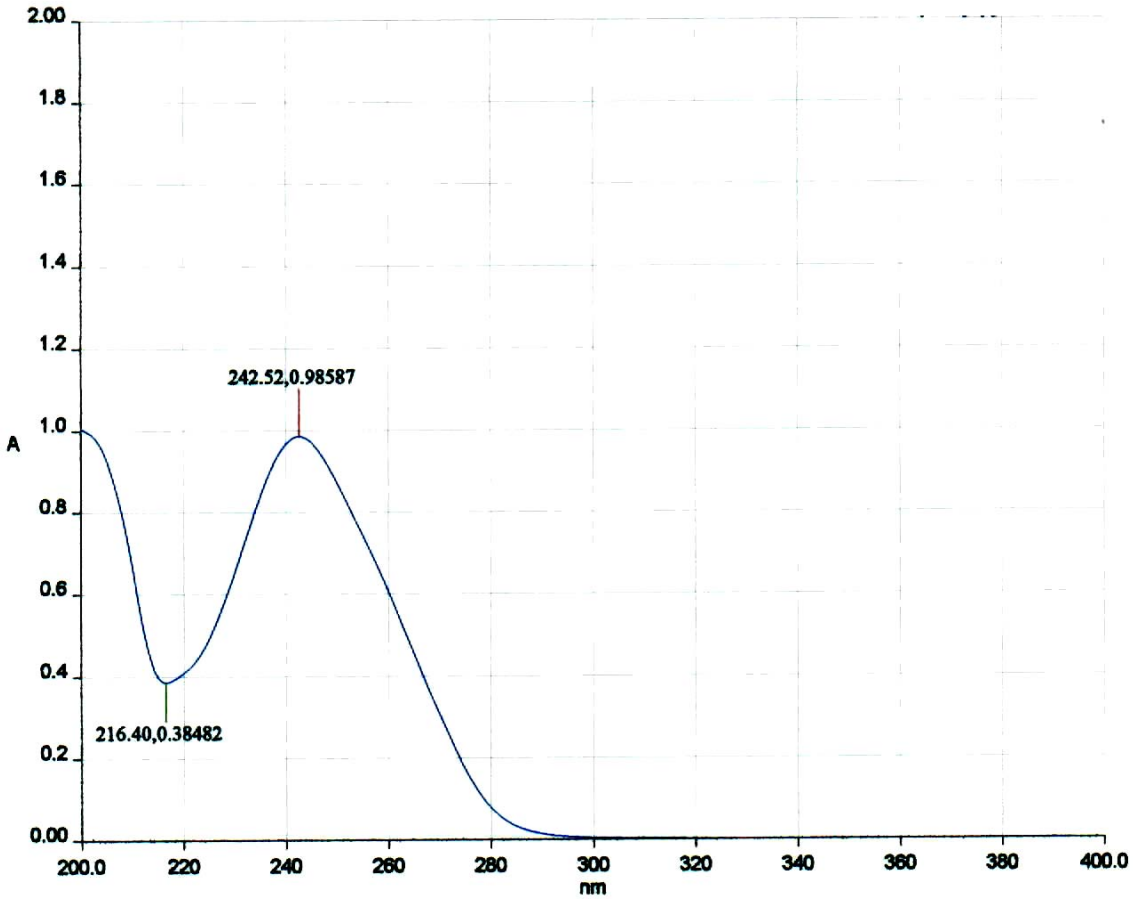


Figure 94: UV-absorption spectrum of **4** in acetonitrile (4.0×10^{-5} M)

Figure 95 shows the UV-absorption spectrum of the same solution before and after four consecutive 10 seconds irradiations at 254 nm. As the figure shows, irradiation is accompanied by a decrease in the absorbance of the band at 242.5 nm from 0.99 to 0.81.

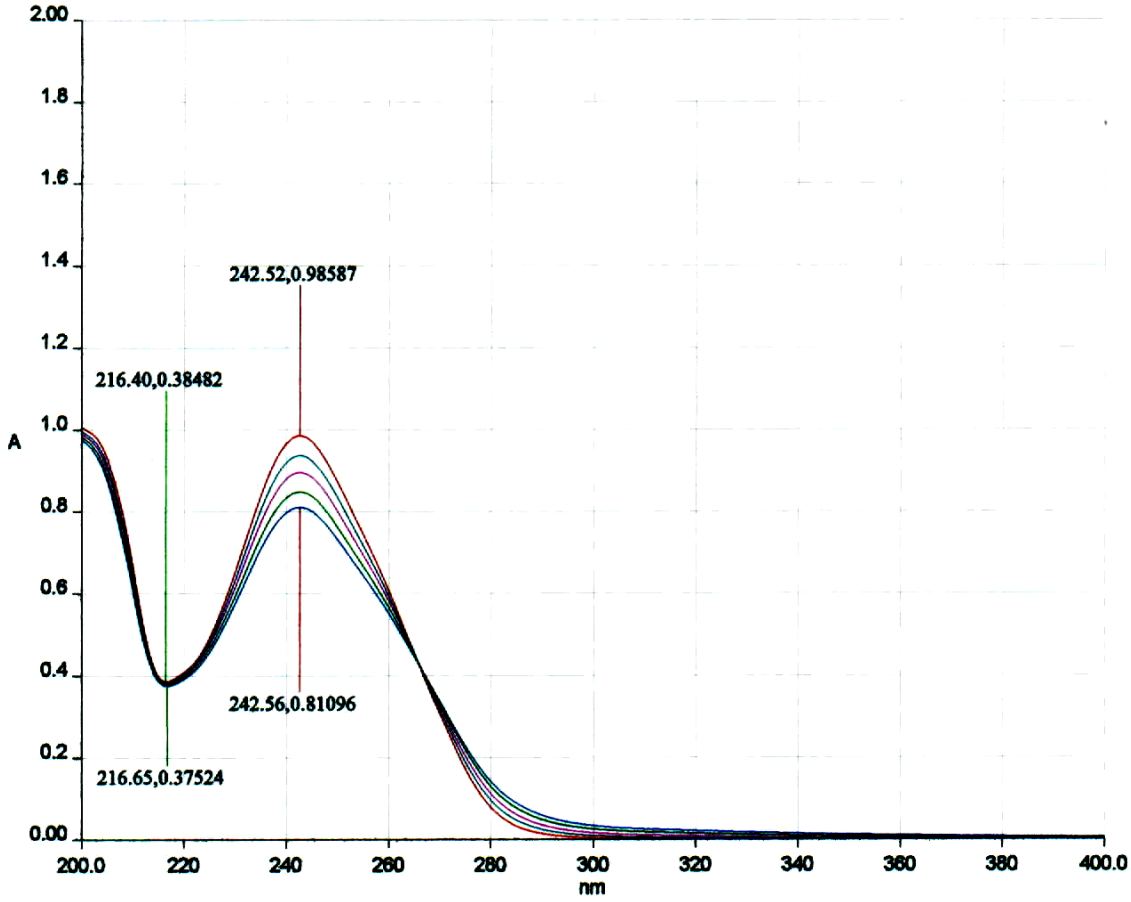


Figure 95: UV-overlay spectrum of the photolysis of **4** in acetonitrile (4.0×10^{-5} M)

The photochemical reaction of **4** was also monitored by HPLC. Figure 96 shows the HPLC trace of **4** (2.0×10^{-2} M) in ACN (methanol 65 : water 35; flow rate = 0.50 ml/ min; detector at 240 nm). The trace shows only one peak due to **4** with a retention of 14.4 minutes. The solution of **4** (2.0×10^{-2} M) in ACN was placed in a quartz tube (20 cm long × 0.7 cm id). The tube was sealed with a rubber septum, purged with helium for 15 minutes, and irradiated at 254 nm with thirteen lamps. Aliquots were removed for HPLC analysis after 5, 20, 45, 75, 120, and 180 minutes of irradiation.

Figure 97 shows the HPLC trace after 5 minutes of irradiation and reveals the formation of a product peak with a retention of 17.4 minutes.

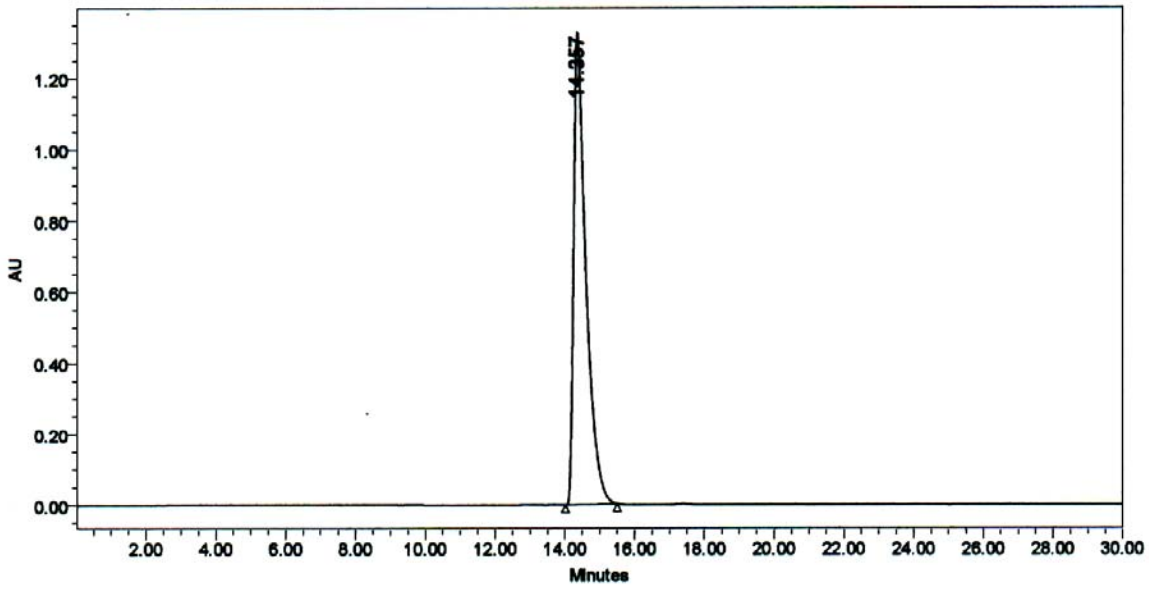


Figure 96: HPLC-trace of the solution **4** before irradiation

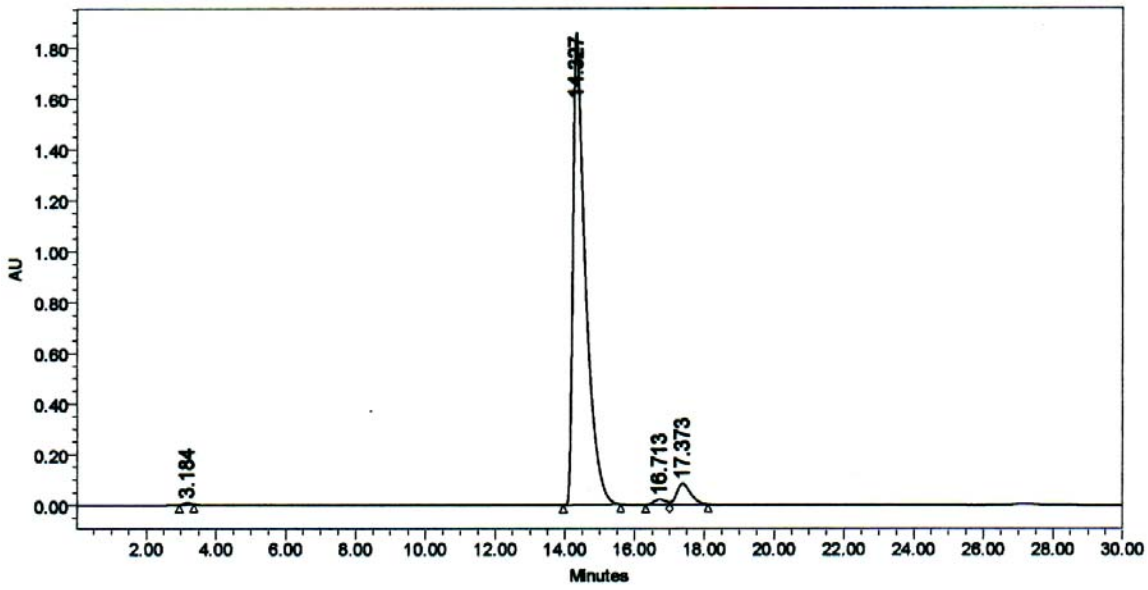


Figure 97: HPLC report of the solution of **4** after 5 minutes of irradiation

Figure 98 shows how these peak areas changed during the irradiation time. The figure shows a continuous decrease in the peak area of the reactant indicating continuous consumption of the reactant during the 180 minutes of irradiation.

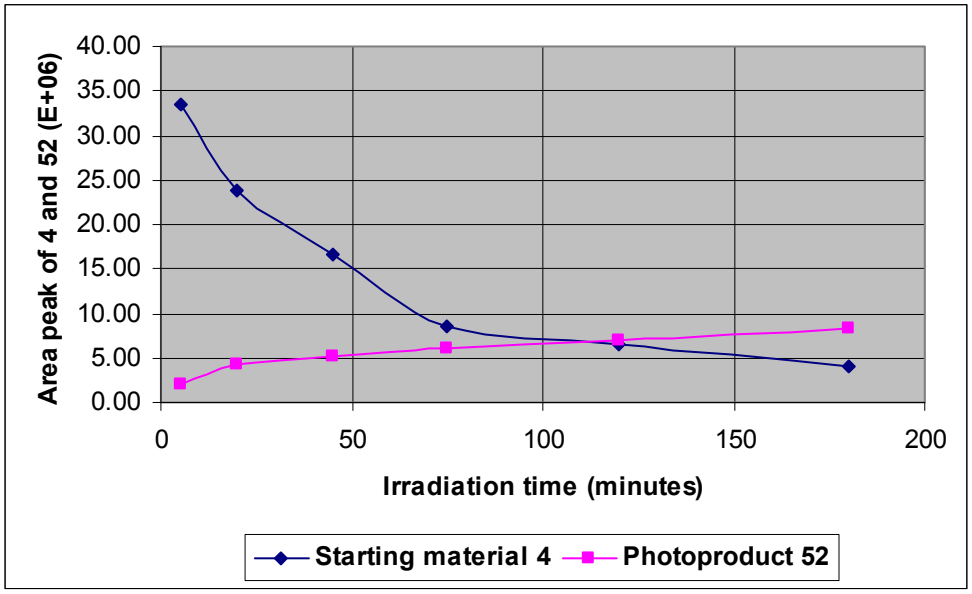


Figure 98: The correlation between the irradiation time of **4** and Area peak of **4** and **52**

As shown in the graph, however, there is a change in the slope at approximately 75 minutes of irradiation indicating that after that time there was a decrease in the rate of reactant consumption. Figure 98 shows that the peak area due to the product slow increases upon longer irradiation time.

In order to isolate the photoproduct, a second solution of **4** (2.0×10^{-2}M) in ACN was irradiated until HPLC analysis indicated maximum formation of the photoproduct. Preparative-layer chromatography of the resulting solution revealed a band at $R_f = 0.45$ due to the unconsumed reactant **4** and five additional bands at $R_f =$ 0.80, 0.70, 0.50, 0.30, and 0. Although extraction of the bands at $R_f = 0.80$, 0.70, 0.30,

and 0 resulted in negligible recovery of any material, extraction of the band at $R_f = 0.50$ provided a white crystalline product, mp 180-181°C.

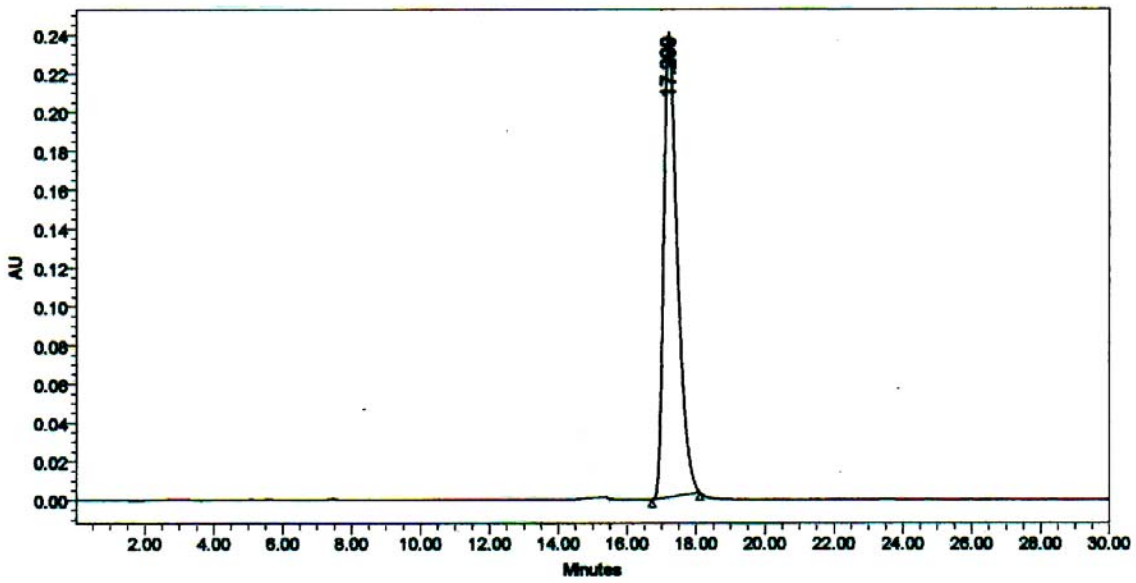


Figure 99: HPLC-trace of an isolated product of **52**

HPLC analysis of an ACN solution of this material in Figure 99 showed the peak with a retention time of 17.4 minutes identical to the retention time of the product peak shown in Figure 97. This confirms that the isolated white crystalline compound is the photoproduct observed by HPLC.

This photoproduct was also analyzed by mass spectrometer. The mass spectrum of the material is shown in Figure 100 and reveals a molecular ion plus proton at (M+H)/Z = 481 with major fragments at M/Z 281, 241, 218, 201, 157, 139, 124, and 82.

