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THE SYNTHESIS OF 2-(2-FURYL) 1,3-DICARBONYL COMPOUNDS†

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Abstract—2-furyl derivatives are easily synthesised by intermolecular condensation of 2,5-dihydro-2,5-dimethoxy furan (DHDMF) with active methylene compounds by a simple and cheap procedure. The reaction applies only to 1,3-dicarbonyl compounds and a general mechanism is proposed.

In our laboratory we have been studying the reactivity of furan derivatives under various conditions; the experimental results confirm that these compounds represent versatile and useful intermediates in synthetic organic chemistry and several applications have been reported.[1]

In this paper we wish to report a new furan synthesis, performed through intermolecular condensation of 2,5-dihydro-2,5-dimethoxy furan (DHDMF) with 1,3-dicarbonyl compounds.

It is known that furans can be prepared by reaction of β-keto esters both with α-hydroxy or α-halo-carbonyl compounds[2] and α-chlorinated acid chlorides,[3] but these methods often suffer from the disadvantage that mixture of furans may result.

In other recent syntheses β-keto esters and other enols are reported to react with allenic sulfonium salts[4] or geminal bromo nitro-olefins[5] to give 2,3,4-trisubstituted furans. These procedures require the use of unreadily available key-intermediates and appear unadequately developed.

DHDMF, the stable precursor of the labile malealdehyde, and its 2-Me derivative have been widely used for syntheses consisting of intermolecular or intramolecular condensations, leading to pyridazines, tropinones, pyridinols, and benzenoid compounds[6]; our novel use of **1** as starting materials in the preparation of furan derivatives reveals other synthetic potentialities of these versatile intermediates. In fact, by reaction of **1** with active methylene compounds of type **2**, at pH = 3–4 for aqueous acetic acid and in presence of $ZnCl_2$ as catalyst, at room temperature for 24 hr, we obtained the products **3** in high yields (Table 1).

All new compounds showed spectral data (IR, ^{1}H-NMR and MS) completely in agreement with the proposed structures. On the ground of ^{1}H-NMR data, compounds **3a**, **3b**, and **3c** showed to be completely in enolic form (enolic protons respectively at 17.95, 13.40, and 13.45δ).

It is interesting to note that this furan synthesis was successful also by reaction of **1** with diethyl oxalpropionate, but the resulting products proved to have lost the oxalyl residue, yielding directly 2-(2-furyl)-propionate **4**.*

Zinc chloride and the starting materials **1** were used in 1.5:1 molar ratio, while 1,3-dicarbonyl compounds acted also as reaction solvents.

The procedure showed to have full applicability with particularly active methylene compounds of type **2**, while it was partially successful with diethyl malonate or failed completely both with linear 1,2-diketones and isolated ketones. This could be attributed to the lower acidic character of the latter (pKa $\geq$ 13.5) than the former (pKa $\simeq$ 9–11).

The reaction mechanism could be explained by the initial formation of a *cis*-unsaturated-1,4-dicarbonyl compound, rapidly obtained by acid hydrolysis of **1**; the electrophilic attack of the formyl group, likely activated by protonation, upon the enolic form **5** of **2**, furnished the intermediate **6**[8] (Scheme 1); the ring closure of the unstable intermediate **6** to furan derivative **3** involved the protonation of the secondary alcoholic function and subsequently the nucleophilic participation of the CO group.

In conclusion, besides allowing the rapid synthesis of 2-furan derivatives, the described method is

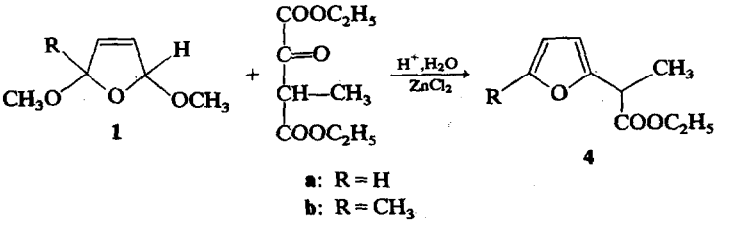
† Dedicated to Professor L. Panizzi in occasion of his 70th birthday.

* This easy loss of an oxalyl residue has been already observed and a probable mechanism involving the zinc ion catalysis, was proposed.[7]

