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AN EFFICIENT SYNTHESIS OF SUBSTITUTED 2H-PYRAN-2-ONE DERIVATIVES VIA THE CONJUGATED ADDITION OF THE ENOLATES OF CARBONYL COMPOUNDS TO ENAMINOESTERS[+]

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Abstract. Short simple synthesis of alkenoic acid esters and their intramolecular cyclization products, 2H-Pyran-2-ones from enolates of carbonyl compounds and enaminoesters are described.

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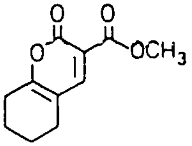
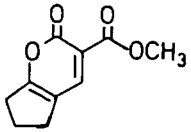
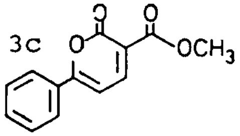
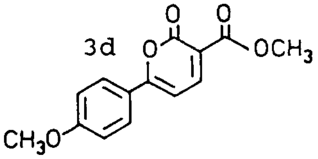
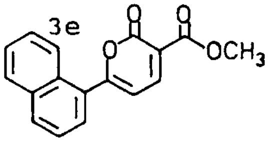
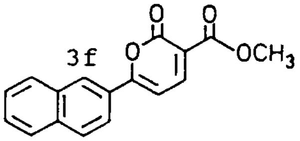
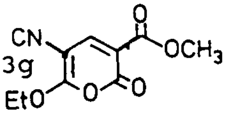
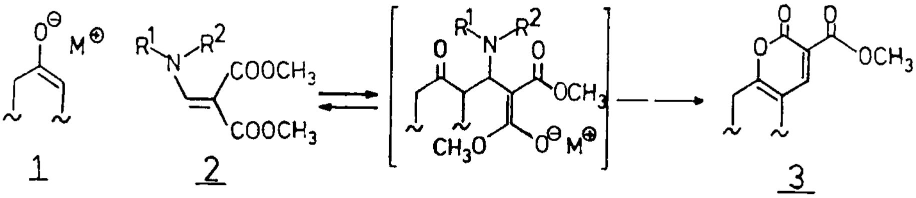
[+] Part of this work presented at GDCh Hauptversammlung, Bonn-Germany, in 1989.

Table 1 Preparation of substituted 2H-Pyran-2-ones.

Starting Materials	Yield(%)	Product
Cyclohexanone	67	3a 
Cyclopentanone	40	3b 
Acetophenone	70	3c 
p-Methoxy- acetophenone	60	3d 
1-Acetonaphthone	48	3e 
2-Acetonaphthone	50	3f 
Cyanoaceticacid ethylester	78	3g 



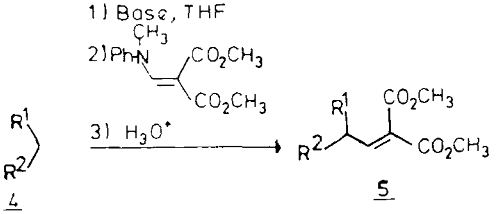
Scheme 1

Substituted α-pyrones are very important structural units of some biologically active compounds[1]. It is well known that there are various ways for the synthesis of substituted α-pyrones given in the literature[2-8].

In this communication, we report an efficient synthetic route for one pot synthesis of substituted 2H-pyran-2-ones.

Various metal enolates of α-methyl and methylene carbonyl compounds **1** react with methyl -2-carbomethoxy-3-(N-methylaniline) acrylate **2** to give directly the corresponding 2H-pyran-2-ones[9] **3** (summarized in table 1) in high yield via addition elimination (Ad_N-E)[10-12] followed by intramolecular cyclization (Scheme 1).

In addition to this, we tried conjugate addition reaction of metalated acetonitrile **4a**, malonodinitrile **4b** and dimethylmalonate **4c** with the same acceptor and got alkenoic acid esters **5** in good yield (Scheme 2).These products occur frequently as structural units of natural products, and they have functionalities suitable for a wide range of chemical manipulations.



