SYNTHESIS AND REACTIONS OF SOME 2(3*H*)- AND 2(5*H*)-FURANONE DERIVATIVES: A COMPARATIVE STUDY

Ahmed I. Hashem,[a] Wael S. I. Abou-Elmagd[a] and Ahmed Abd-Elaziz[a]

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Early, it was found that benzoin condensed with ethyl cyanoacetate in the presence of ethoxide ion to give 3- cyano-3,4-diphenyl-2(5*H*)-furanone **1**. On reinvestigating this reaction, we were able to isolate **1** together with another product, in low yield, which was proved to be 3-cyano-3,4-diphenyl-2(3*H*)-furanone **2**. The latter is formed by isomerization of **1** under the basic conditions employed. Energy calculations revealed that the 2(5*H*)-furanone **1** is more stable than the 2(3*H*)-isomer by 24.5 KJ/mole. The behavior of the two furanones **1** and **2** towards some nitrogen nucleophiles viz. hydrazine hydrate, benzylamine and ammonium acetate is studied. The unfavored 1,4 addition of these nucleophiles to the α,β-unsaturated carbonyl moiety of **1** is explained in terms of steric and electronic effects of the phenyl group at position 4 .The nitrile groups at position 3 of the furanones **1** and **2** were utilized to construct thiazolidine and tetrazole rings by the action of thioglycollic acid and sodium azide respectively. The structures of all the products obtained were illustrated from their analytical and spectral properties.

Corresponding Authors
>   Tel./Fax: +20224831836
>   E-Mail: waelmagd97@yahoo.com
[a]   Chemistry Department, Faculty of Science, Ain Shams University, Abassia, Cairo, Egypt, post code 11566.

Introduction

Furanones represent a group of heterocyclic compounds of special importance. According to the relative positions of the carbonyl group and the double bond in the hetero ring, there are three types of furanones namely; 2(3*H*)-,2(5*H*)- and 3(2*H*)- furanones. Compounds of the first type are characterized by facile ring opening to give acyclic products which can be recyclized to give heterocyclic derivatives of synthetic and biological importance. The nucleus of the second type is the core skeleton in many natural products.

The chemistry of the first two types had been reviewed by one of us.[1,2] Also, our research group were interested during the last decades in the utilization of 2(3*H*)- furanone derivatives in the construction of a variety of heterocyclic systems, viz. pyrrolinones,[3,4] pyridazinones,[5,6,7] isothiazolones,[8] ,oxadiazoles,[9,10] and triazoles .[11,12]

Experimental section

General

Melting points were measured on a Gallen Kamp electric melting point apparatus. The infrared spectra were recorded using potassium bromide disks on FTIR Thermo Electron Nicolet 7600 (USA) infrared spectrometer. The ^{1}H-NMR spectra were run at 300 MHz on a GEMINI 300 BB NMR spectrometer using tetramethyl silane (TMS) as internal standard in deuterated dimethylsulphoxide (DMSO-d$_6$). The mass spectra were recorded on a shimadzu GC-MS QP-1000EX mass spectrometer operating at 70 eV. The reactions were monitored by the thin layer chromatography using Merck Kiesel gel 60 F254 aluminum backed plates.

General procedure for condensation of benzoin with ethyl cyanoacetate.[13]

A mixture of (0.1 mol, 21.2 g) of benzoin in 70 ml of absolute alcohol there was added (0.1 mol, 11.3 ml) of ethyl cyanoacetate followed by 2.3 g of sodium dissolved in 70 ml of absolute alcohol. There was a momentary purple color on adding sodium and heat is developed. On shaking the benzoin dissolved to form a clear reddish solution. This was heated on the water bath under reflux condenser for three hours, after which it was poured into 800 ml of water. A small precipitate of unchanged benzoin was filtered off and the clear filtrate acidified. A granular semi-solid precipitate was filtered off, rubbed with a small amount of ether and the white crystals filtered from ether yield about 85 %. Recrystallization from methanol yielded 3-cyano-4,5-diphenyl-2(5*H*)- furanone **1**. Another precipitate was collected from ether layer and recrystallized from methanol to give 3-cyano-4,5-diphenyl-2(3*H*)- furanone **2**.