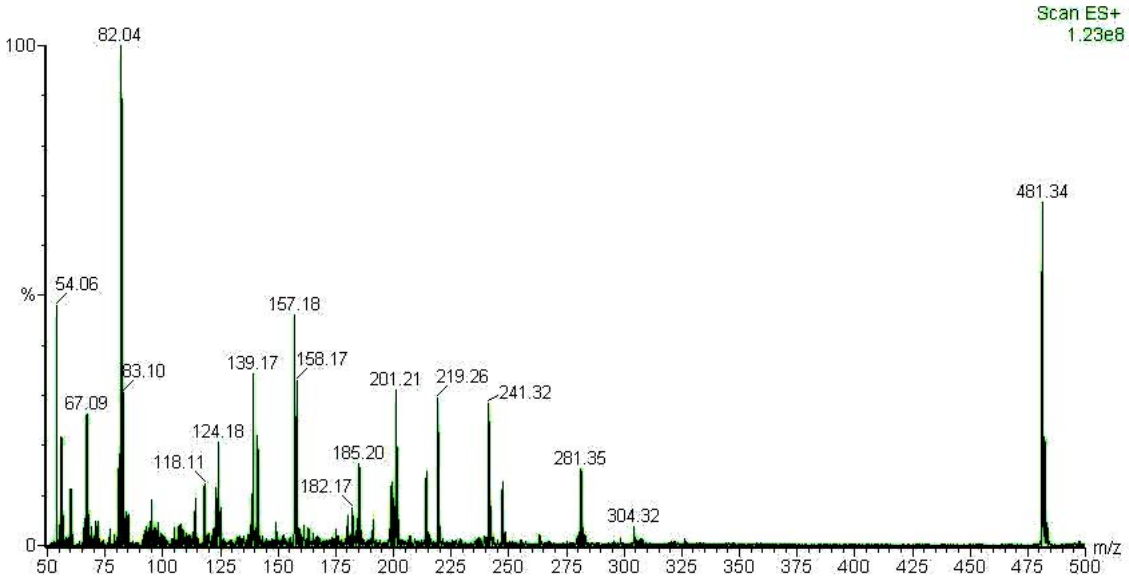
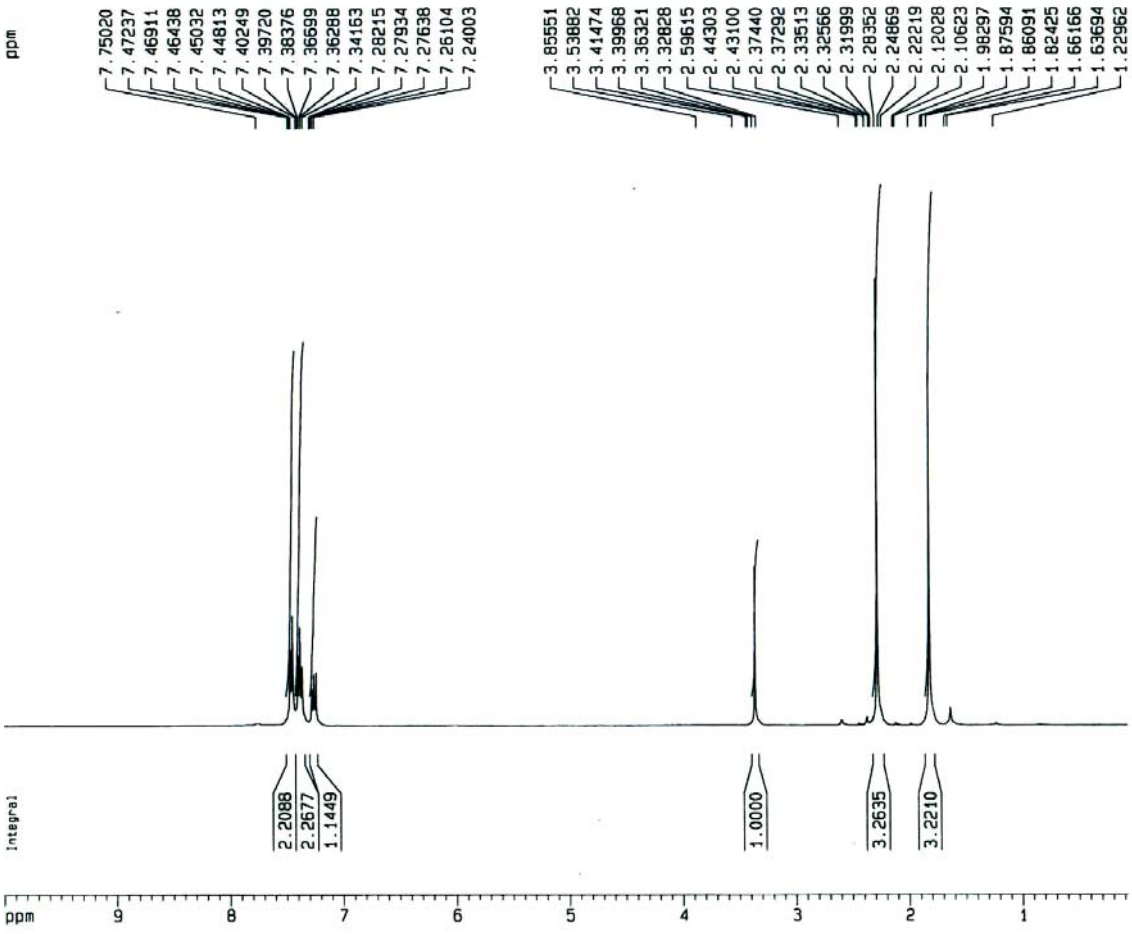


Figure 100: Mass spectrum of the photoproduct **52**

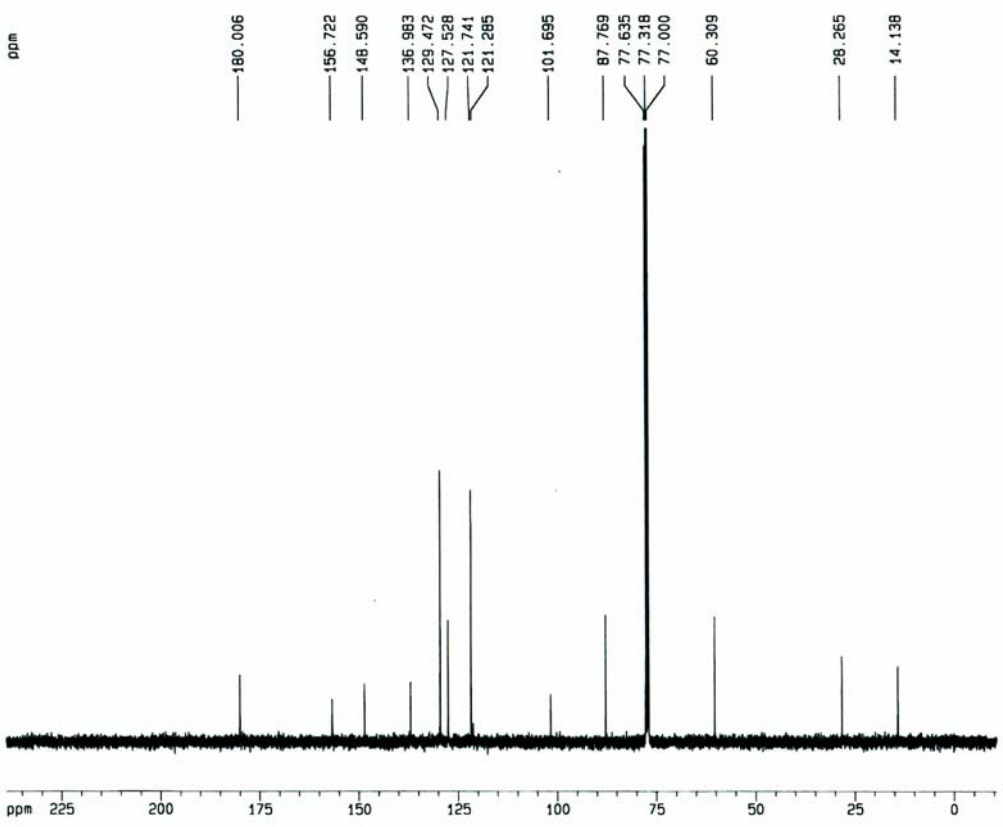
The subtraction of molecular ion at (M+H)/Z 481 by one proton, the molecular weight of this photoproduct is thus 480 which is exactly twice the mass of the reactant which has a molecular weight of 240. Therefore, the mass spectrum shows that the photoproduct is a dimer of the reactant. Elemental analysis of the photoproduct showed 69.75 % carbon, 4.75 % hydrogen, and 11.41 % nitrogen which is consistent with the molecular formula of $C_{28}H_{24}N_4O_4$, the correct formula of a dimer.

(a)



The ^{1}H-NMR spectrum of the photoproduct (Figure 101(a)) shows signals at δ 1.82, 2.28, and 3.23 with an integrated ratio of 3:3:1. The protons of the phenyl rings due to ortho, meta, and para positions appear as a double (J = 7.6 Hz) at δ 7.47, the two triplets (J = 7.3 Hz) at δ 7.39, and (J = 7.6 Hz) at δ 7.26 with an integrated ratio of 2:2:1, respectively. Thus, although the molecular formula is consistent with the presence of two phenyl groups and four methyl groups, the ^{1}H-NMR shows the presence of these different sets of methyl groups.

(b)


ppm
180.006
156.722
148.590
136.983
129.472
127.528
121.741
121.285
101.695
87.769
77.635
77.318
77.000
60.309
28.265
14.138
ppm 225 200 175 150 125 100 75 50 25 0

(c)

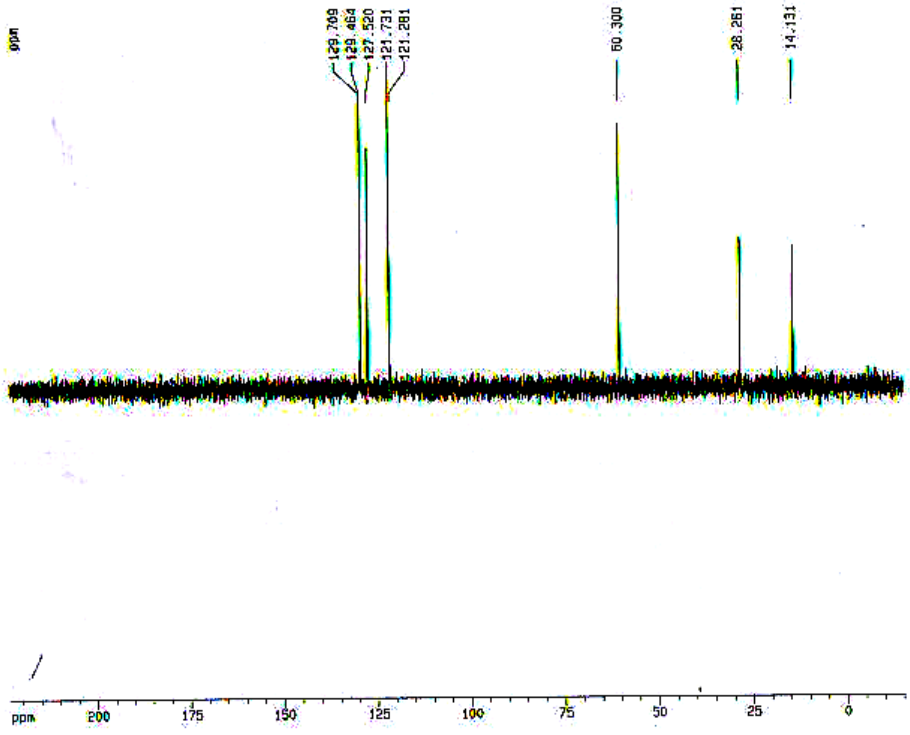

ppm
129.709
129.464
127.520
121.731
121.281
60.300
28.261
14.131
ppm 200 175 150 125 100 75 50 25 0

Figure 101: (a) ^{1}H-NMR of compound **52**; (b) ^{13}C-NMR of compound **52** and (c) ^{13}C-NMR DEPT 135 of compound **52**

The ^{13}C-NMR spectrum in Figure 101(b) shows the presence of twelve different sets of carbon atoms and the ^{13}C-NMR DEPT 135 spectrum in Figure 101(c) shows the presence of six different sets of positive carbon atoms. Since the molecular formula shows that the photoproduct contains 28 carbon atoms. The ^{1}H and ^{13}C spectra indicate that the dimer must have a very symmetric structure with each half identical to the other.

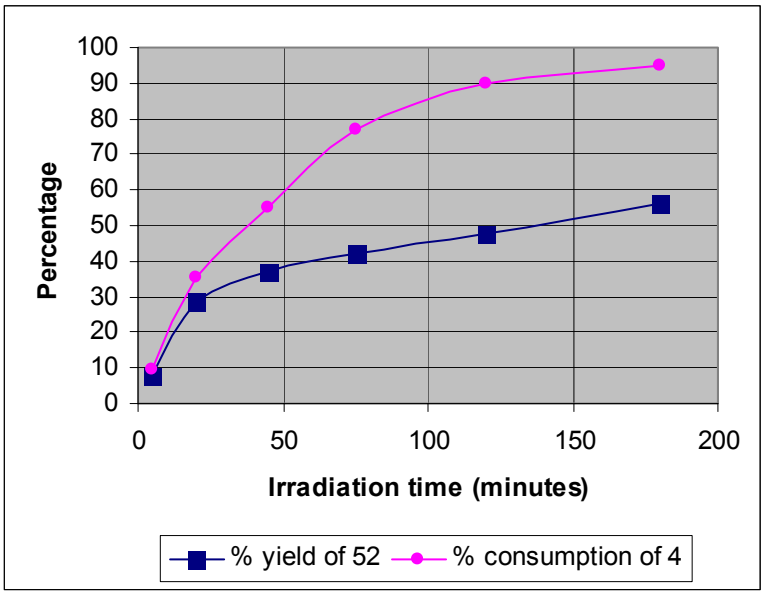


Figure 102: The correlation between the irradiation time of **4** and % consumption of **4** and % yield of **52**.

Based on the results in Figure 98, the results of the HPLC analyses are summarized in Figure 102 where the percent consumption of the reactant **4** and the percent yield of the photoproduct **52** are plotted as a function of irradiation time and were determined by the peak area relative to standard curve. The figure is also

consistent with Figure 14-5 that shows the consumption of the reactant **4** with a decrease in the slope at 75 minutes indicating a decrease in the rate of consumption of **7** after that time. The figure also shows a steady increase in the yield of the photoproduct **52** until a maximum yield of 58 % was reached at 180 minutes of irradiation.

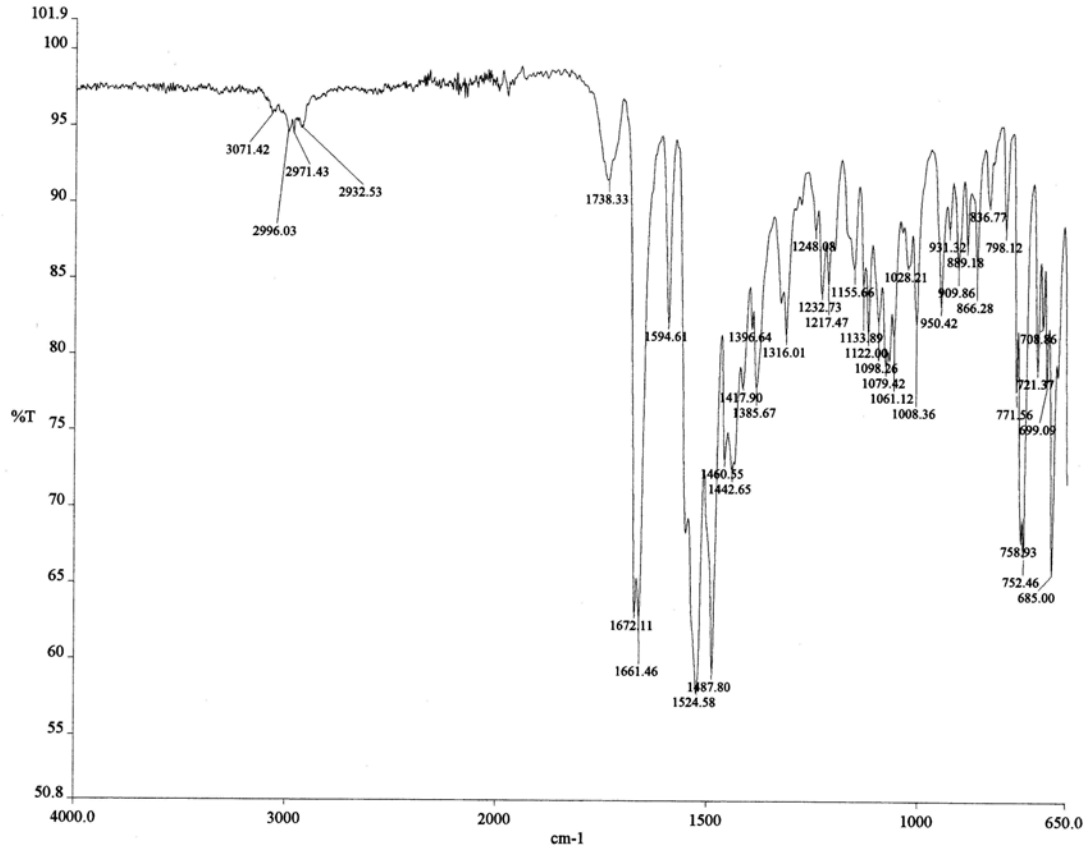
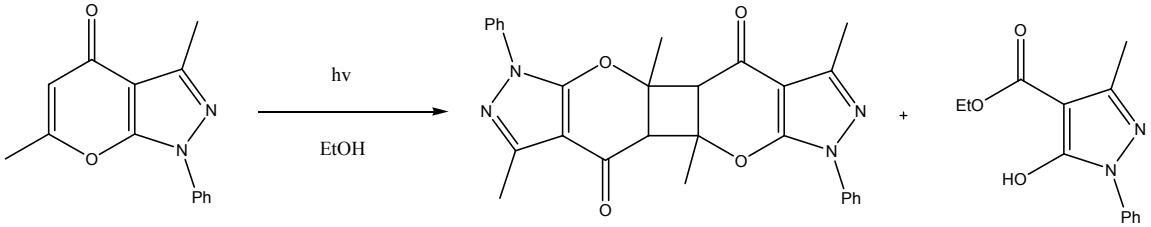


Figure 103: IR spectrum of the photoproduct **52**

Figure 103 shows the IR spectrum of the dimeric product **52** which is consistent with the structure. The =C-H stretching peak of the phenyl ring absorbs at 3,071 cm^{-1}, while the C-H stretching peaks of the aliphatic chain absorbs at 2,996 and 2,971 cm^{-1}. The intense absorption of 1,672 cm^{-1} is due to the carbonyl (C=O) stretching of the ketone group. The strong signals of 1,524 and 1,487 cm^{-1} are consistent with C=C stretching of the pyrazole and phenyl rings.

The photochemistry of pyranopyrazole **4** was also investigated in ethanol solution as shown below.



(4) **(52)** **(53)**

Figure 104 shows the UV-absorption spectrum of an (4.0×10^{-5} M) solution of **4** in ethanol. The spectrum exhibits λ_{max} at 242.8 nm and 204.0 nm with extinction coefficients of 29,622 and 26,867 and L mol^{-1} cm^{-1}, respectively. Considering the magnitude of these extinction coefficients, these two absorptions have been assigned to S_0 to S_1 (π,π^*) and S_0 to S_2 (π,π^*) transitions.

