Facile Synthesis of 5-(α-Alkyl-substituted) Furans

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2-Halo, 2-hydroxy- or 2-alkoxyalkyl substituted furans are easily synthesized under acidic conditions by intramolecular cyclization of α,β-unsaturated 1,4-diketones by a simple and cheap procedure. Some aspects of the mechanism are discussed.

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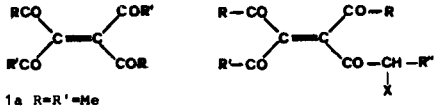
Our interest in the chemistry of activated ethylenic systems prompted us to examine the chemistry of α,β-unsaturated 1,4-dicarbonylic compounds of type **1**, where X and Y were electron-withdrawing groups:

Scheme 1



1a R=R'=Me
1b R=Me,R'=OEt
1c R=Et,R'=OEt

1d

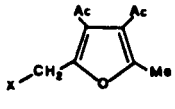
Our preceding research has shown that compounds **1a-c** are a versatile source for several different homocyclic and heterocyclic systems [1-3]. Thus, under basic conditions they can be used as starting material to obtain functionalized cyclopentane derivatives [4].

In the present study we wish to report the behavior of compounds **1a-c** under acidic conditions which gave rise to 2-halo-, 2-hydroxy- or 2-alkoxyalkyl substituted furans **2**.

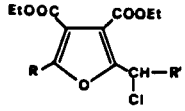
Compounds **2** can represent very useful starting material for preparing functionalized cyclopentenones [5] and also can be converted into monosubstituted α,β-unsaturated 1,4-diketones of type **1d** by oxidation with $^1O_2$ [6]. Moreover they may be of interest as starting products for perfume compositions [7-9].

2-Haloalkylfurans **2a,b,f,g** were prepared directly from diketones **1a-c** on treatment with concentrated hydrochloric or hydrobromic acid in water at room temperature [1].

Scheme 2



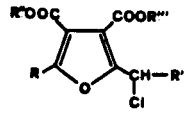
2a X=Cl
2b X=Br
2c X=OH
2d X=OEt
2e X=OMe



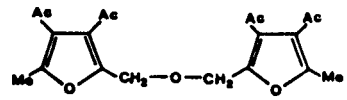
2f R=Me,R'=H,X=Cl
2g R=Et,R'=Me,X=Cl
2h R=Et,R'=Me,X=OH

In the case of **1b** and **1c** we isolated also the hydrolyzed furans **2h**, **3a-c**, possibly because of longer standing in acidic solution (*ca.* 12 hours *vs.* 1 hour for compound **1a**) as a consequence of a slower reaction rate.

Scheme 3



3a R=Me,R'=H,R"=Et,R'''=H,X=Cl
or R=Me,R'=H,R"=H,R'''=Et,X=Cl
3b R=Me,R'=H,R"=Et,R'''=H,X=OH
or R=Me,R'=H,R"=H,R'''=Et,X=OH
3c R=Et,R'=Me,R"=Et,R'''=H,X=OH
or R=Et,R'=Me,R"=H,R'''=Et,X=OH

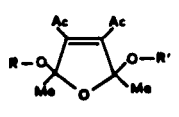


4

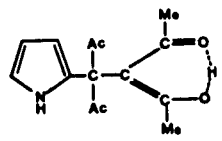
With an aqueous solution of sulfuric acid, which is a strong acid but a poor nucleophile, compound **1a** gave the furan **2c** as main product and the difuryl ether **4** in traces. If the reaction was carried out in ethanolic or methanolic solution at reflux temperature with a trace of sulfuric or hydrochloric acid, we isolated the ethers **2d** and **2e** respectively in good yield.

Formation of these products involves an intermediate of type **5**.

Scheme 4



5a R=R'=H
5b R=R'=Me
5c R=H,R'=N=CH-Ar



6

Actually, in aqueous or alcoholic solution compound **1a** slowly converted into the corresponding dihydrofuran form of type **5** as can be revealed from nmr spectra. By evaporation of a methanolic solution of **1a** containing traces of mineral acid the *cis* and *trans* isomers of **5b** (1:1)

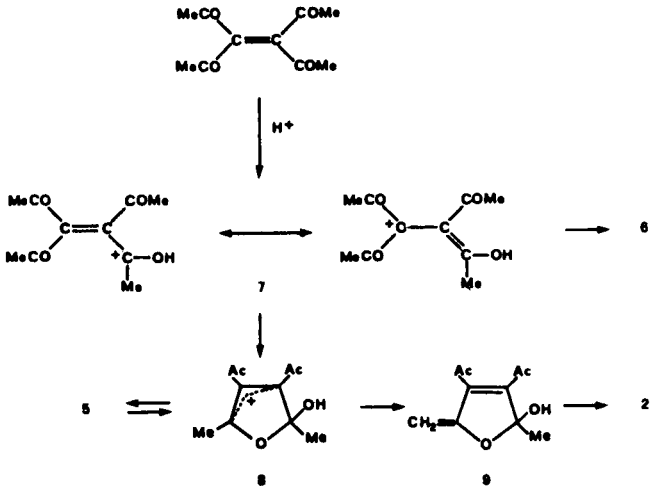
were isolated. On the other hand the dihydrofuran **5b** can be converted quantitatively into 2-methoxymethyl-3,4-diacetyl-5-methylfuran **2e** simply by heating the acidic methanol solution for several hours.