3-cyano-4,5-diphenyl-2(5H)- furanone, (1).

White crystals; m.p: 139-140 ºC, yield 85 %. IR (KBr) (v_{max}, cm^{-1}): 2235 (CN), 1770 (C=O lactone), 1621 (C=C). ^{1}H-NMR (DMSO-d$_6$): δ$_H$ (ppm) 6.17 (s, 1H,CH-Ph) 6.95-7.40 (m, 10H, ArH). MS, m/z (%): 261 (M$^{·+}$, 57), 217 (31), 91(24), 77 (100) . Anal. Calcd. For C$_{17}$H$_{11}$NO$_2$ (261): C, 78.15; H, 4.24; N, 5.36. Found: C, 78.30; H, 4.33; N, 5.76.

3-cyano-4,5-diphenyl-2(3H)- furanone, (2).

Yellow crystals; m.p:167-169 ºC, yield 15 %. IR (KBr) (v_{max}, cm^{-1}): 2252 (CN), 1782 (C=O lactone), 1623 (C=C). ^{1}H-NMR (DMSO-d$_6$): δ$_H$ (ppm) 4.23 (s, 1H,CH-CN) 7.09-7.47 (m, 10H, ArH). MS, m/z (%): 261 (M$^{·+}$, 39), 217 (54), 191(31),77 (100) . Anal. Calcd. For C$_{17}$H$_{11}$NO$_2$ (261): C, 78.15; H, 4.24; N, 5.36. Found: C, 77.96; H, 4.17; N, 5.56.

General procedure for the action of hydrazine hydrate on the 2(5H)-furanone (1)

a) Hydrazine hydrate (1.1 mmol) was added to a solution of the furanone **1** (1 mmol) in ethanol (20 ml). The reaction mixture was left at room temperature with occasional shaking. The product obtained was filtered off, washed with ethanol, and found to be the furanone **2**.

b) The same reaction was carried out at 80 °C in ethanol as solvent for 30 min. The product obtained was filtered off, washed with ethanol, and found to be the acid hydrazide derivative **5**.

c) The reaction mixture was heated under reflux for 3 h . The solvent was distilled off under reduced pressure. The solid obtained was washed thoroughly with ethanol, drained and recrystallized from ethanol to give the pyridazinone derivative **6**. The pyridazinone derivative **6** was also obtained by ring closure of the acid hydrazide **5** by refluxing with HCl/AcOH mixture (1:1).

d) The acid hydrazide and the pyridazinone derivatives **5** and **6** respectively were also obtained when the reaction was carried out on the 2(5H)-furanone **2**.

2-cyano-4-oxo-3,4-diphenyl butanhydrazide, (5).

White crystals; m.p: 265-266 °C, yield 60 %. IR (KBr) (ν_{max}, cm^{-1}): 2250 (CN), 1708.1661 (C=O), 1623 (C=C). ^{1}H-NMR (DMSO-d$_6$): δ_H (ppm) 4.27 (s, 1H,CHCN), 4.53 (s, 1H,CHPh), 5.13(br.s, 2H, NH2), 6.67(br.s, 1H, NHCO), 7.06-7.93 (m, 10H, ArH),. MS, m/z (%): 293 (M$^{.+}$, 27), 262 (73), 195(38), 105(100), 91(86),77 (56) . Anal. Calcd. For C$_{17}$H$_{15}$N$_3$O$_2$ (293): C, 69.61; H, 5.15; N, 14.33. Found: C, 69.95; H, 5.27; N, 5.56.

4-cyano-5,6-diphenyl-1,2,3,4-tetrahydropyridazine-3-one, (6).