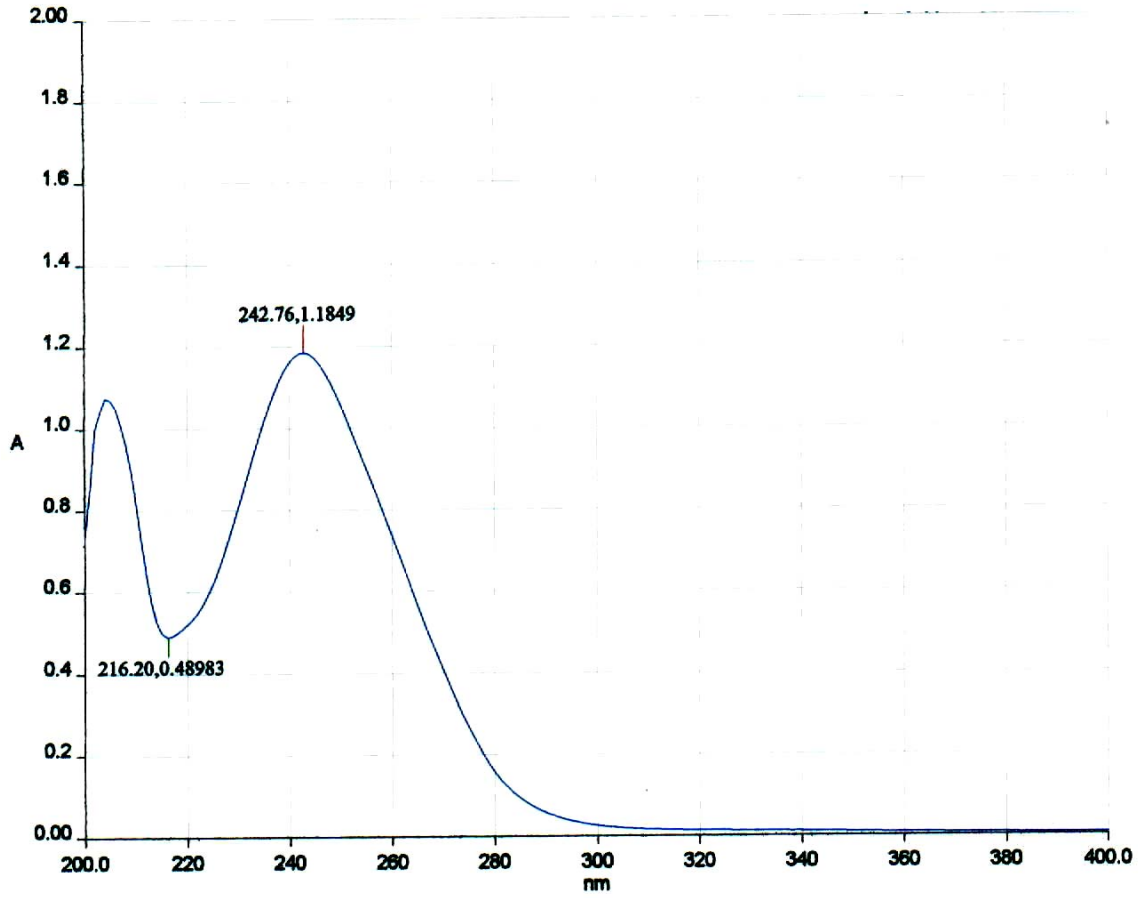


Figure 104: UV-absorption spectrum of **4** in ethanol (4.0×10^{-5} M)

Figure 105 shows the UV-absorption spectrum of the same solution before and after four consecutive 10 seconds irradiation at 254 nm. As the figure shows, irradiation is accompanied by a decrease in the absorbance of the band at 242.8 nm from 1.18 to 0.66 and a shift from 242.8 nm to 240.0 nm. The absorption band at 204.0 nm decreases from 1.07 to 0.92 and a shift from 204.0 to 203.0 nm.

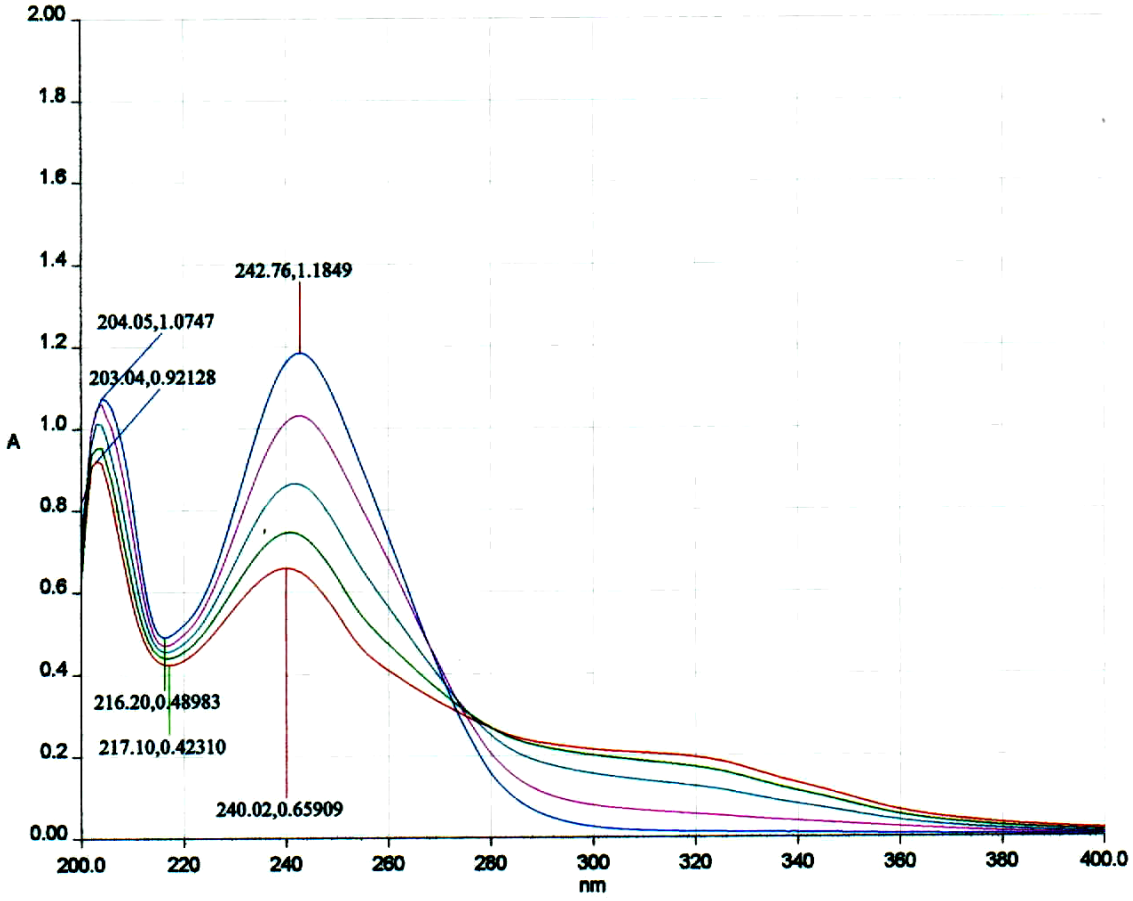


Figure 105: UV-overlay spectrum of the photolysis of **4** in ethanol (4.0×10^{-5} M)

The photochemical reaction of **4** was also monitored by HPLC. Figure 106 shows the HPLC trace of **4** (2.0×10^{-2} M) in ethanol (methanol 65 : water 35; flow rate = 0.50 ml/ min; detector at 240 nm). The trace shows only one peak due to **4** with a retention of 14.4 minutes. The solution of **4** (2.0×10^{-2} M) in ethanol was placed in a quartz tube (20 cm long × 0.7 cm id). The tube was sealed with a rubber septum, purged with helium for 15 minutes, and irradiated at 254 nm with thirteen lamps. Aliquots were removed for HPLC analysis after 5, 20, 45, 75, 120, and 180 minutes of irradiation. Figure 107 shows the HPLC trace after 20 minutes of irradiation and reveals the formation of a product peak with a retention of 17.3 minutes.

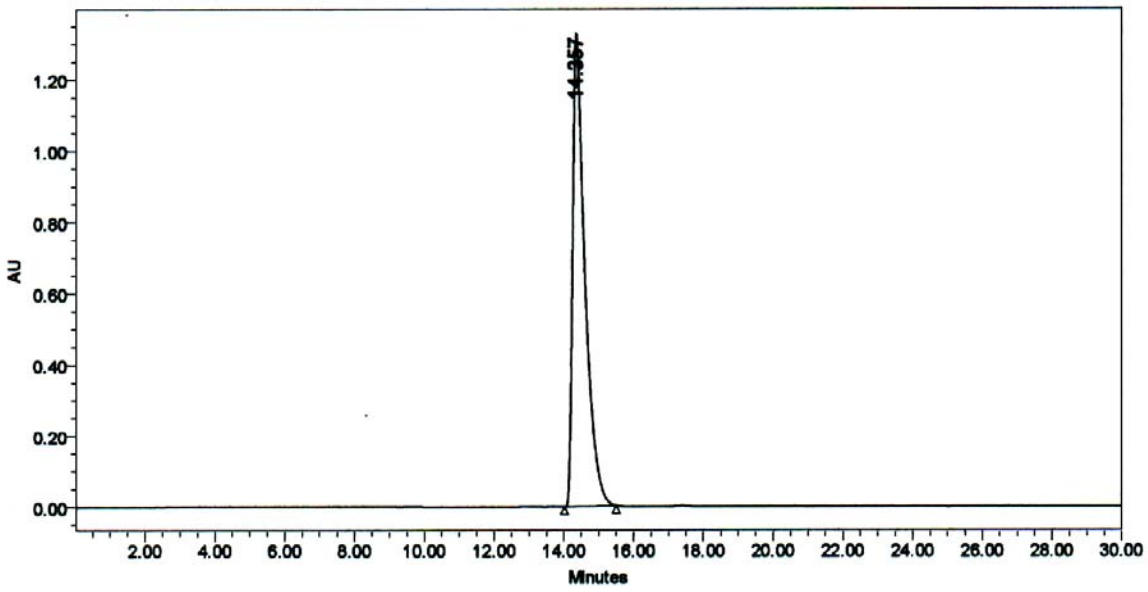


Figure 106: HPLC-trace of the solution **4** before irradiation

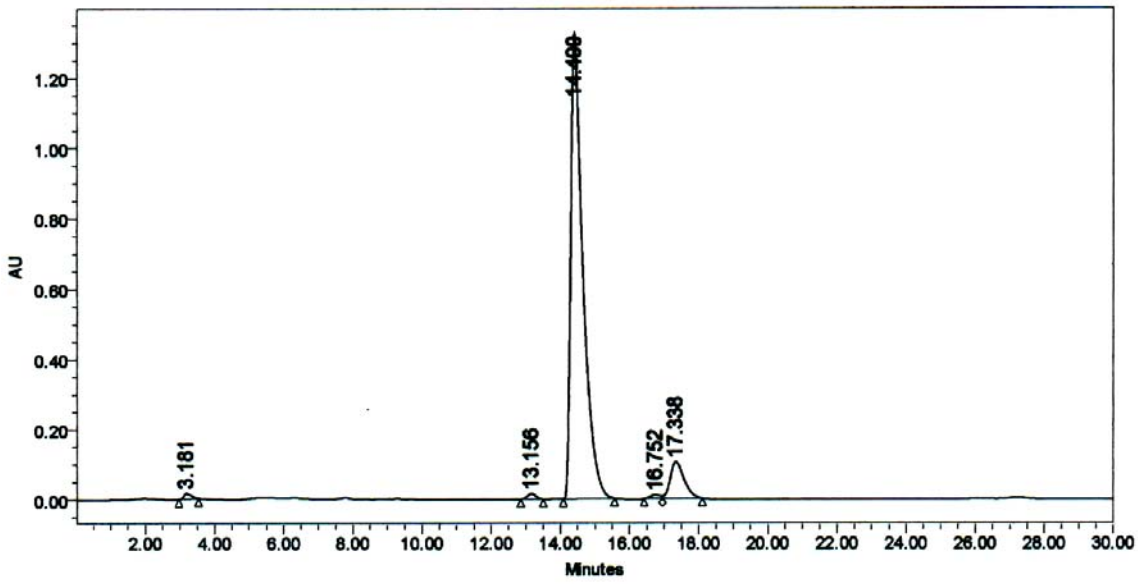


Figure 107: HPLC report of the solution of **4** after 20 minutes of irradiation

Figure 108 shows how these peak areas changed during the irradiation time. The figure shows a continuous decrease in the peak area of the reactant indicating continuous consumption of the reactant during the 180 minutes of irradiation.

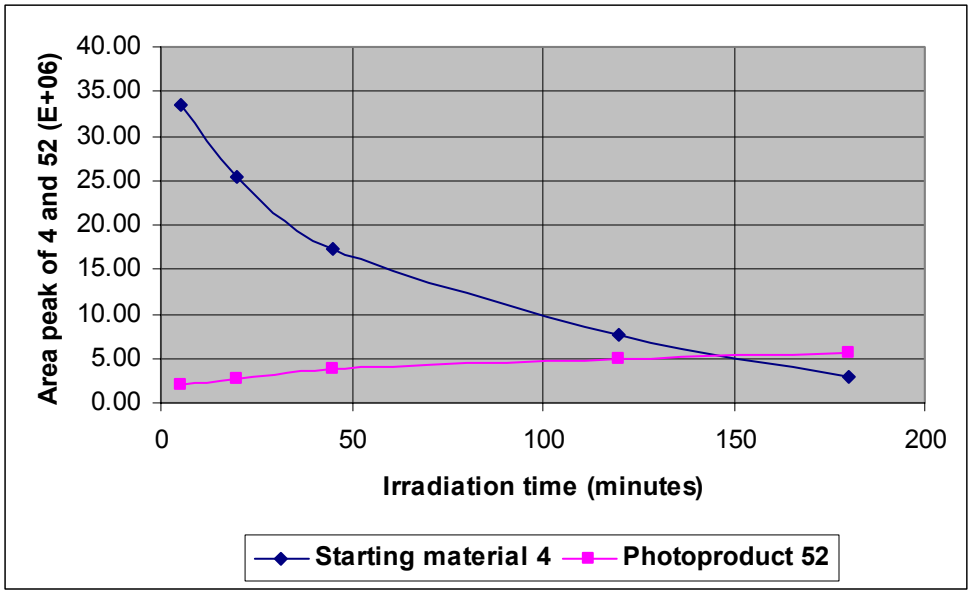


Figure 108: The correlation between the irradiation time of **4** and Area peak of **4** and **52**.

As shown in the graph, however, there was a decrease in the rate of reactant consumption constantly upon longer irradiation time. Also, the figure shows that the peak area due to the product increases during the first 45 minutes of irradiation and then slowly increases upon longer irradiation time.

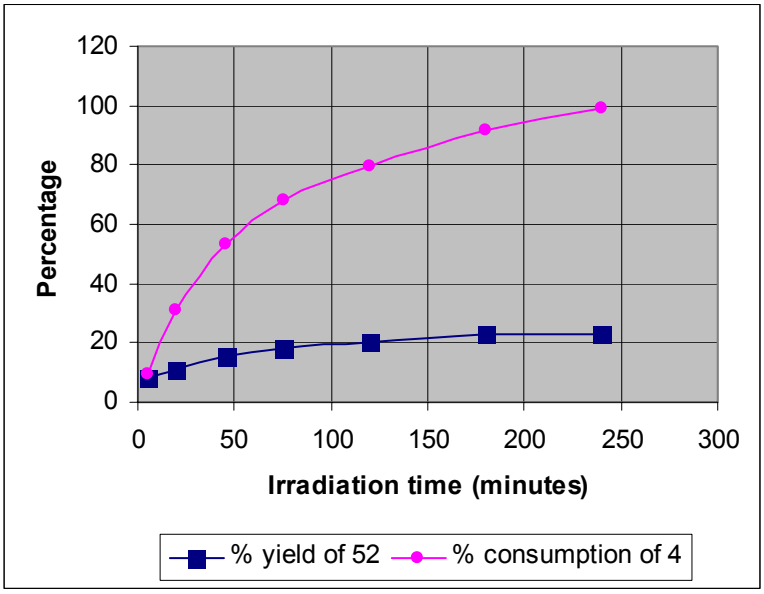


Figure 109: The correlation between the irradiation time of **4** and % consumption of **4** and % yield of **52**.

Figure 109 shows how the consumption of the reactant **7** and the yield of the photodimer **52** changed as a function of irradiation time. Comparison of Figure 109 with Figure 102 shows that rate of consumed **4** is the same upon irradiation when **4** was irradiated in ACN and ethanol solutions. In contrast, comparison of the two figures shows that the yield of the photodimer is much less upon irradiation in ethanol than

upon irradiation in ACN. Thus, whereas in ACN the yield of **52** reaches a maximum of 58 % after 180 minutes of irradiation, in ethanol the maximum yield of **52** is only 22 % after the same irradiation time.

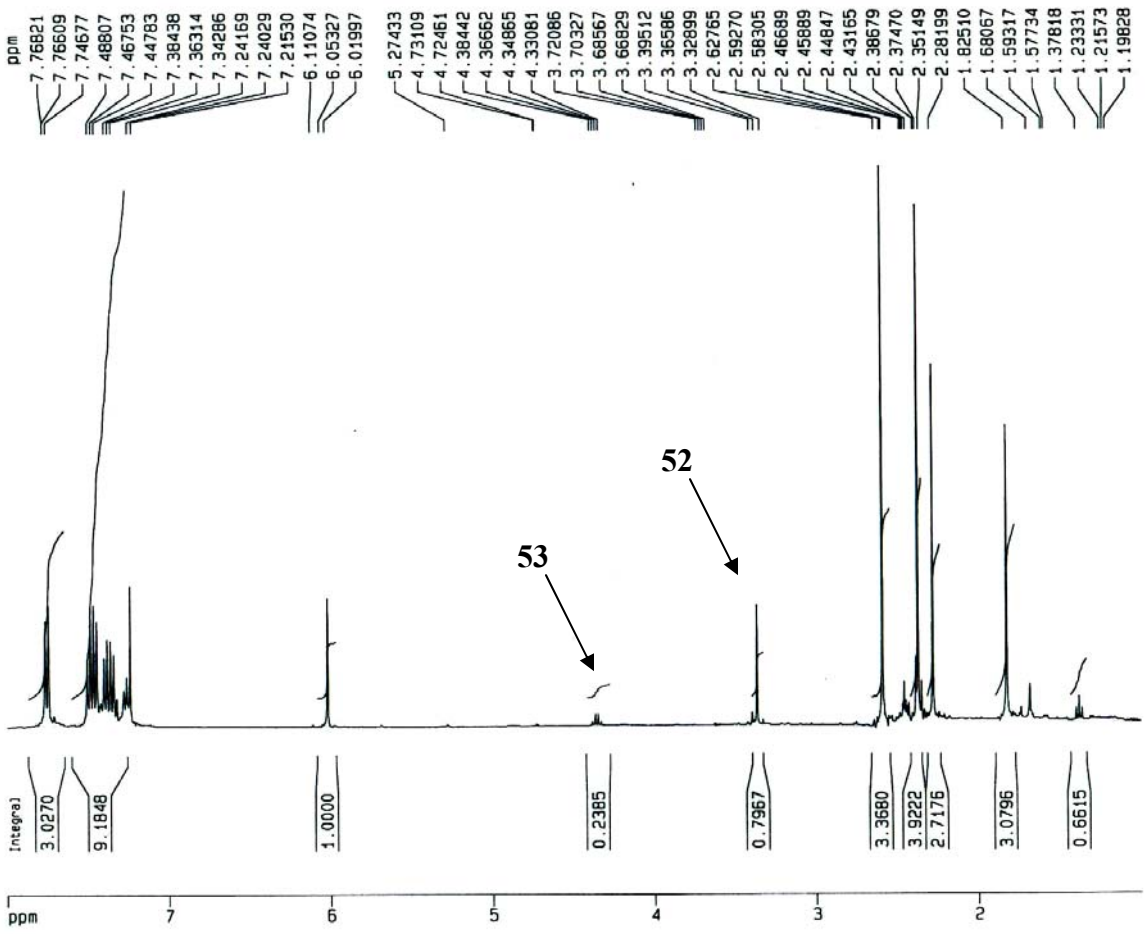


Figure 110: ^{1}H-NMR of the crude product after 20 minutes of irradiation

Surprisingly, the ^{1}H-NMR spectra of the crude product mixture after 20 minutes of irradiation shows the formation of the photodimer **52**, and the formation of a second product **53** which was not detected by 240 nm lamp of the HPLC detector. That means the absorption coefficient of the photoproduct **53** might be low at 240 nm.