The furan system **5** resulted when a nucleophile and a small amount of acid are present, thus, the dihydrofurans **5c** were obtained on heating a benzene solution of **1a** with an aromatic oxime.

If the acidity was not enough the nucleophile added on the carbon-carbon double bond to give the addition compound **6** as in the case of **1a** and pyrrole.

All the results can be rationalized *via* a multi-step mechanism as follows:

Scheme 5



The mechanism involves an initial protonation to give the carbonium ion **7** which may combine with a nucleophilic reagent to yield compound **6**. However **7** may evolve to the carbonium ion **8** which reacts with a nucleophile or loses a proton to give the unsaturated system **9**. At its turn, compound **9**, when is attacked on the exocyclic methylene group by a nucleophile, may lose the OR group to give the aromatic furans **2**.

All new compounds showed analytical and spectroscopic data (ir, uv and nmr) completely in agreement with the proposed structures.

In conclusion, the described method allows the rapid and direct synthesis of 2-halo-, 2-hydroxy- or 2-alkoxy-alkyl-furans **2** through the dihydrofurans **5**, which were isolated.

EXPERIMENTAL

The ir spectra were recorded on a Perkin-Elmer 283 spectrometer using samples in potassium bromide pellets or as a film. The ^{1}H-nmr spectra were recorded for deuteriochloroform solutions with a Perkin-Elmer R-600 instrument, chemical shifts (J in Hz) are reported in ppm downfield from internal tetramethylsilane. The uv spectra were measured for solutions in methanol with a Cary 14 spectrophotometer. Silica gel plates (Merck F_{254}) and silica gel 60 (Merck 70-230 mesh) were used for analytical and preparative tlc and for column chromatography, respectively. Extracts were dried over sodium sulphate and solvents were evaporated *in vacuo*. Petroleum ether refers to the fraction of bp 30-50°.

Reaction of Alkenes **1b** and **1c** with Hydrochloric Acid.

A solution of alkene **1b** (or **1c**) [10] (1 mmole) in concentrated hydrochloric acid (2 ml) was stirred at room temperature for 12 hours. The solution was diluted with water and was extracted with ether. The extracts were evaporated to give an oil, which was purified by column chromatography, using petroleum ether containing an increasing amount of ether as eluent.

In the case of the alkene **1b** a nmr analysis showed the presence of three products in a ratio 56:26:18 (**2f:3a:3b**). Elution with a 90:10 mixture gave 2-chloromethyl-3,4-dicarbethoxy-5-methylfuran **2f** as oil (40%); ir: 1720 cm^{-1} (CO); nmr: δ 1.33 (t, 3, Me), 1.34 (t, 3, Me), 2.50 (s, 3, Me), 4.30 (q, 2, CH_2), 4.33 (q, 2, CH_2), 4.73 (s, 2, CH_2Cl).

Anal. Calcd. for $C_{12}H_{15}ClO_5$: C, 52.46; H, 5.46; Cl, 12.93. Found: C, 52.80; H, 5.59; Cl, 12.45.

Elution with a 20:80 mixture gave the furan **3b** (10%), as white needles, mp 70-72° (crystallized from ether); ir: 3450 (OH), 3000-2000 (OH), 1720 (CO), 1640 cm^{-1} (CO); nmr: δ 1.43 (t, 4, Me + OH), 2.60 (s, 3, Me), 4.48 (q, 2, CH_2), 4.75 (s, 2, CH_2), 8.3 (br s, 1, OH).

Anal. Calcd. for $C_{10}H_{12}O_5$: C, 52.63; H, 5.30. Found: C, 52.92; H, 5.55.

Elution with ether gave the furan **3a** as oil (21%); ir: 3500-2800, 2800-2300 (OH), 1730 (CO), 1640 cm^{-1} (CO); nmr: δ 1.45 (t, 3, Me), 2.65 (s, 3, Me), 4.48 (q, 2, CH_2), 5.04 (s, 2, CH_2Cl).

Anal. Calcd. for $C_{10}H_{11}ClO_5$: C, 48.70; H, 4.50. Found: C, 48.35; H, 4.33.