Table 1

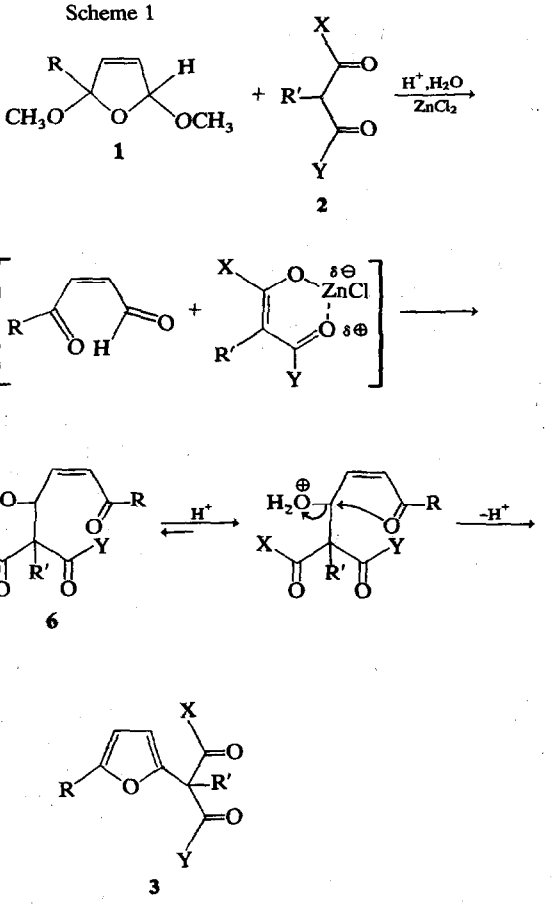
entry	R	R'	X	Y	yields %[a]
3*a*	H	H	CH_3	CH_3	78
3*b*	H	H	CH_3	OC_2H_5	80
3*c*	CH_3	H	CH_3	OC_2H_5	85
3*d*	CH_3	H	OC_2H_5	OC_2H_5	50
3*e*	H	$CH_2—CH_2—CH_3$	CH_3	OC_2H_5	86
3*f*	CH_3	H	ϕ	OC_2H_5	85

[a] All yields refer to isolated, chromatographically pure products and are based upon DHDMF or its 2-Me derivative.



a: R = H
b: R = CH_3

Scheme 1



simple to carry out, proceeds in high yields and utilizes readily available starting materials.

We are now studying the synthetic utility of these compounds.

EXPERIMENTAL

^{1}H-NMR spectra were taken with a Perkin Elmer R-32 spectrometer using CCl_4 soln with TMS as an internal standard. IR spectra were taken with a Perkin Elmer 257 Infracord spectrometer. Mass spectra were obtained with an AEI MS-12 spectrometer at 70 eV, by using direct insertion at source temp. of 150°C. Commercial Merck silica gel and Woelm alumina were used for column chromatography. Carlo Erba precoated silica gel plates were used in tlc. The chromatograms were detected by spraying with 5 N H_2SO_4 and heating at 110 for 10 min. 1,3-dicarbonyl compounds, all commercially available, were utilized directly without purification.

Typical general procedure. 7.5 mmoles of $ZnCl_2$ were rapidly added, with magnetic stirring at room temp to a soln of 5 mmoles of DHDMF (or its 2-Me derivative),

4.5 ml of 1,3-dicarbonyl compound, 0.5 ml of H_2O and 1–1.5 ml of AcOH. After 24 hr, the mixture was poured into water, and extracted many times with Et_2O. The combined organic layers, washed many times with satd $NaHCO_3$ aq and then with water until neutrality, were dried over Na_2SO_4. After the removal of solvent *in vacuo*, the crude product was chromatographed on SiO_2. The elution with hexane-Et_2O 9:1 gave pure **3a–f**, as oils.

For **4a** and **4b**, the procedure was slightly modified: The combined organic layers were washed many times with 5% Na_2CO_3 aq, then with water until neutrality and dried over Na_2SO_4. After the removal of solvent *in vacuo*, the crude product was chromatographed on neutral Al_2O_3 B III. The elution with hexane-Et_2O 9:1 gave pure **4a–b**, as oils.

3-(2-*Furyl*) 2,4-*pentandione* **3a**. Elemental analysis: Found: C, 65.10; H, 6.05. Calc for $C_9H_{10}O_3$: C, 65.05; H, 6.07%. ^{1}H-NMR (C_6D_6, δ): 17.95 (s, 1H), 7.19 (m, 1H), 6.15 (m, 1H), 5.86 (m, 1H), 1.75 (s, 6H). IR (neat, ν_{max} cm^{-1}): 3145, 3115, 3015, 2960, 2925, 1618 (strong), 1582, 1505, 1205, 985, 920, 892, 818, 742. MS, *m/e*: 166 (M^+) in agreement with the proposed formula.

Ethyl 2-(2-*furyl*) *acetoacetate* **3b**. Elemental analysis: Found: C, 61.25; H, 6.22. Calc for $C_{10}H_{12}O_4$: C, 61.22; H, 6.16%. ^{1}H-NMR (CCl_4, δ): 13.40 (s, 1H), 7.20 (m, 1H), 6.20 (m, 1H), 6.00 (m, 1H), 4.13 (q, 2H, J = 7 Hz), 1.90 (s, 3H), 1.22 (t, 3H, J = 7 Hz). IR (neat, ν_{max} cm^{-1}): 3125, 2990, 2940, 1725 (strong), 1652 (strong), 1625, 1595, 1510, 1272, 1238, 970, 901, 870, 745. MS, *m/e*: 196 (M^+) in agreement with the proposed formula.