In order to isolate the photoproduct, a second solution of **4** (2.0×10^{-2}M) in ethanol was irradiated until HPLC analysis indicated maximum formation of the photoproduct. Preparative-layer chromatography of the resulting solution revealed a band at $R_f = 0.45$ due to the unconsumed reactant **4** and four additional bands at $R_f =$ 0.80, 0.50, 0.70, and 0. Although extraction of the bands at $R_f = 0.70$ and 0 resulted in negligible recovery of any material, extraction of the band at $R_f = 0.50$ provided a white crystalline product, mp 180-181°C identical to the dimer, and extraction of the band at $R_f = 0.80$ provided a white crystalline product, mp 114-115°C indicating formation of a new compound **53**.

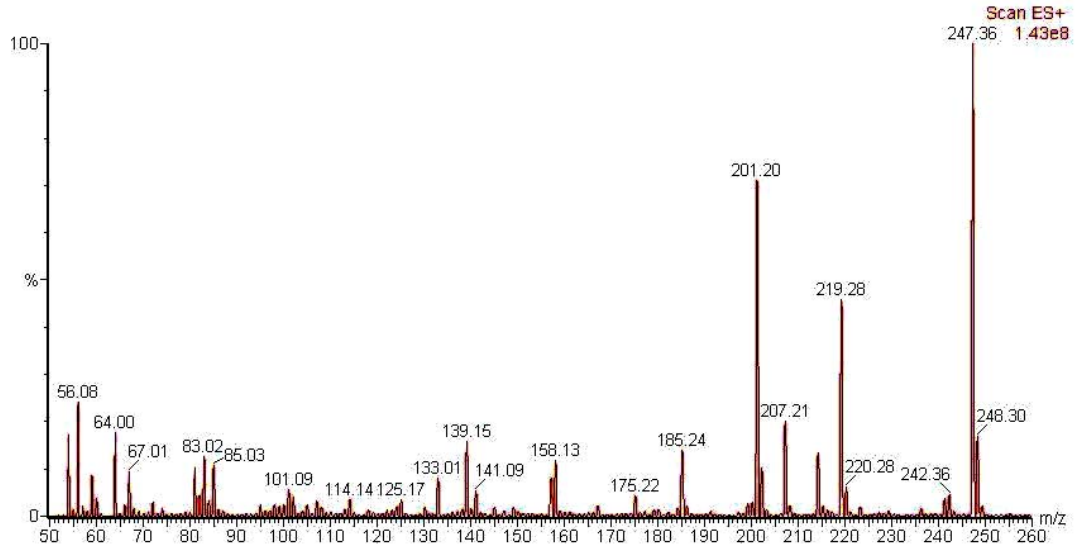
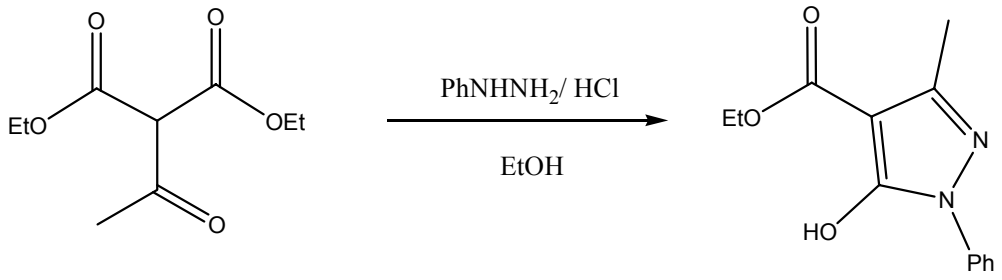


Figure 111: Mass spectrum of photoproduct **53**

This photoproduct was also analyzed by mass spectrometer. The mass spectrum of the material is shown in Figure 111 and reveals a molecular ion plus proton at (M+H)/Z = 247 with major fragments at M/Z 219, 241, 207, 201, 201, 185, 158, and 139.

The subtraction of molecular ion at (M+H)/Z 247 by one proton, the photoproduct has a molecular weight of 246. Therefore, in order to prove the real structure of the photoproduct **53**, our synthesis of ethyl-5-hydroxy-3-methyl-1-phenyl-1*H*-pyrazole-4-carboxylate **(53)** requires suitably substitued malonate **51**.



(51) **(53)**

Scheme 51: Synthesis of ethyl 5-hydroxy-3-methyl-1-phenyl-1H-pyrazole-4-carboxylate **(53)**.

Based on the similar condition of synthesis of **47**, the synthesis of **53** was accomplished by the new methodology by treatment of **51** and phenylhydrazine in acid condition to give **53** in 61% yield; mp 114-115^{o}C (Lit.[15] 114-115^{o}C) (Scheme 51).

(a)

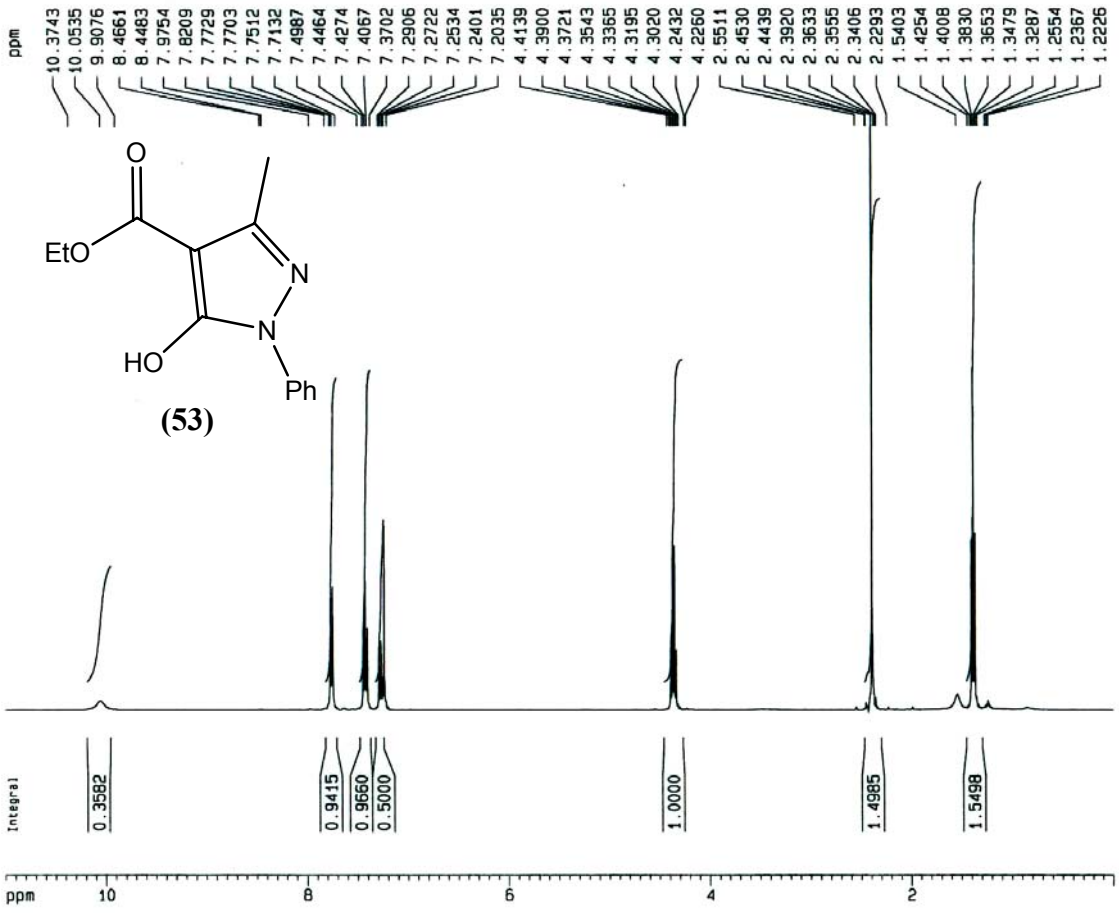
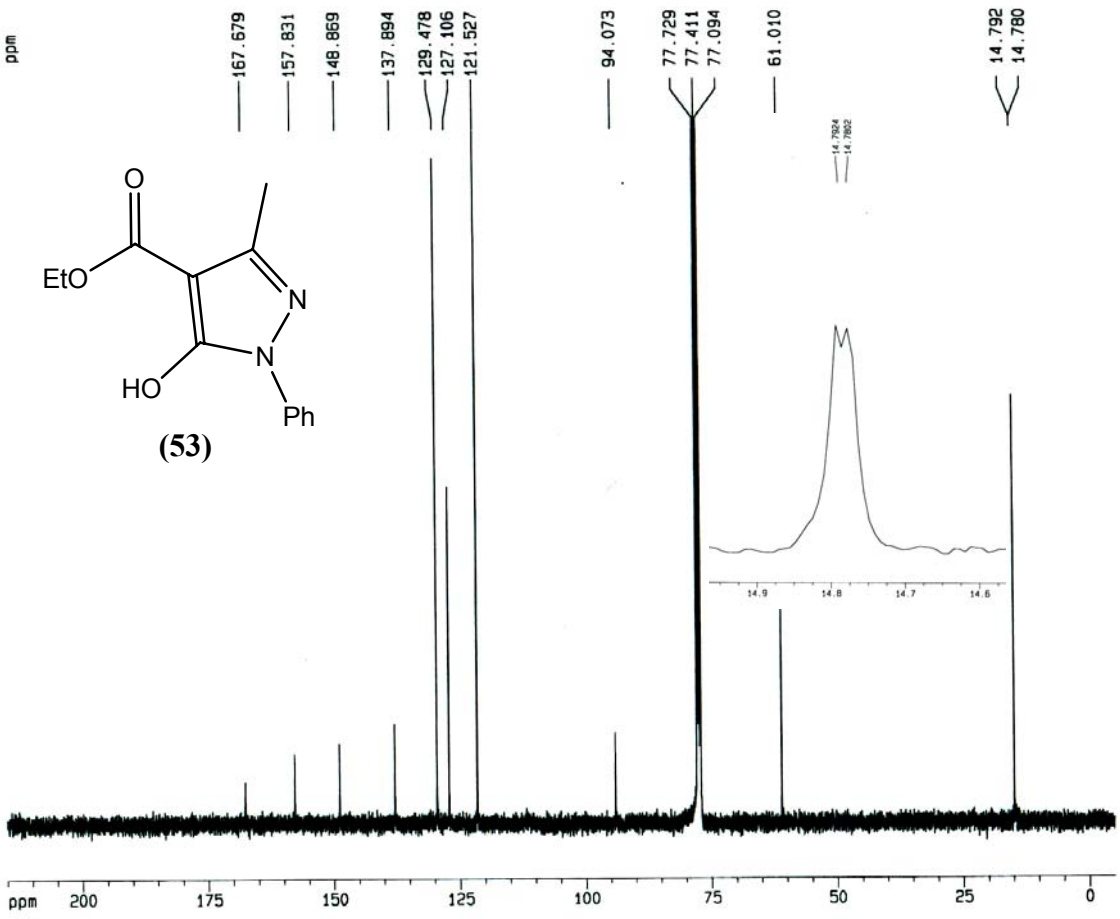


Figure 112(a) shows that the ^{1}H-NMR spectrum of the colorless crystalline product is consistent with the structure of **53**. The protons due to methyl group at C-3 appear as a 3H singlet at δ 2.36, while the ethyl protons appear as a 2H quartet (J = 7.3 Hz) at δ 4.30 and a 3H triplet (J = 7.1 Hz) at δ 1.33. The protons of the phenyl ring due to ortho, meta, and para positions appear as a 2H doublet (J = 7.6 Hz) at δ 7.75, a 2H triplet (J = 8.3 Hz) at δ 7.41, and a 1H triplet (J = 7.6 Hz) at δ 7.25. Unambiguously, the broad signal at δ 10.1 is due to hydroxyl proton.

(b)



(53)

The ^{13}C-NMR spectrum (Figure 112(b)) is also consistent with the structure **53**. The ester carbonyl absorbs the furthest downfield at δ 167.7, while the signals at δ 157.8, 148.9, and 94.07 are consistent with the carbons at C-5, C-3, and C-4, respectively. The carbons of the phenyl ring due to C-1, ortho, meta, and para positions absorb at δ 137.9, 121.5, 129.5, and 127.1. In addition, the carbon of the methyl group due to C-3 appears as at δ 14.79, while the carbons of the ethyl ester appear the signals at δ 61.01 and 14.78.

(c)

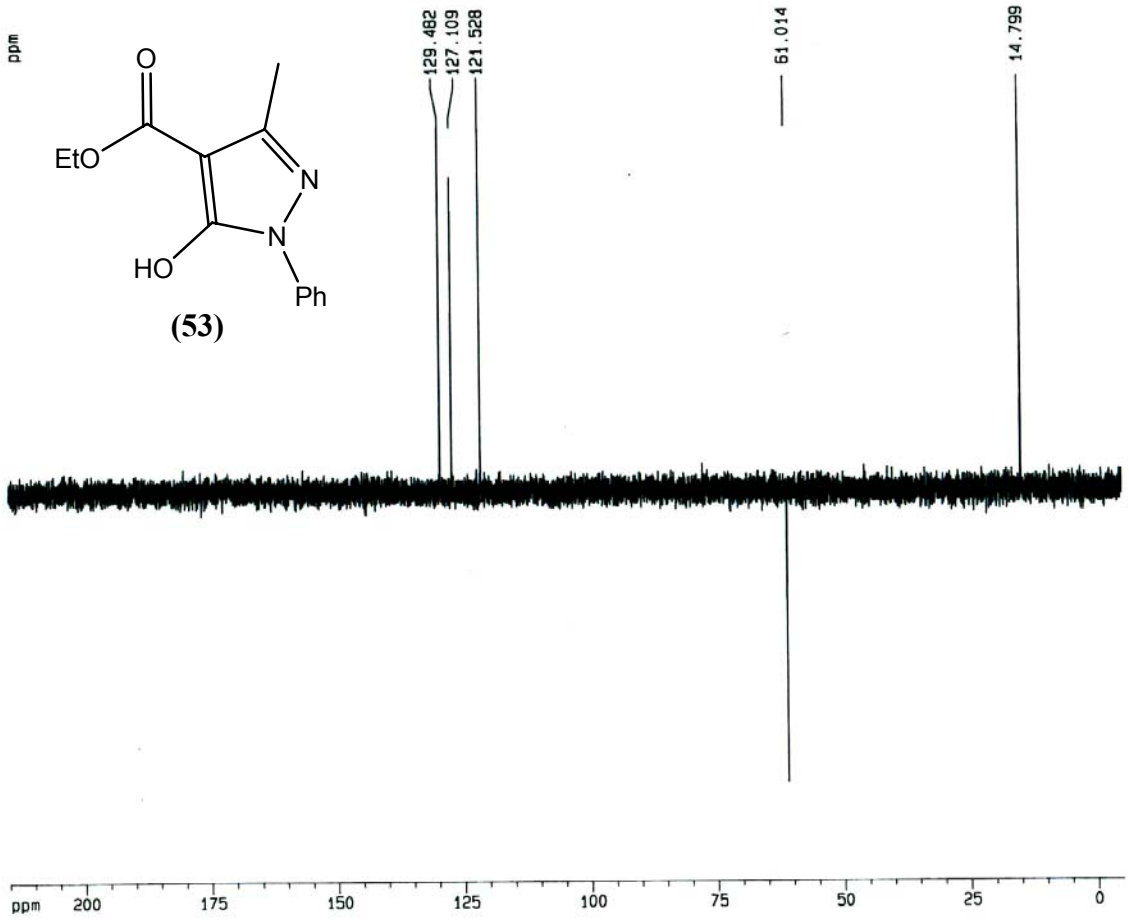


Figure 112: (a) ^{1}H-NMR of compound **53**; (b) ^{13}C-NMR of compound **53**; (c) ^{13}C-NMR DEPT 135 of compound **53**.

As expected, the four signals at δ 167.7, 157.8, 148.9, 137.9, and 94.07 disappeared in the ^{13}C-DEPT 135 spectrum (Figure 112(c)), which is consistent with their assignment to five quaternary carbons. In addition, the positive signals at δ 129.5, 127.1, and 121.5 are due to three different CH type carbon of the phenyl ring, while the positive signals due to two types of the methyl group appear at δ 14.79 and 14.78.

Unambiguously, the negative signal at δ 61.01 is due to the CH_2 type carbon on the ethyl side chain.

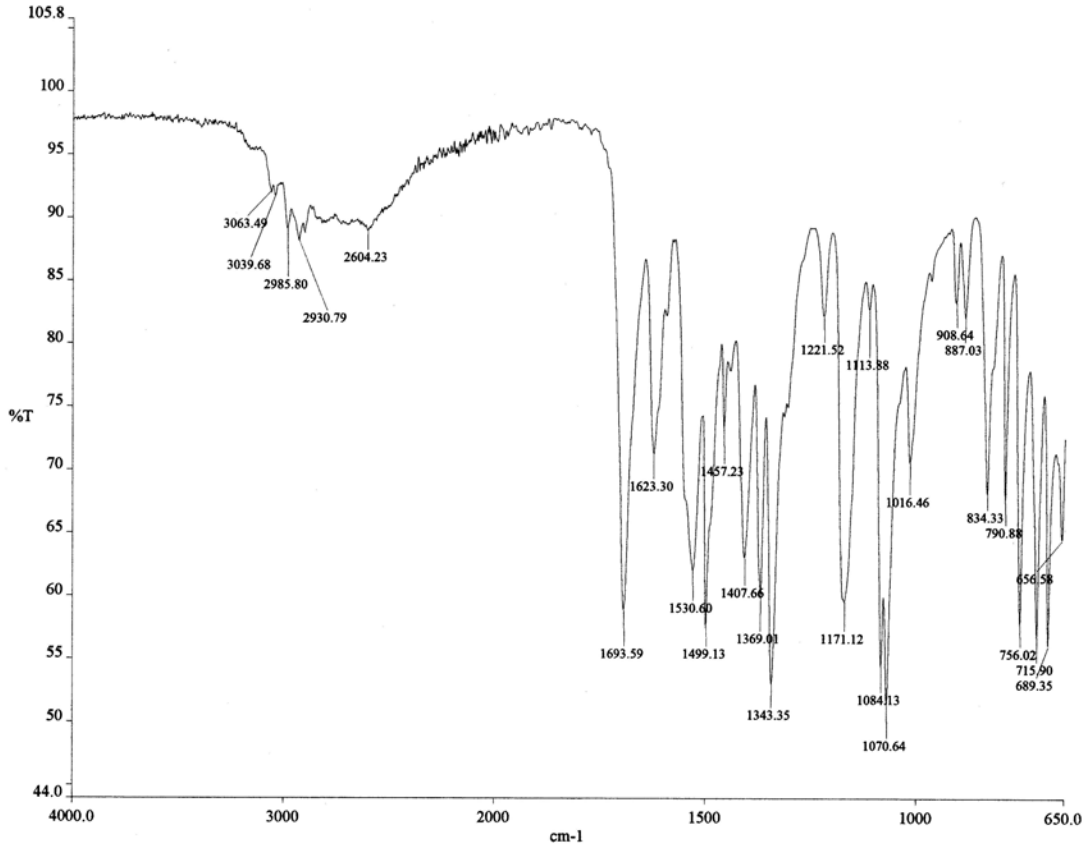


Figure 113: IR spectrum of the photoproduct **53**

Figure 113 shows the IR spectrum of the photoproduct **53** in which the functional group might be suggested. The C-H stretching peaks of the phenyl ring absorb at 3,063 and 3,039 cm^{-1} ,while the C-H stretching peaks of the aliphatic chain absorb at 2,985 and 2,930 cm^{-1}. The intense absorption of 1,693 cm^{-1} is due to the carbonyl (C=O) stretching of the ester group. The strong signals of 1,530 and 1,499 cm^{-1} are consistent with C=C stretching of the pyrazole and phenyl rings.