4,5	R^1	R^2	Yield(%)
a	CN	CN	78
b	CN	H	70
c	CO_2CH_3	CO_2CH_3	75

Scheme 2

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, mass spectra were determined on a VG-TRIO-2 spectrometer. 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 preparation of α-pyrones

A solution of carbonyl compound (4mmol) in THF was added under argon at -78 °C and stirred (5h). and then at -20 °C for 1h .The mixture was cooled to -78 °C and the enaminoester 2 (4mmol) in THF was added. Stirring was continued at this temperature for 14h., after which the mixture was allowed to warm up to 0 ^{o}C within 8-12h. The mixture was then poured into a saturated aq. NH_4Cl solution and extracted 3 times with ether. After drying the organic layer (Na_2SO_4) and concentrating in vacuo, the crude product was purified by PTLC.

General procedure for the preparation of butenoicacid ester

Under argon atmosphere, NaH (2,5 mmol, washed with n-pentane) was suspended into dry THF. The α-methylene compound (2mmol) was added to this suspension. The resultant mixture was allowed to stir for 2h at RT. Then methyl-2-carbomethoxy-3-(N-methylanilin) acrylate (2mmol) disolved in THF was added to this mixture. It was stirred foran additional 4h at RT. Excess NaH was hydrolyzed. The reaction mixture was extracted with ether (3X20ml).The combined extracts were washed with saturated NH_4Cl solution and brine. Ether layer was dried over anhydrous $MgSO_4$, filtered off and evaporated under reduced pressure. Purification was done by PTLC (Hex : EtOAc).

3-Carbomethoxy-5,6,7,8-tetrahydrocoumarin (3a): IR ($CHCl_3$) : 1760, 1720, 1740 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ ppm: 1.8 (m, 4H, CH_2), 2.5 (t, 4H, CH_2), 3.9 (s, 3H, OCH_3), 6.9 (s, 1H, CH); MS (70 eV), m/e (relative intensity) 208 (M^+ 100) for $C_{11}H_{12}O_4$.

Anal. Calcd. for $C_{11}H_{12}O_4$: C, 63.45; H, 5.81

Found: C, 63.81; H, 5.89.

3-Carbomethoxy-6,7-dihydrocyclopenta[b]-2H-pyran-2-one (3b): IR (neat): 1760, 1738, 1670 cm^{-1}; ^1H-NMR ($CDCl_3$) δ ppm: 1.6 (m, 2H, CH_2), 2.25 (t, 4H, CH_2), 3.4 (s, 3H, OCH_3), 6.8 (s, 1H, CH); MS (70 eV), m/e (relative intensity) 194 (M^+ 80) for $C_{10}H_{10}O_4$.

Anal. Calcd. for $C_{10}H_{10}O_4$: C, 61.85; H, 5.19.

Found; C,62.01; H,5.51.

3-Carbomethoxy-6-phenyl-2H-pyran-2-one (3c): IR (neat): 1740, 1700 cm^{-1}; ^1H-NMR ($CDCl_3$) δ ppm: 3.4 (s, 3H, CH_3), 6.1 (d, 1H, CH), 7.1-8.0 (m, 5H, ArH), 8.2 (d, 1H, CH); MS (70 eV), m/e (relative intensity) 230 (M^+ 38) for $C_{13}H_{10}O_4$.

Anal. Calcd. for $C_{13}H_{10}O_4$: C,67.82; H,4.38.
Found: C,67.94; H, 4.79.

3-Carbomethoxy-6-(p-methoxyphenyl)-2H-pyran-2-one(3d): IR (neat): 1750, 1699 cm^{-1}; ^1H-NMR ($CDCl_3$) δ ppm: 3.6 (s, 3H, OCH_3), 3.8 (s, 3H, OCH_3), 6.6 (d, 1H, CH), 6.4-8.1 (m, 4H,ArH), 8.3 (d, 1H, CH); MS (70 eV), m/e (relative intensity) 260 (M^+ 85) for $C_{14}H_{12}O_5$.

