ACID CATALYZED α-PYRONE RING FORMATION REACTIONS

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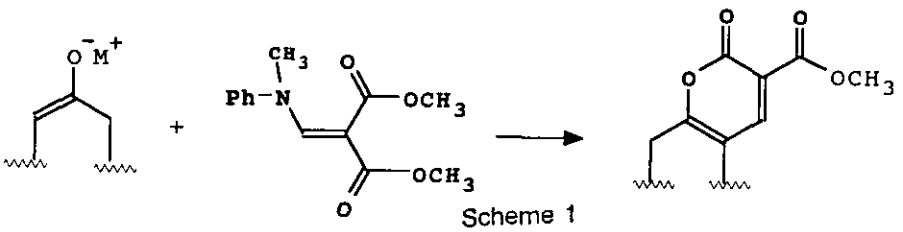
Abstract- The reaction of 1,3-dicarbonyl compounds with methyl 2-carbomethoxy-3-(*N*-methylanilino)acrylate under acidic condition directly gives substituted 2*H*-pyran-2-ones in good yield.

α-Pyrones are an important structural unit of some biologically active compounds.[1] Synthetic approaches to the α-pyrones are still of interest, because of the potential pharmacological importance.[2-9] There are various ways for the construction of α-pyrone ring system given in the literature.[10-16]

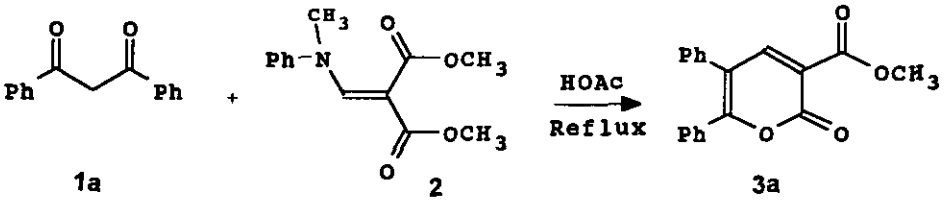
In the earlier study we reported a synthetic route for the synthesis of substituted 2*H*-pyran-2-ones *via* the conjugate addition of the enolates of carbonyl compounds to enamino esters. By this method the enolates of the ketones with methyl 2-carbomethoxy-3-(*N*-methylanilino)acrylate[17] *via* the addition-elimination followed by cyclization gave directly in one step the corresponding α-pyrones as shown in Scheme 1. Similiar reactions with 1,3-dicarbonyl compounds gave the corresponding addition-elimination products but not the α-pyrones.[18]



Scheme 1

In this paper, we report the alternative methods for one pot synthesis of sustituded 2*H*-pyran-2-ones starting with 1,3-dicarbonyl compounds and enamino esters under acidic conditions.

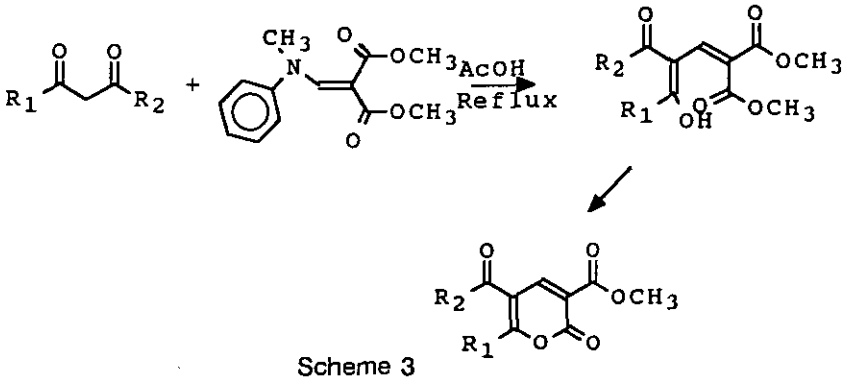
As shown in the Scheme 2 1,3-diphenylpropane-1,3-dione(**1a**) was treated with methyl 2-carbomethoxy-3-(*N*-methylanilino)acrylate(**2**) in the presence of acetic acid. Refluxing of the mixture for 2 h (the reaction was monitored by tlc using EtOAc/Hexane 1:2) gave the corresponding α-pyrone(**3a**) in 60 % yield as an oil.



