Preparation of 2,4,5-Trisubstituted Furans

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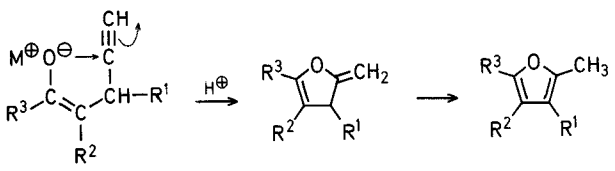
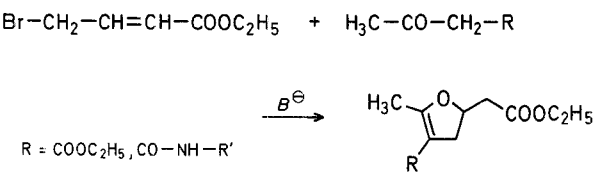
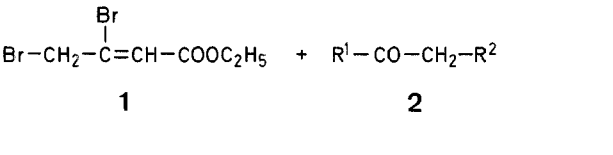
There have been several reports[1-5] on the preparation of furan derivatives via the intramolecular cyclisation of β,γ-unsaturated enolates. The reaction proceeds through a nucleophilic attack at the unsaturated bond by the oxygen of the enolate ion.



This reaction should be facilitated by a decrease of the electron density at the unsaturated bond, e.g. by the presence of groups which are able to stabilise the negative charge. Thus, Kato et al.[5] have recently reported the preparation of 2,3-dihydrofurans from the reactions of ethyl acetoacetate or acetoacetamides with ethyl 4-bromo-2-butenoate (ethyl γ-bromocrotonate).

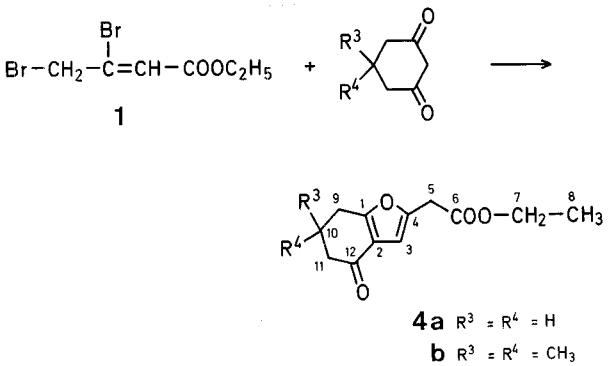


We now report a simple preparation of 2,4,5-trisubstituted furans **3** by the reaction of active methylene compounds **2** with ethyl 3,4-dibromo-2-butenoate (**1**).



2,3	R^1	R^2
a	H_3C	$COOC_2H_5$
b	H_3C	$CO-CH_3$
c	H_3C	$CO-NH-C_6H_5$
d	H_3C	$CO-N(C_2H_5)_2$
e	C_6H_5	SO_2-CH_3

The analogous reaction of cyclic β-diketones, i.e. cyclohexane-1,3-dione and 5,5-dimethylcyclohexane-1,3-dione, afford the condensed furans **4a** and **4b**.



The above reactions are performed either in ethanol in the presence of sodium ethoxide (Method A) or in dimethylformamide in the presence of potassium carbonate (Method B). The reaction of **1** with ethyl acetoacetate was also performed in 50% aqueous sodium hydroxide in the presence of a catalytic amount of benzyltriethylammonium chloride (yield: 57%). The furans **3** and **4** were identified by microanalysis, ^1H and ^{13}C-N.M.R. spectroscopy (see Table).