Faint red powder; m.p: 230-232 °C, yield 65 %. IR (KBr) (ν_{max}, cm^{-1}): 2279 (CN), 1678 (C=O cyclic amide), 1620 (C=C). ^{1}H-NMR (DMSO-d$_6$): δ_H (ppm) 3.45 (br.s, 1H, NH, exchangeable), 5.33 (s, 1H, CHCN), 7.08-7.72 (m, 10H, ArH), 10.38 (br.s, 1H, NHCO). MS, m/z (%): 275 (M$^{.+}$, 27), 273 (85), 257(76), 245(38), 232 (43), 217(29), 91 (23), 77 (100) . Anal. Calcd. For C$_{17}$H$_{13}$N$_3$O (275): C, 74.17; H, 4.76; N, 15.26. Found: C, 74.55; H, 4.62; N, 15.47.

General procedure for the action of benzylamine on the 2(5H)- and 2(3H)-furanones, (1) and (2), respectively.

a) A solution of the furanone derivatives **1** or **2** (0.01 mol) in benzene and benzyl amine (0.02 mol) was refluxed for 3 h. The reaction mixture was left to cool at room temperature. The product obtained was filtered off, recrystallized from ethanol to give N-benzylamide derivative **7**.

b) On fusion of the furanone derivatives **1** and **2** (0.5 g) with benzylamine (1 ml) for 2 h, the product obtained was treated with methanol to give gray powder, filtered off, recrystallized from ethanol to give the pyrrolone derivatives **8** and **9,** respectively .

N-benzyl-2-cyano-4-oxo-3,4-diphenyl butanamide, (7).

White powder; m.p: 212-214 °C, yield 70 %. IR (KBr) (ν_{max}, cm^{-1}): 3283(NH), 2360 (CN), 1682,1654 (C=O), 1625 (C=C). ^{1}H-NMR (DMSO-d$_6$): δ_H (ppm) 4.22 (d, 1H, CHCN, J= 6.6), 4.35 (d-d, 2H, NHCH$_2$, J=11.2), 4.51(d, 1H, CHPh, J= 6.6), 7.24-7.87 (m, 15H, ArH), 9.27(br.s, 1H, NHCO). MS, m/z (%): 368 (M$^+$, 39), 291 (67), 262(71), 213 (52), 184 (56), 105(100), 91(87), 77(63). Anal. Calcd. For C$_{24}$H$_{20}$N$_2$O$_2$ (368): C, 78.24; H, 5.47; N, 7.60. Found: C, 78.75; H, 5.71; N, 7.43.

1-benzyl-3-cyano-4,5-diphenyl-2,5-dihydro-1H-pyrrole-2-one, (8).

Faint yellow crystals; m.p: 142-144 °C, yield 80 %. IR (KBr) (ν_{max}, cm^{-1}): 2223 (CN), 1685 (C=O), 1620 (C=C). ^{1}H-NMR (DMSO-d$_6$): 4.25-5.29 (m, 2H, NCH$_2$), 5.32 (s, 1H, CHPh), 6.93-7.50 (m, 15H, ArH). MS, m/z (%): 350 (M$^{.+}$, 23), 245 (35), 217(47), 91(100), 77(87). Anal. Calcd. For C$_{24}$H$_{18}$N$_2$O (350): C, 82.26; H, 5.18; N, 7.99. Found: C, 82.09; H, 5.23; N, 7.79.

1-benzyl-3-cyano-4,5-diphenyl-2,3-dihydro-1H-pyrrole-2-one, (9).

Faint yellow crystals; m.p: 148-150 °C, yield 55 %. IR (KBr) (ν_{max}, cm^{-1}): 2271 (CN), 1687 (C=O), 1620 (C=C). ^{1}H-NMR (DMSO-d$_6$): 4.09 (s, 1H, CHCN), 4.19-4.23 (m, 2H, NCH$_2$), 7.11-7.76 (m, 15H, ArH). MS, m/z (%): 350 (M$^{.+}$, 52), 245 (42), 217(29), 180(100), 91(89), 77(83). Anal. Calcd. For C$_{24}$H$_{18}$N$_2$O (350): C, 82.26; H, 5.18; N, 7.99. Found: C, 82.17; H, 5.07; N, 7.83.