1a **2** **3a**

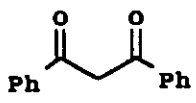
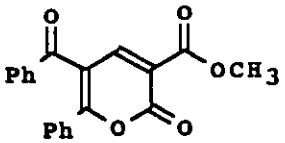
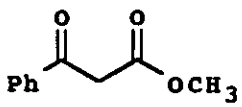
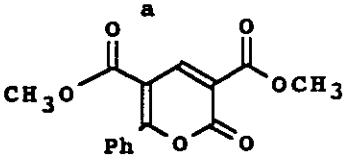
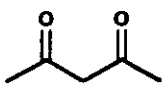
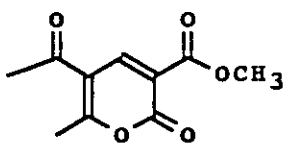
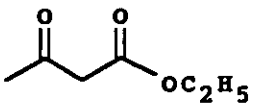
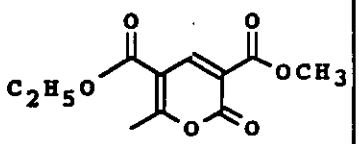
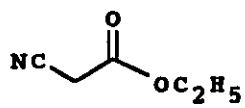
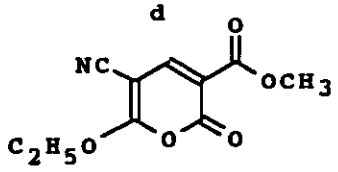
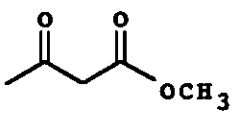
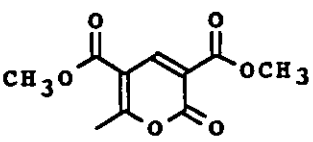
Scheme 2

Under similar conditions different 1,3-dicarbonyl compounds (**1a-f**) gave different substituted α-pyrones (**3a-f**) in moderate yield as shown in Table 1. The reaction proceeds most probably as first nucleophilic substitution of the protonated *N*-methylaniline group of the enamino ester by a carbon nucleophile. The nucleophilic center can easily be created under acidic conditions which abstract one proton of enol structure of the keto part of an intermediate. The anion formed which is stabilized by the delocalization over carbonyl groups can be used in the intramolecular cyclization step in which methanol is eliminated (Scheme 3).



Scheme 3

Table 1 Preparation of some substituted α-pyrone derivatives

Starting material 1	Reaction Time (h)	Product 3	Yield (%)
 a	2	 a	60
 b	3	 b	76
 c	2	 c	73
 d	3	 d	55
 e	4	 e	66
 f	4	 f	68

The cyclic 1,3-diketones (1,3-cyclohexanedione, 1,3-cyclopentanedione, 5,5-dimethyl-1,3-cyclohexanedione) gave under similar conditions the cyclic and noncyclic product mixtures in poor yields. For the synthesis of different enamino esters we used also other amines instead of *N*-methylaniline (pyrrolidine, piperidine, *N*-methylnapthylamine). The reaction of methyl 2-carbomethoxy-3-(*N*-methylnaphthylamino)acrylate with **1a** and **1b** gave **3a** and **3b** in poor yield under similar reaction conditions and we had difficulties by the purification of the products. The enamino esters of pyrrolidine and piperidine gave no reaction. The best results were obtained using *N*-methylaniline.

EXPERIMENTAL SECTION

All reagents were of commercial quality and reagent quality solvents were used without further purification. Ir spectra were determined on a Philips model PU9700. ^{1}H-Nmr were determined on a Bruker AC 80 MHz FT spectrometer and melting points were determined with a Buchi SMP-20 melting point apparatus and are uncorrected. Elemental analysis were performed at the Middle East Technical University analysis center.

General procedure for the acid catalyzed synthesis of α-pyrones from carbonyl compound and enamino ester : Enamino ester (**2**) (0.5 g, 2 mmol) was added to a mixture of carbonyl compound (2 mmol) and acetic acid (4 ml). The reaction mixture was then heated under reflux for 2-4 h. The volatile components were evaporated in vacuo, the residue was extracted with ether (3x30 ml). The combined extracts were washed with 1N HCl solution and brine. The organic layer was dried over $MgSO_4$ and evaporated under reduced pressure. The residue was purified by preparative tlc(n-hexane:ethyl acetate 2:1).