In the case of the alkene **1c**, elution with a 90:10 mixture gave the furan **2g** as oil (45%); ir: 1720 cm^{-1} (CO); nmr: δ 0.95 (t, 3, Me), 1.25 (m, 6, 2 × Me), 1.76 (d, 3, Me, J = 7), 2.81 (q, 2, CH_2), 4.21 (q, 2, CH_2), 4.24 (q, 2, CH_2), 5.39 (q, 1, CH, J = 7).

Anal. Calcd. for $C_{14}H_{19}ClO_5$: C, 55.54; H, 6.28; Cl, 11.73. Found: C, 55.90; H, 6.50; Cl, 12.15.

Elution with a 70:30 mixture gave the furan **2h**, as oil (33%); ir: 3450 (OH), 1725 cm^{-1} (CO); nmr: δ 1.33 (m, 9, 3 × Me), 1.55 (d, 3, Me, J = 6.6), 2.86 (q, 2, CH_2), 3.69 (br, 1, OH), 4.30 (q, 2, CH_2), 4.32 (q, 2, CH_2), 4.98 (q, 1, CH, J = 6.6).

Anal. Calcd. for $C_{14}H_{20}O_6$: C, 59.15; H, 7.04. Found: C, 59.37; H, 6.96.

Elution with a 40:60 mixture gave the furan **3c** (5%), mp 39-42° (crystallized from ether); ir: 3450 (OH), 2700-2200 (OH), 1730 (CO), 1640 cm^{-1} (CO); nmr: δ 1.26 (m, 6, 2 × Me), 1.58 (d, 3, Me, J = 6.6), 3.15 (q, 2, CH_2), 4.49 (q, 3, CH_2 + OH), 5.36 (q, 1, CH, J = 6.6).

Anal. Calcd. for $C_{12}H_{16}O_6$: C, 56.25; H, 6.25. Found: C, 56.05; H, 6.17.

2-Hydroxymethyl-3,4-diacetyl-5-methylfuran (**2c**).

A solution of compound **2a** (0.2 g) in water containing one drop of concentrated sulfuric acid was stirred at room temperature for 2 hours. The solution was evaporated in a dessiccator to yield a residue which was resolved into two components by preparative layer chromatography with ether-petroleum ether (3:1) as developer.

The first band afforded the furan **2c** (0.13 g, 65%), mp 68-69° (crystallized from petroleum ether) (lit [1] mp 68-69°); uv: 267 (3.76); ir: 3400 (OH), 1685 (CO), 1660 cm^{-1} (CO); nmr: δ 2.40 (s, 3, Me), 2.44 (s, 3, Me), 2.52 (s, 3, Me), 3.1 (br, 1, OH), 4.53 (s, 2, CH_2).

The second band afforded bis furyl ether **4** (0.02 g, 5%), mp 105-107° (crystallized from cyclohexane); uv: 268 (4.05); ir: 1665 cm^{-1} (CO); nmr: δ 2.40 (s, 12, 4 × Me), 2.48 (s, 6, 2 × Me), 4.54 (s, 4, 2 × CH_2).

Anal. Calcd. for $C_{20}H_{22}O_7$: C, 64.17; H, 5.88. Found: C, 64.57; H, 5.87.

2-Ethoxymethyl-3,4-diacetyl-5-methylfuran (**2d**).

To a solution of compound **1a** (0.3 g) in ethanol (15 ml) was added one drop of sulfuric acid. The solution was refluxed for 5 hours and then evaporated to give an oil which was resolved into two components by column chromatography, using ether-petroleum ether (3:1) as eluent.

The first fractions contained the furan **2d** (0.25 g, 73%), mp 40-42° (after sublimation at 30°/0.05 mm) (lit [1] mp 40-42°); uv: 266 (3.75); ir: 1685 (CO), 1650 (CO), 1100 cm^{-1} (C-O-C); nmr: δ 1.13 (t, 3, Me), 2.27 (s, 3, Me), 2.33 (s, 3, Me), 2.37 (s, 3, Me), 3.45 (q, 2, CH_2), 4.40 (s, 2, CH_2).

Continued elution with the same solvent combination yielded compound **4** (0.03 g, 5%), identical (mp, ir and nmr spectra) with material prepared as above.

Synthesis of bis[2-(3,4-Diacetyl-5-methyl)furyl]methyl Ether (**4**).

A mixture of the furan **2c** (0.4 g) and 80% sodium hydride (0.05 g) in anhydrous toluene (20 ml) was stirred for two hours. The furan **2b** (0.53 g) was added and the mixture was refluxed for ten hours. The cooled mixture was filtered, was washed with water and was evaporated to give a residue, which showed (tlc) several spots. A preparative layer chromatography with ether-petroleum ether (3:1) as developer afforded the furan **4** (0.15 g, 19%) identical (mp, ir and nmr spectra) with material prepared as above.