Experimental section

Synthesis of 4-hydroxy-6-methyl-3-(1-(2-phenylhydrazono)ethyl)-2H-pyran-2-one **(2)**

Phenylhydrazine (17.8 mmol, 1.92 g, 1.75 ml) was added to a hot (80^{o}C) solution of dehydroacetic acid **1** (17.9 mmol, 3.02 g) in ethanol (20 ml). After a few minutes of heating the yellow solid mass was collected by filtration and the residue (4.55 g) was recrystallized from ethanol to give **2** as a yellow crystalline product: mp 205-206^{o}C (lit.[3] 206-207^{o}C); yield 4.41 g (16.9 mmol, 95%); ^{1}H-NMR ($CDCl_3$) δ 15.6 (s, 1H), 7.33 (t, J = 7.6 Hz, 2H), 6.98 (t, J = 7.1 Hz, 1H), 6.90 (d, J = 8.1 Hz, 2H), 6.43 (s, 1H), 5.78 (s, 1H), 2.71 (s, 3H), 2.16 (s, 3H); ^{13}C-NMR δ 181.0, 169.5, 163.7, 163.6, 145.0, 130.1, 122.5, 113.8, 105.8, 96.6, 20.3, 16.4; MS (ESI): $(M+Na)^{+}$ = 281.2.

Synthesis of 1-(5-hydroxy-3-methyl-1-phenyl-1H-pyrazol-4-yl)butane-1,3-dione **(3)**

Method A

A solution of N-phenylhydrazone **2** (10.2 mmol, 2.64g) in glacial acetic acid (20 ml) was refluxed for 1 hour. After evaporation of the solvent, the residue (2.81 g) was recrystallized from acetonitrile to give **3** as a yellow solid: mp 95-97^{o}C (lit.[3] 101^{o}C); yield 1.90 g (7.34 mmol, 72%); ^{1}H NMR ($CDCl_3$) enol (major) δ 14.9 (s, 1H), 12.2 (br, OH), 7.81 (d, J = 8.3 Hz, 2H), 7.47 (t, J = 7.6 Hz, 2H), 7.33 (t, J = 6.8 Hz, 1H), 5.71 (s, 1H), 2.47 (s, 3H), 2.11 (s, 3H); keto (minor) δ 12.2 (br, OH), 7.81 (d, J = 8.3 Hz, 2H), 7.47 (t, J = 7.6 Hz, 2H), 7.33 (t, J = 6.8 Hz, 1H), 3.89 (s, 2H), 2.46 (s, 3H), 2.35 (s, 3H); ^{13}C NMR major (enol) δ 188.6, 181.2, 158.7, 147.1, 137.2, 129.2, 126.9, 120.9, 100.5, 96.8, 22.5, 15.6; minor (keto) δ 188.6, 181.2, 158.7, 147.1, 137.2, 129.2, 126.9, 120.9, 100.5, 54.9, 30.9, 15.3; MS (ESI): $(M+Na)^{+}$ = 281.1.

Method B

Phenylhydrazine (50.9 mmol, 5.5 g, 5.0 ml) was added to a hot (80°C) solution of dehydroacetic acid **1** (50.0 mmol, 8.40 g) in ethanol (50 ml). After a few minutes of heating a yellow solid was obtained, which was allowed to stand at room temperature for two hours. Evaporation of the solvent gave crude **2** (12.4 g), which was dissolved in glacial acetic acid (50 ml) and refluxed for 1 hour. Evaporation of the solvent gave crude **3** (12.4 g) which was recrystallized from acetonitrile to give **3** as a yellow solid: mp 95-97°C (lit.[3] 101°C); yield 9.30 g (36.0 mmol, 72%).

Synthesis of 3,6-dimethyl-1-phenylpyrano-[2,3-c]pyrazol-4-ones **(4)**

Method A

To a solution of **3** (5.15 mmol, 1.33 g) in glacial acetic acid (15 ml), concentrated sulfuric acid (0.50 ml) was added dropwise and the resulting mixture was refluxed for 1 hour, cooled to room temperature for 2 hours, and then poured into cold water (50 ml). The precipitate was filtered, washed with 5% aqueous Na_2CO_3 solution, water, and dried to furnish crude **4** (1.22 g), which was recrystallized from acetonitrile to yield **4** as colorless crystals: mp 148-149°C (lit.[3] 150°C); yield 0.99 g (4.12 mmol, 80%); ^{1}H-NMR ($CDCl_3$) δ 7.77 (d, J = 8.6 Hz, 2H), 7.49 (t, J = 7.6 Hz, 2H), 7.36 (t, J = 7.6 Hz, 1H), 6.04 (s, 1H), 2.62 (s, 3H), 2.40 (s, 3H); ^{13}C-NMR δ 175.7, 161.6, 153.5, 146.8, 137.1, 129.4, 127.3, 120.9, 112.6, 106.8, 19.6, 14.0; MS (ESI): $(M+Na)^+$ = 263.2.

Method B

N-phenylhydrazone **2** (9.90 mmol, 2.55 g) in glacial acetic acid (25 ml) was refluxed for 1 hour. Concentrated sulfuric acid (1 ml) was added dropwised to the resulting solution of **3**. The solution was refluxed for 1 hour, cooled to room temperature for 2 hours, and poured into cold water (80 ml). The precipitate was filtered, washed with 5% aqueous Na_2CO_3 solution, water, and dried to furnish crude **4** (2.14 g), which was recrystallized from acetonitrile to yield **4** as colorless crystals: mp 148-149^oC (lit.[3] 150^oC); yield 1.72 g (7.23 mmol, 73%).

Method C

Phenylhydrazine (10.2 mmol, 1.1 g, 1.0 ml) was added to a hot (80^oC) solution of dehydroacetic acid **1** (10.0 mmol, 1.66 g) in ethanol (50 ml). After a few minutes of heating, the yellow solid mass was obtained, which was filtered to give the yellow crystal **2** (2.41 g). The crystals of **2** was dissolved in glacial acetic acid (50 ml) and refluxed for 1 hour. The concentrated sulfuric acid (1 ml) was then added dropwised to the resulting solution of **3**, which was refluxed for 1 additional hour, cooled to room temperature for 2 hours, and then poured into cold water (100 ml). The precipitate was filtered, washed with 5% aqueous Na_2CO_3 solution, water, and dried to furnish crude **4** (2.31 g), which was recrystallized from acetonitrile to give **4** as colorless crystals: mp 148-149^oC (lit.[3] 150^oC); yield 1.75 g (7.35 mmol, 74%).

Synthesis of 4-hydroxy-6-methyl-3-(1-(2-methylhydrazono)ethyl)-2H-pyran-2-one **(5)**

A solution of methylhydrazine (21.9 mmol, 1.15 ml, 1.01 g) and ethanol (10 ml) was added dropwise to a solution of dehydroacetic acid **1** (20 mmol, 3.36 g) in ethanol (200 ml) at room temperature during ten minutes. After complete addition, the solution was stirred at room temperature for 2 hours. After the reaction was complete, evaporation of the solvent gave the crude solid mixture of **5** and by product **8**. When the crude solid mixture was dissolved in ethyl acetate (30 ml), **8** was precipitated, filtered (0.65 g), and recrystallized from ethanol to give **8** as colorless crystals: mp 201-202^{o}C (lit.[5] mp 203-204^{o}C); yield 0.57 g (2.97 mmol; 14 %); ^{1}H-NMR ($CDCl_3$) δ 12.7 (br, OH), 5.80 (s, 1H), 3.62 (s, 3H), 3.42 (s, 3H), 2.12 (s, 3H), 1.96 (s, 3H); ^{13}C-NMR δ 156.5, 147.4, 144.3, 135.7, 106.5, 92.8, 36.4, 31.2, 13.2, 11.5; MS (ESI): $(M+Na)^+$ = 229.1. The mother liquid of **5** was collected and evaporated to give crude **5** (2.85 g), which was recrystallized from toluene and hexane to give **5** as a white crystalline product: mp 95-97^{o}C (Lit.[5] mp 100-102^{o}C); yield 1.98 g (10.2 mmol, 51%); ^{1}H-NMR ($CDCl_3$) δ 15.4 (s, br, 1H), 5.71 (s, 1H), 4.07 (q, br, NH), 2.83 (s, 3H), 2.73 (s, 3H), 2.19 (s, 3H); ^{13}C-NMR δ 183.7, 173.6, 164.1, 163.1, 136.8, 107.2, 95.5, 39.1, 20.2, 16.7; MS (ESI): $(M+Na)^+$ = 219.1.

Synthesis of 1-(5-hydroxy-1,3-dimethyl-1H-pyrazol-4-yl)butane-1,3-dione **(6)**

A solution of N-methylhydrazone **5** (5.10 mmol, 1.00 g) in glacial acetic acid (20 ml) was refluxed for 1 hour. Evaporation of the solvent gave the residue **6** (1.06 g), which was recrystallized from ethyl acetate to give **6** as a yellow solid: mp 136-137^{o}C; yield 0.75 g (3.83 mmol, 75%); ^{1}H-NMR ($CDCl_3$) enol (major) δ 15.0 (s, 1H), 11.3 (br, OH), 5.61 (s, 1H), 3.56 (s, 3H), 2.34 (s, 3H), 2.11 (s, 3H); keto (minor) δ 11.3 (br, OH), 3.80 (s, 2H), 3.56 (s, 3H), 2.33 (s, 3H), 2.29 (s, 3H); ^{13}C-NMR major (enol) δ 188.6, 181.5, 158.9, 146.4, 99.9, 97.1, 32.9, 22.8, 15.8; minor (keto) δ 188.6, 181.5, 159.6, 147.1, 103.6, 55.6, 32.9, 31.1, 15.5; MS (ESI): $(M+Na)^+$ = 218.8.

Synthesis of 1,3,6-trimethyl-[2,3-c]pyrazole-4(1H)-one **(7)**

Method A

To a solution of **6** (3.06 mmol, 0.60 g) in glacial acetic acid (15 ml), conc. sulfuric acid (0.30 ml) was added dropwise. The solution mixture was refluxed for 1 hour. After neutralization of the acid with an aqueous solution of sodium carbonate, the solution was extracted with dichloromethane (40 ml). The organic layer was dried over anhydrous sodium sulfate. Evaporation of the solvent afforded the crude product **7** (0.49 g), which was recrystallized from ethyl acetate to give **7** as a white crystalline product: mp 154-155^{o}C; yield 0.40 g (2.27 mmol; 74%); ^{1}H-NMR ($CDCl_3$) δ 5.94 (s, 1H), 3.80 (s, 3H), 2.51 (s, 3H), 2.35 (s, 3H); ^{13}C-NMR δ 176.2, 161.6, 154.8, 145.7, 112.4, 105.5, 34.1, 19.8, 14.2; MS (ESI): $(M+H)^+$ = 179.1; Anal. Calcd for $C_9H_{10}N_2O_2$: C, 60.66; H, 5.66; N, 15.72. Found: C, 60.52; H, 5.94; N, 15.43.

Method B

N-methylhydrazone **5** (5.10 mmol, 1.00 g) in glacial acetic acid (20 ml) was refluxed for 1 hour. Concentrated sulfuric acid (1 ml) was added dropwise to the resulting mixture, which was refluxed for 1 additional hour. After neutralization of the acid with an aqueous solution of sodium carbonate, the mixture was extracted with dichloromethane (40 ml). The organic layer was dried over anhydrous sodium sulfate. Evaporation of the solvent afforded the crude product **7** (0.71 g), which was recrystallized from ethyl acetate to give **7** as a white crystalline product: mp 154-155^{o}C; yield 0.49 g (2.78 mmol; 55%).

Synthesis of 4-hydroxy-6-methyl-3-propionyl-2H-pyran-2-one **(10)**

A solution of 4-hydroxy-6-methyl-2-pyrone **(9)** 1.69 g; 17.2 mmol in propionic anhydride (20 ml, 20.2 g, 156 mmol) containing 2 drops of concentrated sulfuric acid was heated under reflux for 1 hour and then poured while hot into water (80 ml). The solid which formed was collected (2.41 g) and recrystallized from methanol to give **10** as a white crystals: mp 105-106^{o}C (lit.[7] 105-107^{o}C); yield 2.13 g (11.7 mmol, 68%); ^{1}H-NMR ($CDCl_3$) δ 5.92 (s, 1H), 3.06 (q, J = 7.1 Hz, 2H), 2.25 (s, 3H), 1.12 (t, J = 7.3 Hz, 3H); ^{13}C-NMR δ 208.8, 181.4, 169.2, 161.5, 101.9, 99.8, 35.7, 21.1, 8.1; MS (ESI): $(M+H)^{+}$ = 183.1.

Synthesis of 4-hydroxy-6-methyl-3-(1-(2-phenylhydrazono)propyl)-2H-pyran-2-one **(11)**

Phenylhydrazine (5.59 mmol, 0.55 ml, 0.60 g) was added to a hot (80°C) solution of **10** (5.50 mmol, 1.0 g) in ethanol (15 ml). After a few minutes of heating, the yellow solution was allowed to stand at room temperature for 2 hours. The yellow solid was precipitated, collected (1.30 g), and recrystallized from ethanol to give **11** as a yellow crystalline product: mp 154-155°C (lit.[3] 155°C); yield 1.15 g (4.23 mmol, 77%); ^{1}H-NMR ($CDCl_3$) δ 15.4 (s, 1H), 7.27 (t, J = 7.6 Hz, 2H), 6.96 (t, J = 7.3 H, 1H), 6.84 (d, J = 8.1 H, 2H), 6.37 (s, br, 1H), 5.28 (s, 1H), 3.24 (q, J = 7.6 Hz, 2H), 2.15 (s, 3H), 1.23 (t, J = 7.6 Hz, 3H); ^{13}C-NMR δ 182.6, 176.9, 163.6, 163.2, 145.4, 130.1, 122.6, 113.9, 106.4, 95.6, 22.4, 20.3, 11.8; MS (ESI): $(M+Na)^+$ = 295.3.

Synthesis of 1-(3-ethyl-5-methyl-1-phenyl-1H-pyrazol-4-yl)butane-1,3-dione **(12)**

A solution of N-phenylhydrazone **11** (1.42 mmol, 0.395 g) in glacial acetic acid (8 ml) was refluxed for 1 hour. Evaporation of the solvent gave crude **12** (0.43 g), which was recrystallized from acetonitrile to give **12** as white crystals: mp 95-97°C (lit.[3] 95°C); 0.26 g, (0.956 mmol; 67%); ^{1}H-NMR ($CDCl_3$) enol (major) δ 14.9 (s, 1H), 12.5 (br, OH), 7.79 (d, J = 8.6 Hz, 2H), 7.41 (t, J = 7.6 Hz, 2H), 7.25 (t, J = 7.3 Hz, 1H), 5.67 (s, 1H), 2.78 (q, J = 7.3 Hz, 2H), 2.10 (s, 3H), 1.32 (t, J = 7.6 Hz, 3H); keto (minor) δ 12.5 (br, OH), 7.79 (d, J = 8.6 Hz, 2H), 7.41 (t, J = 7.6 Hz, 2H), 7.25 (t, J = 7.3 Hz, 1H), 3.87 (s, 2H), 2.78 (q, J = 7.3 Hz, 2H), 2.33 (s, 3H), 1.32 (t, J = 7.6 Hz, 3H); ^{13}C-NMR major (enol) δ 188.9, 181.6, 159.3, 152.6, 137.8, 129.5, 127.1, 121.4, 100.1, 97.3, 22.3, 22.9, 12.8; minor (keto) δ 188.9, 181.6, 159.3, 152.8, 137.8, 129.5, 127.1, 121.4, 100.8, 55.2, 31.2, 22.9, 12.6; MS (ESI): $(M+Na)^+$ = 295.2.

Synthesis of 3-ethyl-6-methyl-1-phenylpyrano[2,3-c]pyrazole-4(1H)-one **(13)**

Method A

To a solution of **12** (5.51 mmol, 1.50 g) in glacial acetic acid (15 ml), concentrated sulfuric acid (0.50 ml) was added dropwise. The resulting mixture was refluxed for 1 hour, cooled to room temperature for 2 hours, and then poured into cold water (50 ml). The precipitate was filtered, washed with 5% aqueous Na_2CO_3 solution, water, and dried to furnish the crude product **13** (1.30 g), which was recrystallized from acetonitrile to give **13** as colorless crystals: mp 132-133^oC (Lit.[3] mp 132^oC); yield 1.15 g (4.53 mmol, 82%); ^1H NMR ($CDCl_3$) δ 7.71 (d, J = 8.6 Hz, 2H), 7.47 (t, J = 7.6 Hz, 2H), 7.28 (t, J = 7.6 Hz, 1H), 6.02 (s, 1H), 2.95 (q, J = 7.1 Hz, 2H), 2.37 (s, 3H), 1.30 (t, J = 7.3 Hz, 3H); ^{13}C NMR δ 175.8, 161.8, 154.1, 152.6, 137.5, 129.8, 127.6, 121.5, 113.0, 106.6, 22.4, 19.9, 13.2; MS (ESI): $(M+Na)^+$ = 277.2.

Method B

N-phenylhydrazone **11** (0.55 mmol, 0.15 g) in glacial acetic acid (5 ml) was refluxed for 1 hour. Concentrated sulfuric acid (1 ml) was added dropwise and the resulting mixture was refluxed for 1 additional hour, cooled to room temperature for 2 hours, and poured into cold water (80 ml). The precipitate was filtered, washed with 5% aqueous Na_2CO_3 solution, water, and dried to furnish the crude product **13**, which was recrystallized from acetonitrile to give **13** as colorless crystals: mp 132-133^oC (Lit.[3] mp 132^oC); yield 0.11 g (0.433 mmol, 79%).