General procedure for the action of ammonium acetate on the 2(5H)- and 2(3H)-furanones (1) and (2) respectively.

a) A mixture of the furanone derivatives **1** or **2** (0.01 mol) in acetic acid and ammonium acetate (0.1 mol) was refluxed for 3 h. The reaction mixture was left to cool at room temperature. The product obtained was filtered off, recrystallized from ethanol to give pyrrolone derivative **10** and **11,** respectively.

b) Fusion of the furanone derivatives **1** or **2** (0.5 g) with ammonium acetate (1 g) for 1h. The product obtained was treated with water to give gray powder, filtered off, recrystallized from ethanol to give the pyrrolone derivatives **10** and **11,** respectively .

3-Cyano-4,5-diphenyl-2,5-dihydro-1H-pyrrole-2-one, (10).

White powder; m.p: 232-234 °C, yield 40 %. IR (KBr) (ν_{max}, cm^{-1}): 3185(NH), 2194 (CN), 1656 (C=O), 1602 (C=C). ^{1}H-NMR (DMSO-d$_6$): 4.33 (br.s, 1H, OH(lactim form), exchangeable), 5.53 (s, 1H, CHPh), 7.29-7.94 (m, 10H, ArH), 13.42(br.s, 1H, NH, exchangeable). MS, m/z (%): 260 (M$^{.+}$, 46), 217 (67), 129(86), 103(77), 91(79), 77(100). Anal. Calcd. For C$_{17}$H$_{12}$N$_2$O (260): C, 78.44; H, 4.65; N, 10.76. Found: C, 78.59; H, 5.01; N, 10.53.

3-cyano-4,5-diphenyl-2,3-dihydro-1H-pyrrole-2-one (11).

Gray powder; m.p: 297-299 ºC, yield 35 %. IR (KBr) (ν_{max}, cm^{-1}): 2286 (CN), 1679 (C=O), 1605 (C=C). ^{1}H-NMR (DMSO-d$_6$): 4.12 (s, 1H, CHCN), 6.93-7.46 (m, 10H, ArH), 10.74(br.s, 1H, NH, exchangeable). MS, m/z (%): 260 (M$^{\cdot+}$, 35), 217 (59), 180(100), 77(93). Anal. Calcd. For C$_{17}$H$_{12}$N$_2$O (260): C, 78.44; H, 4.65; N, 10.76. Found: C, 78.64; H, 4.87; N, 10.83.

General procedure for the action of thioglycolic acid on the 2(5H)- and 2(3H)-furanones, (1) and (2), respectively.

A mixture of 10 mmol of 2(5H)-furanone, thioglyclic acid (10 mmol) in pyridine (10 ml) was refluxed for 3 h. the solvent was removed under reduced pressure and the solid obtained was filtered off washed with ethanol and recrystallized from methanol/ dioxane mixture to give the thiazolidinone derivatives **12** and **13** respectively .

2-(4,5-diphenyl-2(3H)-furanone-3-yl)thiazol-4(5H)-one, (12)

Bright green crystals; m.p: 206-208 ºC, yield 90 %. IR (KBr) (ν_{max}, cm^{-1}): 3200-3418(br.) (OH), 1754 (C=O lactone), 1620,1600 (C=N, C=C). ^{1}H-NMR (DMSO-d$_6$): 5.88 (s, 1H, CHPh), 7.25-7.55 (m, 11H, ArH), 10.88 (br.s, 1H, OH, exchangeable). MS, m/z (%):337 (M$^{\cdot+}$+2, 4), 335 (M$^{\cdot+}$, 49), 260 (67), 232(43), 188(35), 91(56), 77(100). Anal. Calcd. For C$_{19}$H$_{13}$NO$_3$S (335): C, 68.04; H, 3.91; N, 4.18; S, 9.56. Found: C, 68.29; H, 3.75; N, 4.32; S, 9.72.