Anal. Calcd. for $C_{14}H_{12}O_5$: C,64.61; H,4.65.
Found: C,64.92; H, 4.71.

3-Carbomethoxy-6-(α-naphthyl)-2H-pyran-2-one (3e):Ir (neat): 1760, 1690 cm^{-1}; ^1H-NMR ($CDCl_3$) δ ppm: 3.9 (s, 1H, CH_3), 6.6 (d, 1H, CH), 7.3-8.1 (m, 7H, ArH), 8.3 (d, 1H, CH); MS

(70 eV), m/e (relative intensity) 280 (M^+ 25) for $C_{17}H_{12}O_4$.

Anal. Calcd. for $C_{17}H_{12}O_4$: C, 72.85; H, 4.32. Found: C, 73.17; H, 4.66.

3-Carbomethoxy-6-(β-naphthyl)-2H-pyran-2-one (3f):IR (neat): 1760, 1740, 1710 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ ppm: 3.4 (s, 1H, CH_3), 6.3 (d, 1H, CH), 7.1-8.1 (m, 7H, ArH), 8.2 (d, 1H, CH); MS (70 eV), m/e (relative intensity) 280 (M^+ 40) for $C_{17}H_{12}O_4$.

Anal. Calcd. for $C_{17}H_{12}O_4$: C, 72.85; H, 4.32.

Found: C, 73.01; H, 4.49.

3-Carbomethoxy-5-cyano--6-ethoxy-2H-pyran-2-one (3g): IR ($CHCl_3$): 2230, 1760, 1750 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ ppm: 1.4 (t, 3H, CH_3), 3.8 (s, 3H, OCH_3), 4.3 (q, 2H, CH_2), 8.1 (s, 1H, CH); MS (70 eV), m/e (relative intensity) 223 (M^+ 100) for $C_{10}H_9NO_5$.

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

2-Carbomethoxy-4,4-dicyanocrotonicacid methylester (5a): IR ($CHCl_3$): 2350, 1730, 1700 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ ppm: 3.7 (s, 3H, OCH_3), 3.8 (s, 3H, OCH_3), 4.0 (d, 1H, CH), 8.5 (d, 1H, CH); MS (70 eV), m/e (relative intensity) 208 (M^+ 41) for $C_9H_8N_2O_4$.

Anal. Calcd. for $C_9H_8N_2O_4$: C, 51.92; H, 3.87; N, 13.46.

Found: C,52.15; H,3.91; N, 13.81.

2-Carbomethoxy-4-cyanocrotonicacid methylester(5b): IR (neat): 2260, 1700 cm^{-1}; ^1H-NMR ($CDCl_3$) δ ppm: 3.4 (d, 2H, CH_2), 3.7 (s, 3H, OCH_3), 3.8 (s, 3H, OCH_3), 8.0 (t, 1H, CH); MS (70 eV), m/e (relative intensity) 183 (M^+ 75) for $C_8H_9NO_4$.

Anal. Calcd. for $C_8H_9NO_4$: C, 52.46; H, 4.95; N, 7.65.

Found: C, 52.82; H,5.21; N, 8.12.

2,4-Dicarbomethoxyglutaconicacid dimethylester(5c): IR ($CHCl_3$): 1750, 1730 cm^{-1};^1H-NMR ($CDCl_3$) δ ppm: 3.4 (d, 1H, CH), 3.7 (s, 6H, OCH_3), 3.8 (s, 6H, OCH_3), 8.2 (d, 1H, CH); MS (70 eV) m/e (relative intensity) 274 (M^+ 55) for $C_{11}H_{14}O_8$.

Anal. Calcd. for $C_{11}H_{14}O_8$: C, 48.18; H,5.15.

Found: C, 47.94; H, 5.37.

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