Ethyl 2-(2-*furyl*-5-*methyl*) *acetoacetate* **3c**. Elemental analysis: Found: C, 62.95; H, 6.75. Calc for $C_{11}H_{14}O_4$: C, 62.85; H, 6.71%. ^{1}H-NMR (CCl_4, δ): 13.45 (s, 1H), 5.96 (d, 1H, J = 3 Hz), 5.88 (m, 1H), 4.19 (q, 2H, J = 7 Hz), 2.27 (s, 3H), 1.93 (s, 3H), 1.25 (t, 3H, J = 7 Hz). IR (neat, ν_{max} cm^{-1}): 3120, 2990, 2930, 1725 (strong), 1652 (strong), 1610 (strong), 1570, 1275, 1240, 975, 960, 915, 870, 790. MS, *m/e*: 210 (M^+) in agreement with the proposed formula.

Diethyl 2-(2-*furyl*-5-*methyl*) *malonate* **3d**. Elemental analysis: Found: C, 60.05; H, 6.82. Calc for $C_{12}H_{16}O_5$: C, 59.99; H, 6.71%. ^{1}H-NMR (CCl_4, δ): 6.21 (d, 1H, J = 3 Hz), 5.88 (m, 1H), 4.53 (s, 1H), 4.18 (q, 4H, J = 7 Hz), 2.25 (s, 3H), 1.26 (t, 6H, J = 7 Hz). IR (neat, ν_{max} cm^{-1}): 3120, 2995, 2950, 1745 (strong), 1570, 1230, 960, 930, 870, 795, 750. MS, *m/e*: 240 (M^+) in agreement with the proposed formula.

Ethyl 2-*n*-*propyl*-2′-(2-*furyl*) *acetoacetate* **3e**. Elemental analysis: Found: C, 65.92; H, 7.83. Calc for $C_{13}H_{18}O_4$: C, 65.53; H, 7.61%. ^{1}H-NMR (CCl_4, δ): 7.33 (m, 1H), 6.62 (m, 1H), 6.34 (m, 1H), 4.15 (q, 2H, J = 7 Hz), 2.02 (s, 3H), 1.9–1.6 (broad m, 2H), 1.25 (t, 3H, J = 7 Hz), 1.20–1.00 (broad m, 2H), 0.95 (m, 3H). IR (neat, ν_{max} cm^{-1}): 2970, 2880, 1740–1720 (broad, strong), 1510, 1230, 920, 860, 750. MS, *m/e*: 238 (M^+) in agreement with the proposed formula.

Ethyl 2-(2-*furyl*-5-*methyl*) *benzoylacetate* **3f**. Elemental analysis: Found: C, 70.75; H, 6.24. Calc for $C_{16}H_{16}O_4$: C, 70.58; H, 5.92%. This compound shows as a 1:1 mixture of the enolic and ketonic forms; ^{1}H-NMR (CCl_4, δ): 14.04 (s, $\frac{1}{2}$H), 7.95 (m, 1H), 7.40–7.23 (m, 4H), 6.20 (d, $\frac{1}{2}$H, J = 3 Hz), 5.92–5.82 (broad s, $\frac{1}{2}$H), 5.49 (s, $\frac{1}{2}$H), 4.38–4.05 (m, 2H), 2.20 and 2.22 (two s, 3H), 1.37–1.13 (m, 3H). IR (neat, ν_{max} cm^{-1}): 3090, 2995, 2940, 1745 (strong), 1692 (strong), 1648 (strong), 1600, 1590, 1560, 1500, 1275, 1240, 940, 900, 792, 780, 698. MS, *m/e*: 272 (M^+) in agreement with the proposed formula.

Ethyl 2-(2-*furyl*) *propionate* **4a**. Yield: 70% (based on DHDMF). Elemental analysis: Found: C, 64.35; H, 7.16. Calc for $C_9H_{12}O_3$: C, 64.27; H, 7.19%. ^{1}H-NMR (CCl_4, δ): 7.25 (m, 1H), 6.23 (m, 1H), 6.10 (m, 1H), 4.13 (q, 2H, J = 7 Hz), 3.72 (q, 1H, J = 7.5 Hz), 1.47 (d, 3H, J = 7.5 Hz), 1.25 (t, 3H, J = 7 Hz). IR (neat, ν_{max} cm^{-1}): 3125, 2995, 2950, 1745 (strong), 1600, 1510, 1260, 1230, 935, 895, 870, 820, 800, 745. MS, *m/e*: 168 (M^+) in agreement with the proposed formula.

Ethyl 2-(2-*furyl*-5-*methyl*) *propionate* **4b**. Yield: 60% (based on 2,5-dimethoxy-2-methyl-2,5-dihydrofuran). Elemental analysis: Found: C, 65.95; H, 7.80. Calc for $C_{10}H_{14}O_3$: C, 65.92; H, 7.74%. ^{1}H-NMR (CCl_4, δ): 5.93 (d, 1H, J = 3 Hz), 5.80 (m, 1H), 4.12 (q, 2H, J = 7 Hz), 3.74 (q, 1H, J = 7.5 Hz), 2.22 (s, 3H), 1.42 (d, 3H, J = 7.5 Hz), 1.22 (t, 3H, J = 7 Hz). MS, *m/e*: 182 (M^+) in agreement with the proposed formula. IR (neat, ν_{max} cm^{-1}): 3120, 2995, 2950, 1745 (strong), 1570, 1255, 1225, 950, 870, 790.

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