2-(4,5-diphenyl-2(5H)-furanone-3-yl)-5-hydroxythiazol, (13)

Bright red crystals; m.p: 212-214 ºC, yield 85 %. IR (KBr) (ν_{max}, cm^{-1}): 1768 (C=O lactone), 1712 (C=O thiazolidinone), 1630, 1620 (C=N, C=C). ^{1}H-NMR (DMSO-d$_6$): 3.18 (s, 1H, CHCO), 3.93 (s, 2H, CH$_2$ Thiazolidinone), 7.21-7.54 (m, 10H, ArH). MS, m/z (%):337 (M$^{\cdot+}$+2, 3), 335 (M$^{\cdot+}$, 51), 304 (23), 263(75), 240(43), 180(87), 161(31), 77(100). Anal. Calcd. For C$_{19}$H$_{13}$NO$_3$S (335): C, 68.04; H, 3.91; N, 4.18; S, 9.56. Found: C, 67.76; H, 3.80; N, 4.07; S, 9.38.

General procedure for the action of sodium azide on the 2(5H)- and 2(3H)-furanones, (1) and (2), respectively.

0.01 mol of the furanones **1** or **2**, sodium azide (6 mmol) and NH$_4$Cl (6 mmol) in 15 ml acetic acid were refluxed for 5 h. The resulting crude product was filtered off and recrystalized from methanol to give the tetrazole derivatives **14** and **15** respectively.

**4,5-diphenyl-3-(1-H-tetrazol-5-yl)-2(5H)-furanone, (14).**

Grey powder; m.p: 125-127 ºC, yield 92 %. IR (KBr) (ν_{max}, cm^{-1}): 3213 (NH), 1758 (C=O lactone), 1614, 1600 (C=N, C=C). ^{1}H-NMR (DMSO-d$_6$): 6.13 (s, 1H, CHPh), 7.14-7.63 (m, 10H, ArH), 15.17 (weak br.s, 1H, NH, exchangeable). MS, m/z (%): 304 (M$^{\cdot+}$, 100), 260 (89), 232(23), 91(25), 77(95). Anal. Calcd. For C$_{17}$H$_{12}$N$_4$O$_2$ (304): C, 67.10; H, 3.97; N, 18.41. Found: C, 66.97; H, 3.78; N, 18.23.

4,5-diphenyl-3-(1-H-tetrazol-5-yl)-2(3H)-furanone, (15).

Faint brown powder; m.p: 112-114 ºC, yield 90 %. IR (KBr) (ν_{max}, cm^{-1}): 1767 (C=O lactone), 1623, 1600 (C=N, C=C). ^{1}H-NMR (DMSO-d$_6$): 4.35 (s, 1H, CHCO), 7.08-7.47 (m, 10H, ArH), 15.32 (weak br.s, 1H, NH, exchangeable). MS, m/z (%):337 (M$^{\cdot+}$+2, 3), 335 (M$^{\cdot+}$, 51), 304 (23), 263(75), 240(43), 180(87), 161(31), 77(100). Anal. Calcd. For C$_{17}$H$_{12}$N$_4$O$_2$ (304): C, 67.10; H, 3.97; N, 18.41. Found: C, 66.02; H, 4.05; N, 18.57.

Results and discussion

In this investigation, we wish to report on the synthesis and reactions of two furanones derivatives, one of 2(3H)-type and the other of the 2(5H)- type as a comparative study, in an attempt to show the effect of the position of the double bond on their behavior. McRae and Kuehner,[13] reported that the condensation of benzoin with ethyl cyanoacetate in the presence of sodium ethoxide led to formation of the lactone of α-cyano-β,ɤ-diphenyl-ɤ-hydroxy crotonic acid (m.p. 141 ºC), whose currently present name is 3-cyano-4,5-diphenyl-2(5H)- furanone **1**. Perhaps due to the lack of spectroscopic tools at this earlier time, this compound was not characterized spectroscopically. Its structure was assigned based on chemical transformations. Our interest in the chemistry of furanones, led us to reinvestigate this reaction. On carrying this reaction under the same conditions reported,[13] we were able to isolate the furanone **1** together with another product (m.p 175 c°) to which structure **2** was assigned on the bases of spectroscopic data.
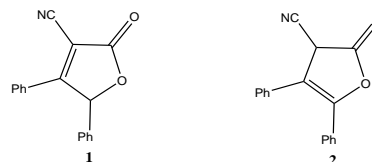
The infrared spectrum of compound **1** showed absorption bands at 2235 cm^{-1} and 1770 cm^{-1} characteristic of the νCN and νC=O respectively. Compound **2** showed νCN and νC=O at 2252 cm^{-1} and 1782 cm^{-1} respectively. The ^{1}H-NMR of the above two compound showed the characteristic signals of the different protons (cf. Experimental part).