Synthesis of 4-hydroxy-6-methyl-3-(1-(2-methylhydrazono)propyl)-3,4-dihydro-2H-pyran-2-one **(14)**

The solution of methylhydrazine (5.50 mmol, 0.29 ml, 0.25 g) and ethanol (5 ml) was added dropwise to a solution of **10** (5.49 mmol, 1.00 g) in ethanol (50 ml) at room temperature during a period of ten minutes. After the complete addition, the mixture was stirred at room temperature for 2 hours. Evaporation of the solvent gave the crude solid mixture of **14** and by product **15**. The crude solid mixture was dissolved in ethyl acetate (20 ml), by product **15** was precipitated, filtered (0.20 g), and recrystallized from ethyl acetate to give **15** as colorless crystals: mp 162-163^{o}C; yield 0.16 g (0.734 mmol, 13%); ^{1}H-NMR ($CDCl_3$) δ 5.75 (s, 1H), 3.63 (s, 3H), 3.49 (s, 3H), 2.36 (q, J = 7.6 Hz, 2H), 2.04 (s, 3H), 1.02 (t, J = 7.8 Hz, 3H); ^{13}C-NMR δ 151.9, 151.4, 148.4, 137.6, 107.5, 89.2, 36.4, 33.4, 21.2, 13.8, 13.5; MS (ESI): $(M+Na)^{+}$ = 242.9; Anal. Calcd for $C_{10}H_{14}N_2O_2$: C, 59.98; H, 7.32; N, 25.44. Found: C, 60.21; H, 7.19; N, 25.41. Evaporation of the mother liquid gave the residue **14** (1.12 g), which was recrystallized from toluene and hexane to give **14** as a white crystalline solid: mp 97-98^{o}C; yield 0.65 g (3.10 mmol; 56%); ^{1}H-NMR ($CDCl_3$) δ 15.2 (s, 1H), 5.68 (s, 1H), 4.03 (br, NH), 3.26 (q, J = 6.1 Hz, 2H), 2.82 (d, J = 5.5 Hz, 3H), 2.11 (s, 3H), 1.21 (t, J = 7.3 Hz, 3H); ^{13}C-NMR δ 184.2, 178.6, 162.7, 162.6, 106.8, 93.9, 39.0, 22.0, 19.8, 11.5; MS (ESI): $(M+Na)^{+}$ = 233.0; Anal. Calcd for $C_{10}H_{14}N_2O_2$: C, 57.13; H, 6.71; N, 13.33. Found: C, 57.26; H, 6.71; N, 13.24.

Synthesis of 1-(3-ethyl-5-hydroxy-1-methyl-1H-pyrazol-4-yl)butane-1,3-dione **(16)**

A solution of N-methylhydrazone **14** (5.86 mmol, 1.23 g) in glacial acetic acid (15 ml) was refluxed for 1 hour. Evaporation of the solvent gave the residue **16** (1.31 g), which was recrystallized from acetonitrile to give **16** as while crystals: mp 123-124^{o}C; yield 0.86 g (4.10 mmol, 70%); ^{1}H-NMR ($CDCl_3$) enol (major) δ 15.0 (s, 1H), 11.5 (br, OH), 5.59 (s, 1H), 3.57 (s, 3H), 2.78 (q, J = 7.6 Hz, 2H), 2.06 (s, 3H), 1.32 (t, J = 7.3 Hz, 3H); keto (minor) δ 11.5 (br, OH), 3.80 (s, 2H), 3.57 (s, 3H), 2.78 (q, J = 7.6 Hz, 2H), 2.30 (s, 3H), 1.32 (t, J =7.3 Hz, 3H); ^{13}C-NMR major (enol) δ 188.1, 180.9, 158.8, 151.3, 98.6, 96.7, 32.5, 22.7, 22.5, 12.6; minor (keto) δ 188.6, 180.9, 158.8, 151.3, 98.6, 55.2, 32.5, 30.8, 22.4, 12.5; MS (ESI): $(M+Na)^{+}$ = 232.9; Anal. Calcd for $C_{10}H_{14}N_2O_2$: C, 57.13; H, 6.71; N, 13.33. Found: C, 57.13; H, 7.04; N, 13.17.

Synthesis of 3-ethyl-1,6-dimethylpyrano[2,3-c]pyrazole-4(1H)-one **(17)**

Method A

To a solution of **16** (1.67 mmol, 0.35 g) in glacial acetic acid (10 ml), concentrated sulfuric acid (0.20 ml) was added dropwise and resulting mixture was refluxed for 1 hour. After neutralization of the acid with an aqueous solution of sodium carbonate, the solution was extracted with dichloromethane (30 ml). The organic layer was dried over anhydrous sodium sulfate. Evaporation of the solvent afforded the crude product **17** (0.29 g), which was recrystallized from cyclohexane to give **17** as a white crystalline product: mp 99-100^{o}C; yield 0.255 g (1.33 mmol, 79%); ^{1}H-NMR ($CDCl_3$) δ 5.92 (s, 1H), 3.79 (s, 3H), 2.91 (q, J = 7.6 Hz, 2H), 2.32 (s, 3H), 1.29 (t, J = 7.8 Hz, 3H); ^{13}C-NMR δ 175.9, 161.3, 154.9, 151.4, 112.5, 104.9, 34.1, 22.3, 19.8, 13.4; MS

(ESI): $(M+Na)^+$ = 214.9; Anal. Calcd for $C_{10}H_{12}N_2O_2$: C, 62.49; H, 6.29; N, 14.57. Found: C, 62.63; H, 6.34; N, 12.78.

Method B

N-methylhydrazone **14** (1.43 mmol, 0.30 g) in glacial acetic acid (10 ml) was refluxed for 1 hour. Concentrated sulfuric acid (0.20 ml) was added dropwised to the resulting mixture, which was refluxed for 1 additional hour. After neutralization of the acid with an aqueous solution of sodium carbonate, the mixture was extracted with dichloromethane (30 ml). The organic layer was dried over anhydrous sodium sulfate. Evaporation of the solvent afforded the crude product **17** (0.26 g), which was recrystallized from cyclohexane to give **17** as a white crystalline product: mp 99-100^{o}C; yield 0.18 g (0.938 mmol, 66%).

Synthesis of 3-butyryl-4-hydroxy-6-methyl-2H-pyran-2-one **(18)**

A solution of 4-hydroxy-6-methyl-2-pyrone **(9)** (4.0 g; 31.7 mmol) in n-butyric anhydride (19.4 g, 20 ml, 122 mmol) containing 2 drops of concentrated sulfuric acid was heated under reflux for 1 hour and then poured while hot into water (80 ml). The solution was extracted with dichloromethane (70 ml). The organic layer was dried over anhydrous sodium sulfate. Evaporation of the solvent afforded crude **18** (4.21 g), which was recrystallized from methanol to give **18** as a white crystalline product: mp 57-58^{o}C (lit.[7] 57-59^{o}C); yield 3.55 g (18.1 mmol; 57%); ^{1}H-NMR ($CDCl_3$) δ 5.91 (s, 1H), 3.04 (t, J = 6.8 Hz, 2H), 2.25 (s, 3H), 1.66 (sextet, J = 7.3 Hz, 2H), 0.97 (t, J = 7.3 Hz, 3H); ^{13}C-NMR δ 208.2, 181.6, 169.2, 161.4, 101.9, 99.9, 43.9, 21.1, 17.7, 14.1; MS (ESI): $(M+H)^+$ = 197.1.

Synthesis of 4-hydroxy-6-methyl-3-(1-(2-phenylhydrazono)butyryl)-2H-pyran-2-one **(19)**

Phenylhydrazine (1.22 mmol, 0.12 ml, 0.13 g) was added to a hot (80^{o}C) solution of **18** (1.17 mmol, 0.23 g) in ethanol (5 ml). After a few minutes of heating, the yellow solution was allowed to stand at room temperature for 2 hours. Evaporation of the solvent gave a crude product **19** (0.37 g), which was recrystallized from ethanol and water to give **19** as a yellow crystalline product: mp 72-75^{o}C; yield 0.31 g (1.08 mmol, 93%); ^{1}H-NMR ($CDCl_3$) δ 15.6 (s, 1H), 7.27 (t, J = 7.6 Hz, 2H), 6.97 (t, J = 7.1 Hz, 1H), 6.84 (d, J = 8.6 Hz, 2H), 6.42 (s, 1H), 5.75 (s, 1H), 3.20 (t, J = 7.6 Hz, 2H), 2.14 (s, 3H), 1.65 (sextet, J = 8.1 Hz, 2H), 1.04 (t, J = 7.1 Hz, 3H); ^{13}C-NMR δ 182.9, 176.0, 163.6, 163.0, 145.4, 130.1, 122.6, 113.9, 106.3, 95.7, 30.6, 21.3, 20.3, 14.9; MS (ESI): $(M+Na)^{+}$ = 309.2; Anal. Calcd for $C_{16}H_{18}N_2O_3$: C, 67.12; H, 6.34; N, 9.78. Found: C, 67.21; H, 6.30; N, 9.91.

Synthesis of 1-(5-hydroxy-3-propyl-1-phenyl-1H-pyrazol-4-yl)butane-1,3-dione **(20)**

Method A

A solution of N-phenylhydrazone **19** (3.50 mmol, 1.00 g) in glacial acetic acid (10 ml) was refluxed for 1 hour. Evaporation of the solvent gave crude **20** (1.12 g),which was recrystallized from acetonitrile to give **20** as a white crystalline solid: mp 93-95^{o}C; yield 0.74 g (2.73 mmol, 78%); ^{1}H-NMR ($CDCl_3$) enol (major) δ 14.9 (s, 1H), 12.5 (br, OH), 7.79 (d, J = 7.8 Hz, 2H), 7.43 (t, J = 7.8 Hz, 2H), 7.27 (m, 1H), 5.64 (s, 1H), 2.74 (t, J = 7.8 Hz, 2H), 2.09 (s, 3H), 1.78 (sextet, J = 7.6 Hz, 2H), 1.04 (t, J = 7.3 Hz, 3H); keto (minor) δ 12.5 (br, OH), 7.79 (d, J = 7.8 Hz, 2H), 7.43 (t, J = 7.8 Hz, 2H), 7.27 (m, 1H), 3.86 (s, 2H), 2.74 (q, J = 7.8 Hz, 2H), 2.33 (s, 3H), 1.78 (sextet, J = 7.6 Hz, 2H), 1.04 (t, J = 7.3 Hz, 3H); ^{13}C-NMR major (enol) δ 188.9, 181.5, 159.3, 151.5, 137.7, 129.5, 127.1, 121.5, 100.2, 97.3, 31.8, 23.0, 22.0, 14.5; minor (keto) δ 188.9, 181.5, 159.3, 151.5, 137.7, 129.5, 127.1, 121.5, 100.2, 55.1, 31.5, 31.2, 22.1, 14.5; MS (ESI): $(M+Na)^{+}$ = 309.2; Anal. Calcd for $C_{16}H_{18}N_2O_3$: C, 67.12; H, 6.34; N, 9.78. Found: C, 67.26; H, 6.15; N, 9.62.

Method B

Phenylhydrazine (2.95 mmol, 0.29 ml, 0.32 g) was added to a hot (80^{o}C) solution of **18** (2.81 mmol, 0.55 g) in ethanol (10 ml). After a few minutes of heating, the yellow solid mass was obtained and allowed to stand at room temperature for two hours. Evaporation of the solvent gave **19** (0.91 g), which was dissolved in 10 ml of acetic acid and refluxed for 1 hour. After evaporation of the solvent, the crude product **20** (0.95 g) was recrystallized from acetonitrile to give **20** as a white crystalline product: mp 95-97^{o}C; yield 0.51 g (1.78 mmol, 64%).

Synthesis of 6-methyl-1-phenyl-3-propylpyrano[2,3-c]pyrazole-4(1H)-one **(21)**

Method A

To a solution of **20** (1.75 mmol, 0.50 g) in glacial acetic acid (10 ml), concentrated sulfuric acid (0.20 ml) was added dropwise. The mixture was refluxed for 1 hour, cooled to room temperature for 2 hours, and then poured into cold water (30 ml). The precipitate was filtered, washed with 5% aqueous Na_2CO_3 solution, water, and dried to furnish the crude **21** (0.42 g), which was recrystallized from acetonitrile to give **21** as a colorless crystals: mp 105-106^oC; yield 0.35 g (1.31 mmol; 75%); ^{1}H-NMR ($CDCl_3$) δ 7.78 (d, J = 7.6 Hz, 2H), 7.49 (t, J = 8.1 Hz, 2H), 7.34 (t, J = 6.8 Hz, 1H), 6.02 (s, 1H), 2.93 (t, J = 7.6 Hz, 2H), 2.38 (s, 3H), 1.82 (sextet, J = 7.8 Hz, 2H), 0.996 (t, J = 7.3 Hz, 3H); ^{13}C-NMR δ 175.9, 161.8, 154.0, 151.4, 137.5, 129.8, 127.7, 121.5, 113.0, 106.8, 30.8, 22.2, 19.9, 14.3; MS (ESI): $(M+Na)^+$ = 291.2; Anal. Calcd for $C_{16}H_{16}N_2O_2$: C, 71.62; H, 6.01; N, 10.44. Found: C, 71.82; H, 5.76; N, 10.67.

Method B

Phenylhydrazine (2.75 mmol, 0.27 ml, 0.30 g) was added to a hot (80^oC) solution of **18** (2.55 mmol, 0.50 g) in ethanol (10 ml). After a few minutes of heating, the yellow solid mass was obtained, which was allowed to stand at room temperature for two hours. Evaporation of the solvent gave the residue **19** (0.82 g), which was dissolved in 10 ml of acetic acid, and refluxed for 1 hour. Concentrated sulfuric acid (0.2 ml) was added dropwise to the solution, which was refluxed for 1 additional hour, cooled to room temperature for 2 hours, and then poured into cold water (20 ml). The precipitate was filtered, washed with 5% aqueous Na_2CO_3 solution, water, and dried to

furnish the crude **21** (0.52 g), which was recrystallized from acetonitrile to give **21** as colorless crystals: mp 105-106^{o}C; 0.41 g (1.53 mmol, 60%).

Synthesis of 4-hydroxy-6-methyl-3-(1-(2-methylhydrazono)butyryl)-3,4-dihydro-2H-pyran-2-one **(22)**

A solution of methylhydrazine (18.1 mmol, 0.95 ml, 0.83 g) and ethanol (10 ml) was added dropwise to a solution of **18** (17.2 mmol, 3.38 g) in ethanol (40 ml) at room temperature for over ten minutes. After the complete addition, the mixture was stirred at room temperature for 2 hours. After the reaction was complete, evaporation of the solvent gave the crude product (4.15 g), which was purified by double of thin layer chromatography in dichloromethane 10 : ethanol 1 and recrystallized from toluene and hexane to give **22** (R_f = 0.30) as white crystals: mp 70-71^{o}C; yield 1.73 g (7.72 mmol, 45%); ^{1}H-NMR ($CDCl_3$) δ 15.3 (s, 1H), 5.67 (s, 1H), 4.02 (q, J = 5.1 Hz, NH), 3.21 (t, J = 7.6 Hz, 2H), 2.80 (d, J = 5.8 Hz, 3H), 2.10 (s, 3H), 1.57 (sextet, J = 7.8 Hz, 2H), 1.04 (t, J = 7.3 Hz, 3H); ^{13}C-NMR δ 184.6, 177.7, 163.1, 163.2, 107.2, 94.6, 39.3, 30.6, 21.4, 20.2, 14.8; MS (ESI): $(M+Na)^{+}$ = 247.1; Anal. Calcd for $C_{11}H_{16}N_2O_3$: C, 58.91; H, 7.19; N, 12.49. Found: C, 58.94; H, 6.97; N, 12.46.

Synthesis of 1-(3-ethyl-5-hydroxy-1-methyl-1H-pyrazol-4-yl)butane-1,3-dione **(23)**

A solution of N-methylhydrazone **22** (0.80 mmol, 0.18 g) in glacial acetic acid (5 ml) was refluxed for 1 hour. Evaporation of the solvent gave **22** (0.19 g), which was recrystallized from ethyl acetate and hexane to give **23** as a white crystalline solid: mp 96-97^{o}C; yield 0.11 g (0.491 mmol, 61%); ^{1}H-NMR ($CDCl_3$) enol (major) δ 15.0 (s, 1H), 11.5 (br, OH), 5.57 (s, 1H), 3.56 (s, 3H), 2.63 (t, J = 7.6 Hz, 2H), 2.06 (s, 3H), 1.67 (sextet, J = 7.8 Hz, 2H), 0.982 (t, J = 7.3 Hz, 3H); keto (minor) δ 11.5 (br, OH), 3.80 (s, 2H), 3.57 (s, 3H), 2.63 (t, J = 7.6 Hz, 2H), 2.29 (s, 3H), 1.67 (sextet, J = 7.8 Hz, 2H), 0.982 (t, J = 7.3 Hz, 3H); ^{13}C-NMR major (enol) δ 188.6, 181.3, 159.2, 150.5, 99.2, 97.1, 33.0, 31.7, 22.9, 22.2, 14.4; minor (keto) δ 188.6, 181.3, 159.2, 150.5, 102.9, 55.6, 31.4, 31.2, 22.4, 14.4; MS (ESI): $(M+Na)^+$ = 247.0; Anal. Calcd for $C_{11}H_{16}N_2O_3$: C, 58.91; H, 7.19; N, 12.49. Found: C, 58.60; H, 6.93; N, 12.30.

Synthesis of 1,6-dimethyl-3-propylpyrano[2,3-c]pyrazole-4(1H)-one **(24)**

To a solution of **23** (0.54 mmol, 0.12 g) in glacial acetic acid (5 ml), concentrated sulfuric acid (0.10 ml) was added dropwise and the mixture was refluxed for 1 hour. After neutralization of the acid with an aqueous solution of sodium carbonate, the mixture was extracted with dichloromethane (20 ml). The organic layer was dried over anhydrous sodium sulfate. Evaporation of the solvent afforded the crude product **24** (0.10 g), which was recrystallized from cyclohexane to give **24** as a white crystalline product: mp 61-62^{o}C**;** yield 0.082 g (0.398 mmol, 74%); ^{1}H-NMR ($CDCl_3$) δ 5.92 (s, 1H), 3.79 (s, 3H), 2.82 (t, J = 7.6 Hz, 2H), 2.32 (s, 3H), 1.76 (sextet, J = 7.6 Hz, 2H), 0.946 (t, J = 7.3 Hz, 3H); ^{13}C-NMR δ 175.9, 161.3, 154.9, 150.2, 112.6, 105.1,

34.1, 30.8, 22.3, 19.7, 14.2; MS (ESI): $(M+H)^+$ = 207.1; Anal. Calcd for $C_{11}H_{14}N_2O_2$: C, 64.06; H, 6.84; N, 13.58. Found: C, 63.86; H, 6.85; N, 13.53.

Synthesis of 6-methyl-2-oxo-2H-pyran-4-yl benzoate **(25)**

Benzoyl chloride (5.0 ml, 6.0 g, 43.1 mmol) was added dropwise over a period of 10 minutes to a stirred solution of **9** (5.0 g, 39.6 mmol) in pyridine (30 ml) at 0°C. After the addition was complete the mixture was stirred at room temperature for 1 hour and then allowed to stand overnight. The mixture was poured into 140 ml of 10% hydrochloric acid. The product was precipitated, collected (8.62 g), and recrystallized from ethanol to give **25** as colorless crystal: mp 85-86°C (lit.[7] 87-89°C); yield 6.24 g (27.1 mmol, 69%); ^{1}H-NMR ($CDCl_3$) δ 8.12 (d, J = 7.6 Hz, 2H), 7.52 (t, J = 8.1 Hz, 1H), 7.32 (t, J = 8.1 Hz, 2H); ^{13}C-NMR δ 164.1, 163.9, 163.8, 163.2, 134.9, 130.8, 129.3, 128.3, 101.9, 101.8, 20.6.