2-Methoxymethyl-3,4-diacetyl-5-methylfuran (**2e**).

a) To a solution of compound **1a** (0.3 g) in methanol (15 ml) was added one drop of concentrated hydrochloric acid. The solution was refluxed for five hours and then was evaporated to give an oil, which was diluted with ether and filtered through silica gel. The filtrate was evaporated to give the furan **2e** as oil (quantitative yield); ir: 1670 cm^{-1} (CO); nmr: δ 2.38 (s, 3, Me), 2.41 (s, 3, Me), 2.48 (s, 3, Me), 3.34 (s, 3, OMe), 4.40 (s, 2, CH_2).

Anal. Calcd. for $C_{11}H_{14}O_4$: C, 62.86; H, 6.67. Found: C, 62.83; H, 6.59.

b) A solution of the dihydrofuran **5b** was refluxed in methanol containing a trace of concentrated hydrochloric acid for five hours. Evaporation of the solution gave the furan **2e** (quantitative yield) identical (nmr spectrum) with material obtained by method (a).

2,5-Dimethoxy-2,5-dimethyl-3,4-diacetylfuran (**5b**) (*cis* and *trans*).

A solution of **1a** (0.5 g) in methanol containing one drop of concentrated hydrochloric acid was stirred for ten minutes. Evaporation of the solution yielded an oil, which was diluted with ether and was filtered through silica gel. The filtrate was evaporated to give the dihydrofuran **5b** (quantitative yield) as oil (mixture of the *cis* and *trans* isomers); ir: 1700 (CO), 1690 (CO), 1640 cm^{-1} (C=C); nmr: δ 1.60 (s, 3, Me), 1.68 (s, 3, Me), 2.35 (s, 6, 2 × Me), 3.28 (s, 3, OMe), 3.37 (s, 3, OMe).

Anal. Calcd. for $C_{12}H_{18}O_5$: C, 59.50; H, 7.43. Found; C, 59.69; H, 7.42.

Reaction of Compound **1a** with Oximes.

A solution of compound **1a** (1 mmole) and 2,6-dichlorobenzaldoxime (or 4-nitrobenzaldoxime) (1 mmole) in benzene (17 ml) was refluxed for 12 hours. Evaporation of the solution gave a residue which was recrystallized to give the furan **5c**.

The furan **5c** [R' = N=CH-$C_6H_3Cl_2$ (2,6)] was recrystallized from cyclohexane, mp 124-127° (60%); ir: 3440 (OH), 1700 (CO), 1690 (CO), 1640 cm^{-1} (C=C); nmr: δ 1.66 (s, 3, Me), 1.76 (s, 3, Me), 2.31 (s, 3, Me), 2.42 (s, 3, Me), 4.83 (br, 1, OH), 7.36 (m, 3, C_6H_3), 8.53 (s, 1, CH).

Anal. Calcd. for $C_{17}H_{17}Cl_2NO_5$: C, 52.85; H, 4.40; Cl, 18.39; N, 3.63. Found: C, 53.09; H, 4.53; Cl, 17.95; N, 3.51.

The furan **5c** [R' = N=CH-C_6H_4-NO_2 (4)] was recrystallized from benzene, mp 141-143° (65%); ir: 3460 (OH), 1700 (CO), 1680 (CO), 1650 cm^{-1} (C=C); nmr: δ 1.68 (s, 3, Me), 1.77 (s, 3, Me), 2.28 (s, 3, Me), 2.49 (s, 3, Me), 4.75 (br, 1, OH), 7.98 (AA'BB', 4, C_6H_4), 8.33 (s, 1, CH).

Anal. Calcd. for $C_{17}H_{18}N_2O_7$: C, 56.35; H, 4.97; N, 7.73. Found: C, 56.24; H, 5.09; N, 7.61.

2-(3,4-Diacetyl-2,5-dioxoesan-3-yl)pyrrole (**6**).

A mixture of **1a** (0.3 g) and pyrrole (0.118 ml) in benzene (20 ml) was refluxed for four hours. Evaporation of the solution gave a residue which was purified by column chromatography. Elution with ether-petroleum ether (1:2) gave compound **6** (0.2 g, 50%), mp 84-86° (recrystallized from petroleum ether); ir: 3365 (NH), 3500-2200 (OH), 1750 (CO), 1600 cm^{-1} ($C-O^-$); nmr: δ 1.97 (s, 6, 2 × Me), 2.06 (s, 3, Me), 2.29 (s, 3, Me), 4.19 (br, 1, NH), 6.28 (m, 2, 2 × CH), 6.81 (m, 1, CH), 16.64 (s, 1, OH).

Anal. Calcd. for $C_{14}H_{17}NO_4$: C, 63.87; H, 6.51; N, 5.32. Found: C, 63.83; H, 6.88; N, 5.01.

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