We believe that the formation of **2**, namely 2-cyano-4,5-diphenyl-2(3H)-furanone is not unexpected under the basic conditions at which the reaction was carried out. Thus, the formation of **2** may be explained on the basis of isomerization of **1** in the presence of the strong base ethoxide ion. Such isomerization might involve the intermediate formation of resonance stabilized carbanions as previously reported by our research group.[14] Therefore, the formation of the 2(3H)-furanone **2** may be represented by Scheme 1.
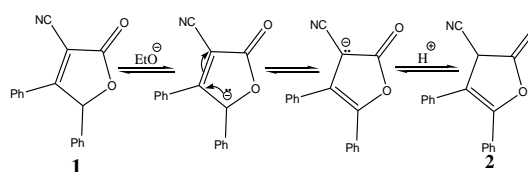
Scheme 1.

The formation of the 2(3H)-furanone **2** in a relatively smaller yield compared with 2(5H)-isomer **1** (cf. the experimental part), reflects the higher stability of the latter. This led us to determine the relative stabilities of these two isomers applying the UMPW1K/6-31+g(d) method, of calculation.[15] The results of these calculations revealed that **1** is more stable than **2** by 24.5 kJ mol^{-1}. Border er al,[16] reported that generally 2(5H)-furanones are thermodynamically more stable than their tautomers, the 2(3H)-furanones. SCF- MO calculations showed that the energy of **3** is less than that of its tautomer **4** by 53 kJ/mole.[16]

The lower energy difference obtained in our case may be attributed to the presence of two phenyl groups attached to the ring double bond of **2** which impart some degree of stability to this isomer.

The study was extended to explore the effect of the relative positions of the double bond and the carbonyl group in **1** and **2** on their behavior towards some nitrogen nucleophiles. The 2(5H)-furanone **1** reacted with hydrazine hydrate in ethanol at room temperature to give its tautomer **2**. However, when the reaction was carried out at 80°C the propionic acid hydrazide **5** was obtained as the only isolable product. On the other hand, the reaction of the furanone **1** with hydrazine hydrate in refluxing ethanol, led to the formation of the pyridazinone derivative **6**.

The same two products **5** and **6** were obtained from the reaction of the 2(3H)- furanone **2** under the same reaction conditions. This behavior led us to believe that the reaction of the 2(5H)- furanone **1** with hydrazine follows the following sequence:
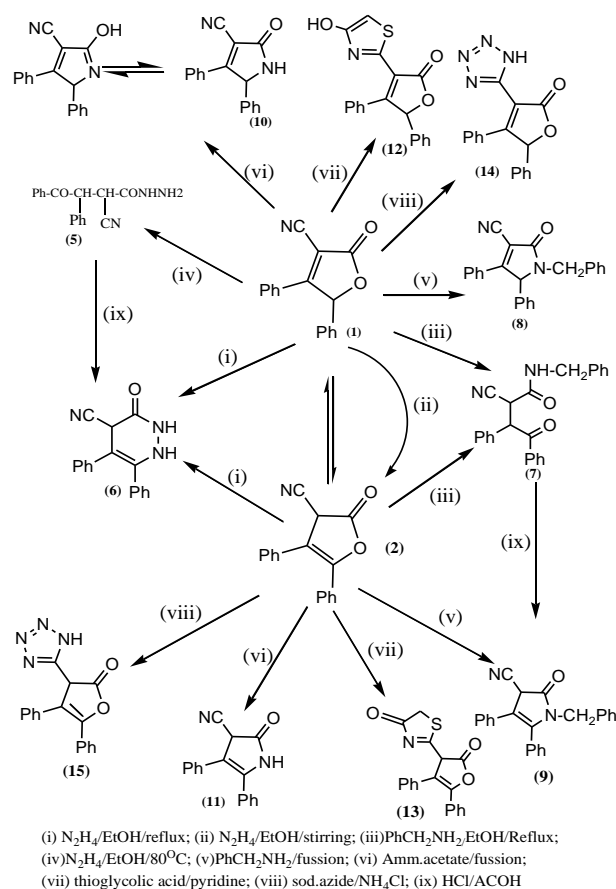
Firstly, the furanone isomerizes to the its 2(3H)-isomer, followed by ring opening to give the open chain hydrazide **5**, which undergoes ring closure to give the pyridazinone **6**. The latter was obtained also by cyclization of **5** in HCl/AcOH mixture. Benzylamine reacted with **1** in refluxing benzene to give the benzylamide derivative **7**. The same product **7** was obtained from the reaction of the 2(3H)-isomer **2** with benzylamine under the same reaction conditions.