Synthesis of 3-benzoyl-4-hydroxy-6-methyl-2H-pyran-2-one **(26)**

A mixture of finely powdered **25** (10.2 g; 44.3 mmol) and anhydrous aluminum chloride (40.8 g) was heated at 100°C for 2.5 hours. The resulting complex was decomposed with ice and 5% hydrochloric acid (100 ml), and the solid which separated was collected by filtration and extracted with diluted aqueous sodium carbonate solution. Acidification of the carbonate solution gave solid **26** (8.21 g). The crude **26** was recrystallized from methanol to give **26** as a yellow solid: mp 105-107°C (lit.[7] 108-110°C); yield 6.21 g (27.0 mmol, 61%) of **26**; ^{1}H-NMR ($CDCl_3$) δ 7.63-7.32 (m, 5H), 5.84-5.86 (s, 1H), 2.18-2.20 (s, 3H); ^{13}C-NMR δ 197.6, 183.8, 169.2, 162.8, 138.3, 132.8, 129.1, 128.2, 106.5, 102.4, 21.0.

Synthesis of 4-hydroxy-6-methyl-3-(1-(2-phenylhydrazono)benzyl)-2H-pyran-2-one **(27)**

To a solution of **26** (0.39 g; 1.70 mmol) in benzene (10 ml) was added phenylhydrazine (0.17 ml, 0.19 g, 1.73 mmol). The mixture was refluxed for 5 minutes and allowed to stand at room temperature for 2 hours. N-phenylhydrazone **27** was precipitated and collected (0.51 g), which was recrystallized from ethanol to give **27** as orange crystals: mp 158-159^{o}C (Lit.[3] mp 160^{o}C); yield 0.45 g (1.41 mmol; 84%); ^{1}H-NMR ($CDCl_3$) δ 14.7 (s, 1H), 7.40-7.19 (m, 5H), 7.13 (t, J = 7.6 Hz, 2H), 6.77 (t, J = 7.1 Hz, 1H), 6.69 (d, J = 8.1 Hz, 2H), 5.79 (s, 1H), 2.10 (s, 3H); ^{13}C-NMR δ 171.9, 163.6, 162.1, 148.9, 143.3, 131.2, 130.0, 129.9, 129.8, 128.8, 121.4, 112.9, 101.9, 97.2, 20.5; MS (ESI): $(M+Na)^{+}$ = 343.3.

Synthesis of 1-(5-hydroxy-1,3-diphenyl-1H-pyrazol-4-yl)butane-1,3-dione **(28)**

A solution of N-phenylhydrazone **27** (1.0 g, 3.12 mmol) in glacial acetic acid (15 ml) was refluxed for 1 hour. Evaporation of the solvent gave **28** (1.12 g), which was recrystallized from acetonitrile to give **28** as a yellow solid: mp 146-147^{o}C (Lit.[3] mp 148^{o}C); yield 0.75 g (2.34 mmol, 75%); ^{1}H-NMR ($CDCl_3$) enol (major) δ 14.7 (s, 1H), 12.6 (br, OH), 7.91 (d, J = 8.3 Hz, 2H), 7.63 (t, J = 7.8 Hz, 2H), 7.50 (m, 5H), 7.34 (t, J = 6.8 Hz, 1H), 5.47 (s, 1H), 1.91 (s, 3H); keto (minor) δ 12.6 (br, OH), 7.91 (d, J = 8.3 Hz, 2H), 7.63 (t, J = 7.8 Hz, 2H), 7.50 (m, 5H), 7.34 (t, J = 6.8 Hz, 1H), 3.59 (s, 2H), 2.03 (s, 3H); ^{13}C-NMR major (enol) δ 189.2, 181.3, 159.1, 151.1, 137.7, 133.4, 129.9, 129.6, 129.5, 128.8, 127.4, 121.7, 100.4, 97.8, 22.7; minor (keto) δ 189.2, 181.3, 159.1, 151.1, 137.7, 133.4, 129.9, 129.6, 129.5, 128.8, 127.4, 121.7, 104.7, 54.4, 30.9; MS (ESI): $(M+Na)^{+}$ = 343.3.

Synthesis of 6-methyl-1,3-phenylpyrano[2,3-c]pyrazole-4(1H)-one **(29)**

To a solution of **28** (0.50 g; 1.56 mmol) in glacial acetic acid (10 ml), concentrated sulfuric acid (0.40 ml) was added dropwise and the resulting mixture was refluxed for 1 hour, cooled to room temperature for 2 hours, and then poured into cold water (40 ml). The precipitate was filtered, washed with 5% aqueous Na_2CO_3 solution, water, and dried to furnish crude **29** (0.43 g), which was recrystallized from acetonitrile to give **29** as colorless crystals: mp 170-171^{o}C (Lit.[3] mp 171^{o}C); yield 0.35 g (1.16 mmol, 74%); ^{1}H-NMR ($CDCl_3$) δ 8.42 (d, J = 7.2 Hz, 2H), 7.85 (d, J = 8.6 Hz, 2H), 7.52 (t, J = 7.6 Hz, 2H), 7.43 (t, J = 7.8 Hz, 2H), 7.36 (m, 2H), 6.08 (s, 1H), 2.38 (s, 3H); ^{13}C-NMR δ 175.1, 161.1, 154.6, 148.9, 137.5, 131.9, 129.9, 129.7, 128.9, 128.8, 128.1, 121.9, 113.4, 106.2, 19.7.

Synthesis of 4-hydroxy-6-methyl-2-oxo-2H-pyran-3-carbaldehyde **(30)**

4-hydroxy-6-methyl-2-pyrone (**9)** (3.0 g, 23.8 mmol) in anhydrous dichloromethane (30 ml) and dichloromethyl ether (32.2 ml, 42.6 g, 356 mmol) was cooled at -10^{o}C. Titanium tetrachloride (26.0 ml, 45.0 g, 238 mmol) was added under a continuous nitrogen atmosphere and the temperature of the reaction mixture was allowed to rise from -10^{o}C to room temperature over 24 hours. After the reaction was complete, ice water (50 g) was carefully added to the solution mixture. The product was extracted with dichloromethane (40 ml) and the organic layer was dried over anhydrous sodium sulfate. Evaporation of the solvent afforded crude **30** (3.12 g), which was recrystallized from ethanol to give **30 as** a white crystalline product: mp 93-94^{o}C (Lit.[8] 108^{o}C); yield 2.60 g (16.9 mmol, 71%); ^{1}H-NMR ($CDCl_3$) δ 14.4 (s, 1H), 9.82 (s, 1H), 5.89 (s, 1H), 2.29 (s, 3H); ^{13}C-NMR δ 194.6, 179.5, 171.9, 162.4, 101.2, 100.8, 21.6.

Synthesis of 4-hydroxy-6-methyl-3-(1-(2-phenylhydrazono)methyl)-2H-pyran-2-one **(31)**

Phenylhydrazine (2.70 mmol, 0.26 ml, 0.29 g) was added to a hot (80^{o}C) solution of **30** (2.70 mmol, 0.34 g) in ethanol (20 ml). After a few minutes of heating, the solution mixture turned yellow, which was allowed to stand in the refrigerator overnight. The yellow crystals were collected (0.51 g) by filtration and recrystallized from ethanol to give **31** as a yellow crystalline product: mp 212-213^{o}C; yield 0.47 g (1.93 mmol, 71%); ^{1}H-NMR (DMSO) δ 13.2 (s, 1H), 10.2 (s, 1H), 7.95 (s, 1H), 7.12 (t, J = 8.1 Hz, 2H), 6.67 (m, 3H), 2.30 (s, 3H); ^{13}C-NMR δ 171.5, 163.6, 162.4, 144.4, 141.6, 129.5, 119.9, 111.9, 102.0, 95.9, 19.6; MS (ESI): $(M+Na)^{+}$ = 267.1; Anal. Calcd for $C_{13}H_{12}N_2O_3$: C, 63.93; H, 4.95; N, 11.47. Found: C, 64.05; H, 4.81; N, 11.47.

Synthesis of methyl 5-hydroxy-1-methyl-1H-pyrazole-4-carboxylate **(35)**

A solution of methylhydrazine (6.30 ml, 5.51 g, 120 mmol) in methanol (20 ml) was added dropwise to a solution of dimethyl(methoxymethylene)malonate **(34)** (20.0 g; 115 mmol) in methanol (90 ml) during a period of ten minutes. After the complete addition of methylhydrazine solution, the solution was refluxed for 4 hours and cooled to room temperature. Evaporation of solvent gave the crude product **35**(18.1 g), which was recrystallized from ethanol to give **35** as a white crystalline product: mp 122-123^{o}C (Lit.[9] 125-126^{o}C); yield 13.6 g (87.2 mmol, 76%); ^{1}H-NMR ($CDCl_3$) (A) δ 7.52 (s, 1H), 5.96 (br, OH), 3.72 (s, 3H), 2.80 (s, 3H); (B) δ 7.79 (s, 1H), 3.63 (s, 3H), 2.81 (s, 3H); ^{13}C-NMR (A) δ 165.4, 156.7, 132.8, 97.67, 51.87, 39.79; (B) δ 166.5, 165.4, 137.9, 94.2, 51.8, 33.8; MS (ESI): $(M+Na)^{+}$ = 179.0.

Synthesis of 1-methyl-1H-pyrazol-5(4H)-one **(36)**

Sodium hydroxide (3.60 g; 90 mmol) was dissolved in the solution of **35** (5.0 g; 32.1 mmol) and water (40 ml). The mixture was heated at 100°C for 2 hours. Concentrated sulfuric acid was added dropwise (CO_2 evolution) with cooling in an ice bath. The resulting acidic mixture (pH 1) was heated at 100°C for 10 hours to complete the decarboxylation. The product was isolated from solution by continuous extraction with ethyl acetate for two days. Evaporation of solvent gave the pyrazolone crude product (2.52 g), which was recrystallized from ethyl acetate to give **36** as a white crystalline product: mp 109-110°C (Lit.[9] mp 110-111.5°C); yield 2.30 g (23.5 mmol, 73%); ^{1}H NMR ($CDCl_3$) δ 7.27 (s, 1H), 3.31 (s, 3H), 3.19 (s, 2H); ^{13}C NMR δ 172.0, 146.4, 39.6, 31.6; MS (ESI): $(M+H)^+$ = 98.8.

Synthesis of (E)-1-(5-hydroxy-1-methyl-1H-pyrazol-4-yl)-3-phenylprop-2-en-1-one **(37)**

Under stirring and cooling, to a mixture of **36** (0.50 g; 5.10 mmol) and $Ca(OH)_2$ (0.88 g, 11.9 mmol) in dioxane (25 ml) was added *trans*-cinnamoyl chloride (0.918 g; 5.5 mmol) within 10 minutes and the mixture was heated at reflux for 2 hours. After it was allowed to cool to room temperature, 2M HCl (25 ml) was added, the mixture was stirred for one additional hour and poured into water (100 ml). The mixture was extracted with dichloromethane, the organic phase was dried (Na_2SO_4), and evaporated under reduced pressure. The residue **37** (0.62 g) was recrystallized from acetonitrile to give **37** as brown-yellow crystals: mp 136-137°C (Lit.[10] mp 140-142°C); yield 0.52 g (2.37 mmol, 45%); ^{1}H NMR ($CDCl_3$) δ 7.80 (d, J = 15.8 Hz, 1H), 7.75 (s, 1H), 7.60 (m, 2H), 7.40 (m, 3H), 6.98 (d, J = 15.8 Hz, 1H), 3.65 (s, 3H); ^{13}C NMR δ 183.9, 160.6,

143.8, 137.5, 134.8, 131.2, 129.4, 128.9, 121.4, 104.6, 33.2; MS (ESI): $(M+Na)^+$ = 251.2.

Synthesis of 5-bromo-1-methyl-6-phenyl-5,6-dihydropyrano[2,3-c]pyrazole-4(1H)-one **(39)**

At 40°C, to a solution of **37** (0.41 g; 1.80 mmol) in glacial acetic acid (30 ml), a solution of bromine (0.10 ml, 0.31g, 2.0 mmol) in glacial acetic acid (10 ml) was added dropwise within one hour and stirring was continued for two hours. Then the reaction mixture was cooled and treated with water (50 ml). The solution was neutralized with saturated sodium carbonate and extracted with dichloromethane (20 ml). The organic phase was dried (Na_2SO_4) and evaporated under reduced pressure. The crude **39** (0.55 g) was recrystallized from acetonitrile to give **39** as a white product: mp 177-178°C; yield 0.49 g (1.59 mmol, 88%); ^{1}H-NMR ($CDCl_3$) δ 7.77 (s, 1H), 7.42 (m, 2H), 7.37 (m, 3H), 5.49 (d, J = 11.7 Hz), 5.26 (d, J = 11.6 Hz, 1H), 3.69 (s, 3H); ^{13}C-NMR δ 188.1, 158.3, 137.9, 137.2, 129.4, 128.9, 128.2, 101.9, 49.0, 48.6, 33.3; MS (ESI): $(M+Na)^+$ = 331.2.

Synthesis of 1-methyl-6-phenylpyrano[2,3-c]pyrazole-4(1H)-one **(40)**

To a solution of **39** (0.10 g; 0.326 mmol) in dioxane (10 ml), 1,8-diazabicyclo[5.4.0]-undec-7-ene (DBU) (0.06 ml, 0.06 g, 0.40 mmol) was added and the resulting mixture was stirred for 1 hour at 90°C. After cooling, 15 ml of water was added and stirring was continued for 30 minutes. The solution was extracted with dichloromethane (30 ml) and the organic phase was washed by 2N HCl (10 ml), dried (Na_2SO_4), and evaporated under reduced pressure. The resulting product **40** was collected (0.091 g) and recrystallized from ethyl acetate to give **40** as a white crystalline product: mp 147-148°C; yield 0.051 g (0.226 mmol, 69%);^{1}H-NMR ($CDCl_3$) δ 7.95 (s, 1H), 7.77 (m, 2H), 7.52 (m, 3H), 6.64 (s, 1H), 3.99 (s, 3H); ^{13}C-NMR δ 175.3, 160.4, 154.4, 134.8, 131.9, 131.2, 129.6, 126.5, 109.9, 107.9, 34.8; MS (ESI): $(M+Na)^+$ = 249.2; Anal. Calcd for $C_{13}H_{10}N_2O_2$: C, 69.00; H, 4.46; N, 12.39. Found: C, 68.79; H, 4.77; N, 12.43.

Synthesis of diethyl 2-[(2-phenylhydrazinyl)methylene]malonate **(41)**

A solution of the phenylhydrazine (6.0 ml, 6.6 g, 60.1 mmol) in methanol (10 ml) was added dropwise to a solution of **34** (10 g; 57.7 mmol) in methanol (50 ml) within 10 minutes. After the complete addition of the phenylhydrazine, the solution was stirred for two hours. Evaporation of the solvent gave a gum of crude product **41** (14.54 g), which was purified by recrystallization from ethyl acetate and cyclohexane to give **41** as an orange crystalline product: mp 72-73°C; yield 14.1 g (56.4 mmol, 98%); ^{1}H-NMR ($CDCl_3$) δ 9.58 (d, J = 10.5 Hz, 1H), 8.12 (d, J = 12.4 Hz, 1H), 7.11 (t, J = 6.6 Hz, 2H), 6.78 (t, J = 7.6 Hz, 1H), 6.69 (d, J = 8.69 Hz, 2H), 6.20 (s, NH), 3.70 (s, 3H),

3.61 (s, 3H); ^{13}C-NMR δ 169.6, 166.0, 162.6, 147.2, 129.9, 122.5, 113.8, 90.5, 52.0, 51.8.

Synthesis of methyl 5-hydroxy-1-phenyl-1H-pyrazole-4-carboxylate **(42)**

A solution of **41** (10 g; 40.0 mmol) in glacial acetic acid (40 ml) was refluxed for one hour. Evaporation of solvent gave the crude product **42** (8.42 g), which was recrystallized from methanol to give **42** as a white crystalline product: mp 151-153^{o}C; yield 7.42 g (34.0 mmol, 85 %); ^{1}H-NMR ($CDCl_3$) δ 7.74 (d, J = 7.6 Hz, 2H), 7.71 (s, 1H), 7.43 (t, J = 7.8 Hz, 2H), 7.29 (t, J = 7.6 Hz, 1H), 3.89 (s, 3H); ^{13}C-NMR 167.1, 157.0, 138.9, 137.9, 129.6, 127.6, 121.7, 95.3, 52.1; MS (ESI): $(M+Na)^+$ = 241.1.

Synthesis of 1-phenyl-1H-pyrazol-5(4H)-one **(43)**

Sodium hydroxide (4.5 g; 112.5 mmol) was dissolved in a solution of N-phenyl pyrazole **42** (4.5 g; 28.1 mmol) in ethanol (20 ml) and water (40 ml). The mixture was heated at 100^{o}C for 2 hours. Concentrated sulfuric acid was added dropwise (CO_2 evolution) with cooling in an ice bath. The resulting acidic mixture (pH 1) was heated at 100^{o}C for 10 hours to complete the decarboxylation. The resulting product was extracted with dichloromethane (30 ml) and the organic phase was dried by Na_2SO_4. Evaporation of solvent gave the pyrazolone crude product **43** (3.69 g), which was recrystallized from acetonitrile to give **43** as a white crystalline product: mp 110-111^{o}C (Lit.[11] 118^{o}C); yield 3.37 g (21.1 mmol, 75%); ^{1}H-NMR ($CDCl_3$) δ 7.45 (s, 1H), 7.83 (d, J = 8.6 Hz, 2H), 7.36 (t, J = 7.8 Hz, 2H), 7.18 (t, J = 7.6 Hz, 1H), 3.50 (s, 2H); ^{13}C-NMR δ 170.3, 147.3, 138.3, 129.3, 125.9, 119.4, 41.4; MS (ESI): $(M+H)^+$ = 161.0.

Synthesis of (E)-1-(5-hydroxy-1-phenyl-1H-pyrazol-4-yl)-3-phenylprop-2-en-1-one **(44)**

A mixture of N-phenylpyrazole **43** (0.25 g; 1.56 mmol) and $Ca(OH)_2$ (0.55 g, 3.1 mmol) in dioxane (20 ml) was refluxed for 30 minutes and allowed to stand at room temperature for two hours. Under stirring and cooling in an ice bath, *trans*-cinnamoyl chloride (0.283 g; 1.7 mmol) was added within 10 minutes and then the resulting reaction mixture was heated to reflux for 1.5 hours. After it was allowed to cool to room temperature, 2M HCl (20 ml) was added, the mixture was stirred for one additional 1 hour, and poured into water (40 ml). The resulting product **44** was precipitated and collected (0.47 g), which was recrystallized from ethanol to give **44** as a orange crystalline product: mp 175-176^{o}C (Lit.[10] mp 182-183^{o}C); yield 0.40 g (1.38 mmol, 88%); ^{1}H-NMR ($CDCl_3$) δ 7.93 (s, 1H), 7.93 (m, 2H), 7.88 (d, J = 15.8 Hz, 1H), 7.64 (m, 2H), 7.46 (m, 2H), 7.44 (m, 3H), 7.29 (m, 1H), 7.05 (d, J = 15.8 Hz, 1H); ^{13}C-NMR δ 180.6, 162.3, 144.1, 137.9, 137.6, 134.2, 131.1, 129.1, 129.1, 128.7, 126.5, 120.3, 119.6, 105.2; MS (ESI): $(M+Na)^+$ = 313.3.