5-Benzoyl-3-carbomethoxy-6-phenyl-2*H*-pyran-2-one (**3a**): 0.40 g (60% yield) as a colorless oil. Ir(neat): 3100-2850, 1760, 1640, 1500, 1350, 1120, 900-675 cm^{-1}. ^{1}H-Nmr($CDCl_3$) δ ppm: 3.12(s, 3H, OCH_3),

6.81-7.43(m, 10H, Ar-H), 8.43(s, 1H, C-H). Anal. Calcd for $C_{20}H_{14}O_5$: C, 71.85, H, 4.22. Found: C, 71.45, H, 4.06.

3,5-Dicarbomethoxy-6-phenyl-2*H*-pyran-2-one (**3b**): 0.44 g (76% yield) as a colorless oil. Ir(neat): 3010-2850, 1760, 1745, 1440, 1360, 1210 cm^{-1}. ^{1}H-Nmr($CDCl_3$) δ ppm: 3.76 and 3.83(2s, 6H, 2 -OCH_3), 7.20-7.41(m, 5H, Ar-H), 8.48(s, 1H, C-H). Anal. Calcd for $C_{15}H_{12}O_6$: C, 62.44, H, 4.20. Found: C, 62.40, H, 4.25.

5-Acetyl-3-carbomethoxy-6-methyl-2*H*-pyran-2-one (**3c**): 0.31 g (73% yield) as a colorless oil. Ir(neat): 2985-2810, 1730, 1640, 1400, 1370, 1210 cm^{-1}. ^{1}H-Nmr($CDCl_3$) δ ppm: 1.94(s, 3H, $COCH_3$), 2.96(s, 3H, CH_3), 3.73(s, 3H, OCH_3), 8.41(s, 1H, C-H). Anal. Calcd for $C_{10}H_{10}O_5$: C, 57.13, H, 4.80. Found: C, 57.09, H, 4.86.

5-Carboethoxy-3-carbomethoxy-6-methyl-2*H*-pyran-2-one (**3d**): 0.26 g (65% yield) as a colorless oil. Ir(neat): 2975-2800, 1720, 1640, 1410, 1360 cm^{-1}. ^{1}H-Nmr($CDCl_3$) δ ppm: 1.42(t, J=7.0 Hz, 3H, CH_3), 3.44(s, 3H, CH_3), 3.70(s, 3H, OCH_3), 4.24(q, J=7.0 Hz, 2H, CH_2), 8.52(s, 1H, =C-H). Anal. Calcd for $C_{11}H_{12}O_6$: C, 55.00, H, 5.03. Found: C, 55.10, H, 5.40.

3-Carbomethoxy-5-cyano-6-ethoxy-2*H*-pyran-2-one (**3e**): 0.29 g(66% yield) as a colorless oil. Ir($CHCl_3$): 3060-2900, 2230, 1760, 1750, 1610, 1490, 1375, 1240 cm^{-1}. ^{1}H-Nmr($CDCl_3$) δ ppm: 1.40(t, J=7.1 Hz, 3H, CH_3), 3.80(s, 3H, OCH_3), 4.30(q, J=7.1 Hz, 2H, CH_2), 8.10(s, 1H, C-H). Anal. Calcd for $C_{10}H_9NO_5$: C, 53.81, H, 4.06, N, 6.28. Found: C, 54.02, H, 4.21, N, 6.10.

3,5-Dicarbomethoxy-6-methyl-2*H*-pyran-2-one (**3f**): 0.31 g(68% yield) as a colorless oil. Ir(neat): 3010-2820, 1760, 1740, 1410, 1350 cm^{-1}. ^{1}H-Nmr($CDCl_3$) δ ppm: 2.98(s, 3H, CH_3), 3.73 and 3.81(2s, 6H, 2 OCH_3), 8.58(s, 1H, C-H). Anal. Calcd for $C_{10}H_{10}O_6$: C, 53.09, H, 4.46. Found: C, 53.11, H, 4.40.

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