This behavior again indicates that under these conditions, the 2(5H)- isomer **1** isomerizes firstly to its tautomer **2** before ring opening by benzylamine. On fusion of the furanone **1** with benzylamine in neat, the pyrrolone derivative **8** was obtained as the only isolable product. Under the same reaction conditions, the 2(3H)-isomer **2** gave another pyrrolone derivative **9**. This behavior excludes the possibility of isomerization of **1** into **2** under these reaction conditions. The compound **9** was also obtained by cyclization of **7** in HCl/AcOH mixture.

The reaction of the furanones **1** and **2** with ammonium acetate was also tried. On refluxing **1** or **2** and ammonium acetate in acetic acid, the reaction failed to give any product.

However, fusion of **1** and **2** with ammonium acetate led to the formation of the pyrrolone derivatives **10** and **11** respectively.

The presence of cyano group at position-3 in both the 2(5H) - and 2(3H) furanones promoted our interest to construct thiazolidinone and tetrazole rings at this position. Thus, **1** and **2** reacted with thioglycolic acid to give the thiazolidinone derivatives **12** and **13** respectively. The tetrazolyl derivatives **14** and **15** were obtained by reacting the 2(5H)- and 2(3H)- furanones respectively with sodium azide in the presence of ammonium chloride. The structures of all the products obtained were elucidated from their spectral analyses (cf. experimental part). All the foregoing reactions are illustrated by scheme (2).


(i) N$_2$H$_4$/EtOH/reflux; (ii) N$_2$H$_4$/EtOH/stirring; (iii)PhCH$_2$NH$_2$/EtOH/Reflux; (iv)N$_2$H$_4$/EtOH/80°C; (v)PhCH$_2$NH$_2$/fussion; (vi) Amm.acetate/fussion; (vii) thioglycolic acid/pyridine; (viii) sod.azide/NH$_4$Cl; (ix) HCl/ACOH

Scheme 2

De lange et al.,[17] reported that the addition of amines to 5-methoxy-2(5H)-furanone **16** led to the formation of the aminolactone **17** which was formed by 1,4-addition to the α,β-unsaturated carbonyl moiety with the furanone ring remaining intact.
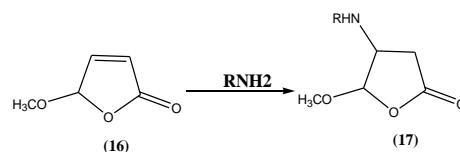
Also, the enantioselective synthesis of the N-benzyl substituted β-lactam **19**. A precursor for *carbapenem* antibiotics was synthesized by 1,4 addition of benzylamine to the chiral synthon 5(R)-methyloxy-2(5H)-furanone **18**.[18]
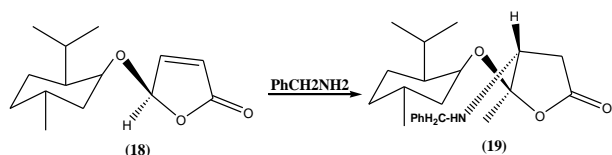
It is evident that the 2(5*H*)-furanone **1** behaved differently towards the nitrogen nucleophiles studied. The unfavored 1,4 addition in our case may be attributed to the presence of a phenyl group at position 4 which exerts a combination of steric and electronic effects retarding the approach of the nucleophile at this position.

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