Synthesis of 5-bromo-1,6-diphenyl-5,6-dihydropyrano[2,3-c]pyrazole-4(1H)-one **(45)**

To a solution of **44** (0.37 g; 1.27 mmol) in glacial acetic acid (30 ml) at 60^{o}C, a solution of bromine (0.13 ml, 0.40 g, 2.54 mmol) in glacial acetic acid (15 ml) was added dropwise within one hour and stirring was continued for two hours. Then the reaction mixture was cooled, treated with water (50 ml), the resulting product **45** was precipitated and filtered (0.37 g). The crude product was dissolved in dichloromethane (20 ml), decolorized by charcoal, and filtered. Evaporation of the solvent gave the crude product **45** (0.35 g), which was recrystallized from acetonitrile to give **45** as a white product: mp 195-196^{o}C; yield 0.22 g (0.596 mmol, 47%); ^{1}H-NMR ($CDCl_3$) δ 7.96 (s, 1H), 7.81 (d, J = 7.8, 2H), 7.46 (m, 4H), 7.37 (m, 3H), 7.35 (m, 1H), 5.53 (d, J = 11.4 Hz, 1H), 5.09 (d, J = 11.4 Hz, 1H); ^{13}C-NMR δ 189.1, 158.8, 138.5, 138.3, 137.3, 129.9, 129.7, 129.4, 128.7, 128.1, 121.8, 103.2, 49.3, 49.1; MS (ESI): $(M+Na)^{+}$ = 393.3.

Synthesis of 1,6-diphenylpyrano[2,3-c]pyrazole-4(1H)-one **(46)**

To a solution of **45** (0.155 g; 0.421 mmol) in dioxane (10 ml), 1,8-diazabicyclo[5.4.0]-undec-7-ene (DBU) (0.11 ml, 0.11 g, 0.736 mmol) was added and the resulting mixture was stirred for 1 hour at 90^{o}C. After cooling, 15 ml of water was added and stirring was continued for 30 minutes. The resulting product **46** was precipitated and collected (0.113 g), which was recrystallized from acetonitrile to give **46** as a white crystalline product: mp 184-185^{o}C (Lit.[10] mp 177-180^{o}C); yield 0.095 g (0.330 mmol, 78%); ^{1}H NMR ($CDCl_3$) δ 8.18 (s, 1H), 7.89 (m, 2H), 7.82 (m, 2H), 7.59 (m, 2H), 7.53 (m, 3H), 7.45 (m, 1H) 6.77 (s, 1H); ^{13}C NMR δ 175.1, 160.9, 153.5,

137.4, 136.1, 132.1, 131.1, 130.1, 129.8, 128.9, 126.5, 121.7, 110.2, 109.3; MS (ESI): $(M+Na)^+ = 311.3$.

Synthesis of diethyl 2-acetylmalonate (**51**)

A flame-dried 100 mL round-bottom flask equipped with septum inlet was flushed with argon. The sodium hydride (60% dispersion) (30 mmol, 1.20 g) and tetrahydrofuran (25 ml) were added to the flask and kept stirring. Diethyl malonate (25 mmol, 3.80 ml, 4.01 g) was added to the stirred mixture. After the solution was stirred for 15 min at 0^oC, acetyl chloride (562 mmol, 40 ml) was added dropwise. The resulting mixture was stirred 1 hour at 0^oC and 12 hours at room temperature. The acetyl chloride and tetrahydrofuran were removed under vacuum to give the crude product. After being cooled to 0^oC, the crude product was quenched with 25 mL of water. The resulting solution was extracted two times with 20 mL of dichloromethane. The combined organic layer extracts were dried (Na_2SO_4). The organic solvent was removed under vacuum to give crude product (7.12 mL), which was purified by bulb to bulb distillation (90^oC, 0.25 mm) to give **51** as a colorless liquid; yield 3.03 g (15.0 mmol, 60%); ^{1}H-NMR ($CDCl_3$) δ 13.7(s, OH), 4.41 (s, 1H), 4.20-4.29 (m, 4H), 2.17-2.32 (s, 3H), 1.25-1.32 (m, 6H); ^{13}C-NMR major (enol) δ 181.5, 171.9, 166.8, 101.5, 61.6, 62.2, 21.5, 14.8, 14.7; minor (keto) δ 197.5, 165.2, 66.6, 63.3, 29.8, 14.6; MS (ESI): $(M+Na)^+ = 225.0$.

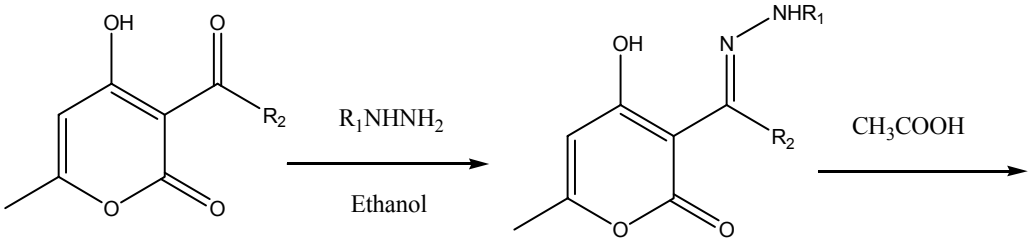
Synthesis of ethyl 5-hydroxy-1,3-dimethyl-1H-pyrazole-4-carboxylate **(48)**

A solution of methylhydrazine (0.05 ml, 0.044 g, 1.0 mmol) was added to a solution of **51** (0.21 g, 1.0 mmol) and 30% hydrochloric acid (0.20 ml) in ethanol (10 ml). After the mixture was refluxed for 2 hours and cooled at room temperature, the solution was treated with water (10 ml), extracted by dichloromethane (20 ml), and dried (Na_2SO_4). Evaporation of the solvent gave the crude product **48** (0.166 g), which was recrystallized from acetonitrile to give **48** as a colorless crystalline product: mp 124-125^oC (Lit.[14] 142-143^oC); yield 0.114 g (0.62 mmol, 62%); ^{1}H-NMR ($CDCl_3$) δ 9.24 (br, OH), 4.28 (q, J = 7.1 Hz, 2H), 3.58 (s, 3H), 2.29 (s, 3H), 1.24 (t, J = 7.1 Hz, 3H); ^{13}C-NMR δ 167.2, 157.7, 147.6, 92.7, 60.7, 33.3, 14.8, 14.6; MS (ESI): $(M+H)^+$ = 185.3.

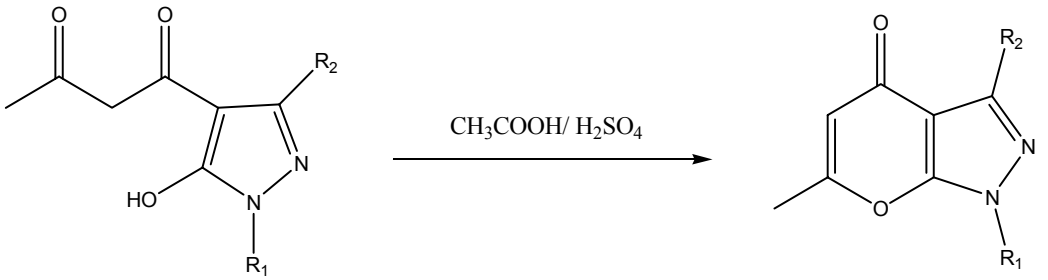
Synthesis of ethyl 5-hydroxy-3-methyl-1-phenyl-1H-pyrazole-4-carboxylate **(53)**

A solution of phenylhydrazine (0.10 ml, 0.11 g, 1.08 mmol) was added to the solution of **51** (0.21 g, 1.0 mmol) and concentrated hydrochloric acid (0.20 ml) in ethanol (10 ml). After the solution was refluxed for 2 hours and cooled to room temperature, the solution was treated with water (10 ml), extracted with dichloromethane (20 ml), and dried (Na_2SO_4). Evaporation of the solvent gave the crude product **53** (0.221 g), which was recrystallized from methanol and water to give **53** as a white crystalline product: mp 114-115^oC (Lit.[15] 114-115^oC); yield 0.150 g (0.610 mmol, 61%); ^{1}H-NMR ($CDCl_3$) δ 10.1 (br, OH), 7.75 (d, J = 7.6, 2H), 7.41 (t, J = 8.3, 2H), 7.25 (t, J = 7.6, 1H), 4.30 (q, J = 7.3 Hz, 2H), 2.36 (s, 3H), 1.33 (t, J = 7.1 Hz, 3H); ^{13}C-NMR δ 167.7, 157.8, 148.9, 137.9, 129.5, 127.1, 121.5, 94.1, 61.0, 14.8, 14.8; MS (ESI): $(M+H)^+$ = 247.4.

Conclusion



	R_1	R_2	
1	Ph	Me	**2**
	Me	Me	**5**
10	Ph	Et	**11**
	Me	Et	**14**
18	Ph	Pr	**19**
	Me	Pr	**22**
26	Ph	Ph	**27**
30	Ph	H	**31**

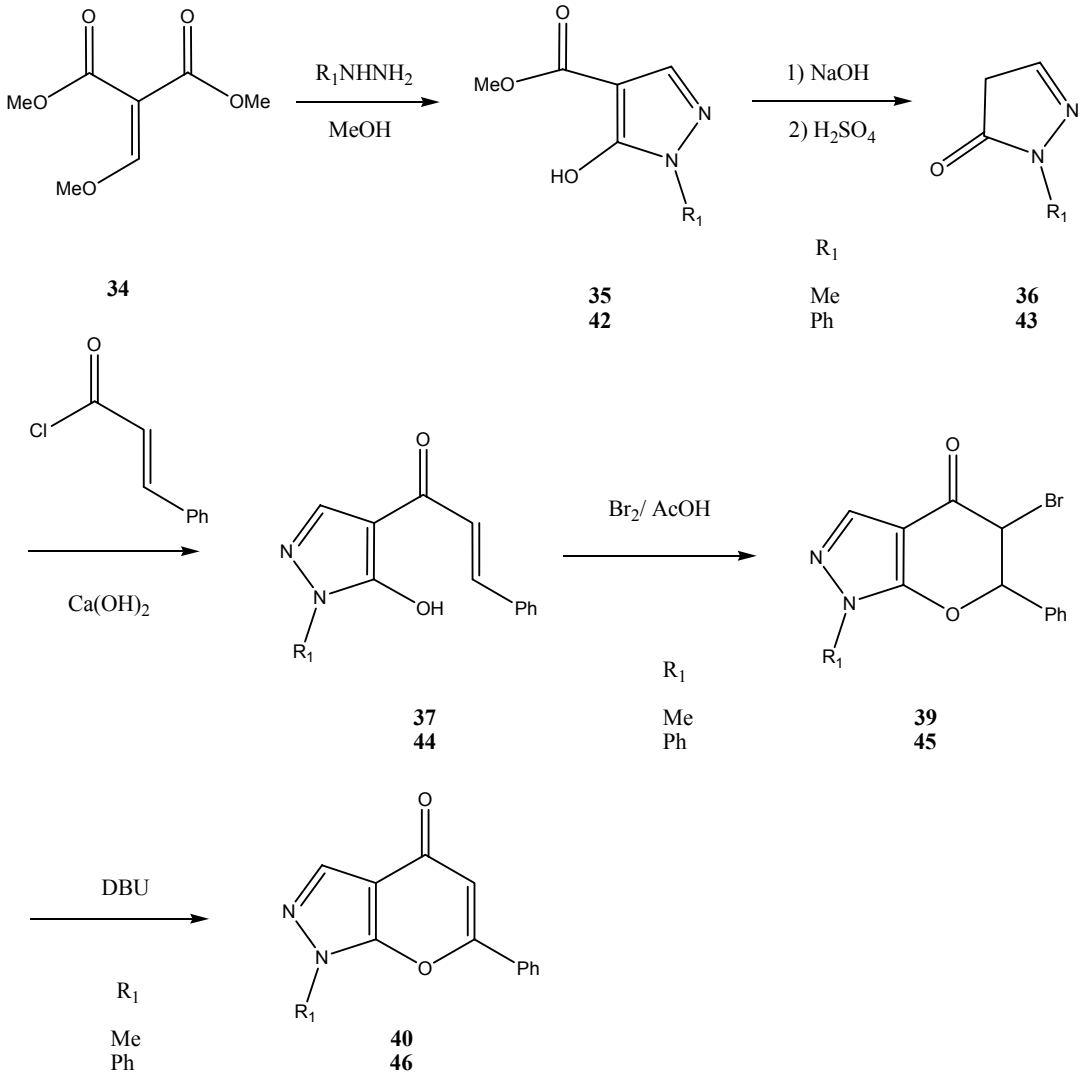


	R_1	R_2	
3	Ph	Me	**4**
6	Me	Me	**7**
12	Ph	Et	**13**
16	Me	Et	**17**
20	Ph	Pr	**21**
23	Me	Pr	**24**
28	Ph	Ph	**29**

Scheme 52: Synthesis of pyrano[2,3-c]pyrazoles derivatives by Gelin's method

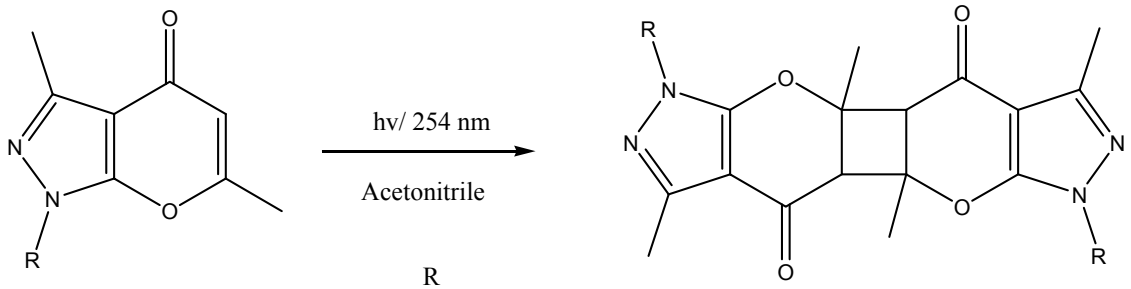
Two different synthetic approaches to pyrano[2,3-*c*]pyrazole have been investigated. In one approach, dehydroacetic acid was treated with phenylhydrazine[3] to obtain the 3,6-dimethyl-1-phenylpyrano-[2,3-*c*]pyrazol-4-ones **(4)**. In addition,

Sanchez-Ferrando, F. and colleagues[5] reported that methylhydrazine reacts readily with dehydroacetic acid to yield 4-hydroxy-6-methyl-3-(1-(2-methylhydrazono)ethyl)-2*H*-pyran-2-one **(5)**. We now report a new successful conversion of the deydroacetic acid **1** and derivatives **10**, **18**, **26**, **30** to the N-substitued hydrazones **2**, **5**, **11**, **14**, **19**, **22**, **27**, **31**, 1,3-disubstituted-4-(acylacetyl)-2-pyrazolin-5-ones **3**, **6**, **12**, **16**, **20**, **23**, **28**, and their subsequent use in the synthesis of pyrano[2,3-*c*]pyrazole derivatives **4**, **7**, **13**, **17**, **21**, **24**, and **29**, a class of new compounds which has not been reported.



Scheme 53: Synthesis of pyrano[2,3-*c*]pyrazoles by Heinish's method

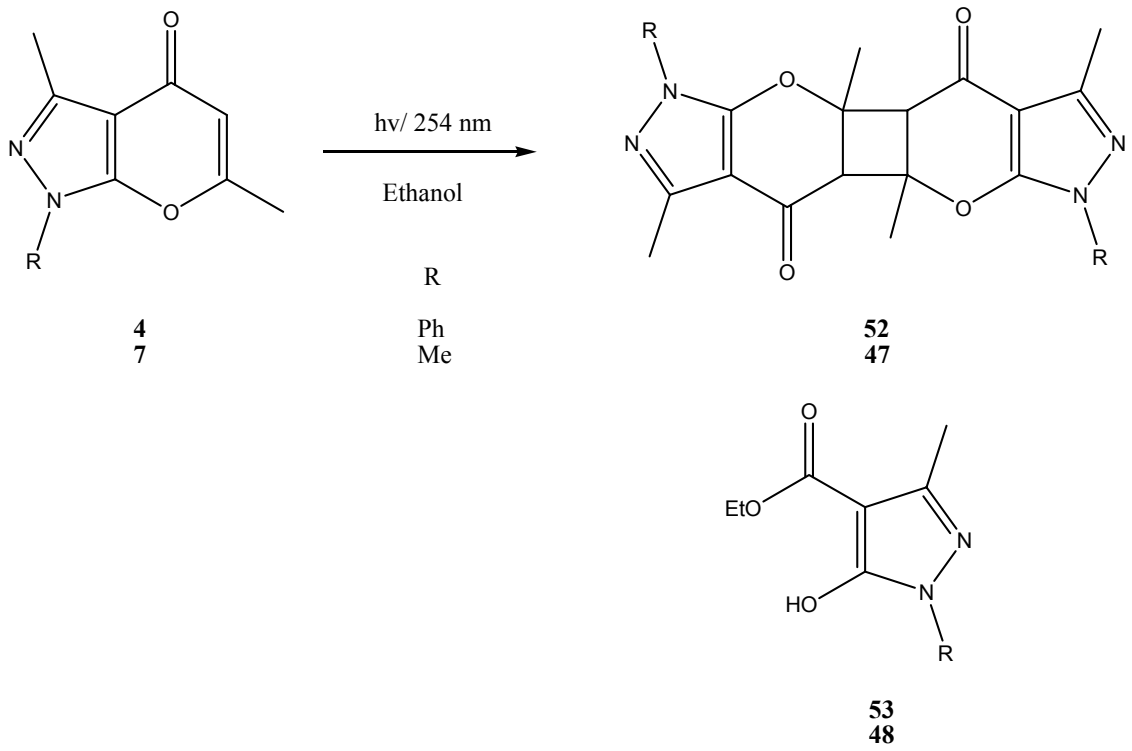
Secondly, in order to synthesize pyrano[2,3-*c*]pyrazol-4-one derivatives based on Heinish, G. and colleagues's procedure,[4] the N-methylpyrazolone **36** and N-phenylpyrazolone **43** were prepared by Shimizu, T. and colleagues's method.[8] The phenylhydrazine and methylhydrazine readily react with dimethyl(methoxymethylene)malonate **(34)** to give N-substitued pyrazole ester derivatives **35**, **42** which were converted to N-substitued pyrazolone derivatives **36**, **43** by hydrolysis and decarboxylation. C-acylation of these compound with trans-cinnamoyl chloride gave α,β-unsaturated-4-acetyl-5-hydroxypyrazoles **37**, **44**. Bromination of these α,β-unsaturated-4-acetyl-5-hydroxypyrazoles with spontaneous cyclization to dihydrobromo derivatives **39**, **45**, followed by dehydrobromination led to pyrano[2,3-*c*]pyrazol-4-one derivatives **40**, **46**, respectively shown in scheme 53.



4 **52**
7 **47**

Scheme 54: Photolysis of pyrano[2,3-*c*]pyrazoles in acetonitrile

Phototochemical excitation of 1-phenyl and 1-methylpyrano[2,3-*c*]pyrazol-4-ones leads to the formation of cis-head-to-tail [2+2] cycloaddition adducts **47**, **52** in acetonitrile, while they underwent photodimerization and photofragmentation



Scheme 55: Photolysis of pyrano[2,3-*c*]pyrazoles in ethanol

in ethanol to yield the cis-head-to-tail [2+2] cycloaddition adducts **47**, **52** and ethylpyrazole ester derivatives **48**, **53**.

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