In addition to the expected product **3c** (yield: 36%), the reaction of **1** with *N*-phenylacetoacetamide (**2c**) results in the formation of the 2-pyrrolidone derivatives **5a** and **5b**. The reaction of **1** with *N,N*-diethylacetoacetamide (**2d**) gives rise to the expected product **3d** in poor (10%) yield; the major product (50%) is the furan isomer **6**, resulting from substitution of the vinylic hydrogen atom. Further,

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Table. Furans **3**, **4**, **6**, and **7** and Pyrrolidones **5a** and **5b** Prepared

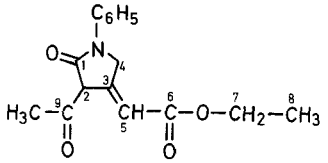
Product	Yield [%] A	B	b.p./torr or m.p.	Molecular formula[a]	^{1}H-N.M.R. ($CDCl_3$/TMS)[b] δ [ppm]	^{13}C-N.M.R. ($CDCl_3$/TMS)[c] δ [ppm]
3a	70	60	132–133 °C/0.4	$C_{12}H_{16}O_3$ (240.3)	6.4 (s, 1H); 4.19 (q, 4H, J = 7 Hz); 3.55 (s, 2H); 2.52 (s, 3H); 1.25 (t, 6H, J = 7 Hz)	168.9 (C-6); 158.5 (C-4); 145.9 (C-1); 114.4 (C-2); 108.89 (C-3); 61.2 (C-7); 59.9 (C-5); 14.16 (C-8); 33.78 (R^1); 163.8, 59.9, 13.64 (R^2)
3b	55	50	—[d]	$C_{11}H_{14}O_4$ (210.2)	6.5 (s, 1H); 4.2 (q, 2H, J = 7 Hz); 3.65 (s, 2H); 2.55 (s, R^1); 2.4 (s, R^2); 1.30 (t, 3H, J = 7 Hz)	168.9 (C-6); 157.9 (C-4); 145.7 (C-1); 122.2 (C-2); 108.6 (C-3); 61.33 (C-7); 29.1 (C-5); 14.09 (C-8); 33.72 (R^1); 193.9, 14.2 (R^2)
3c	—	36	121–122 °C	$C_{16}H_{17}NO_4$ (287.3)	7.8 (m, 1H); 7.6–7.4 (m, 2H); 7.4–7.2 (m, 3H); 6.4 (s, 1H); 4.2 (q, 2H, J = 7 Hz); 3.6 (s, 2H); 2.55 (s, 3H); 1.3 (t, 3H, J = 7 Hz)	162.23 (C-6); 157.29 (C-4); 145.60 (C-1); 116.75 (C-2); 106.87 (C-3); 61.4 (C-7); C-5 (33.72); 14.09 (C-8); 13.51 (R^1); 169.32, 138.06, 128.77, 124.1, 120.26 (R^2)
3d	—	10	—[d]	$C_{14}H_{21}NO_4$ (267.3)	6.2 (s, 1H); 4.1 (q, 2H, J = 7 Hz); 3.6 (s, 2H); 3.45 (q, 4H); 2.3 (s, 3H); 1.20 (td, 9H)	165.6 (C-6); 152.4 (C-4); 145.6 (C-1); 117.99 (C-2); 107.98 (C-3); 61.11 (C-7); 29.43 (C-5); 14.22 (C-8); 33.98 (R^1); 170.87, 40.54, 13.51 (R^2)
3e	—	44	87–88 °C	$C_{15}H_{16}O_5S$ (308.3)	7.9 (m, 3H); 7.5 (m, 2H); 6.72 (s, 1H); 4.2 (q, 2H, J = 7 Hz); 3.72 (s, 2H); 3.0 (s, 3H); 1.30 (t, 3H, J = 7 Hz)	168.55 (C-6); 154.22 (C-1); 147.71 (C-4); 124.15 (C-2); 110.86 (C-3); 61.65 (C-7); 43.88 (C-5); 14.12 (C-8); 130.33, 128.96, 128.44 (R^1); 33.85 (R^2)
4a	50	—	—[d]	$C_{12}H_{14}O_4$ (222.2)	6.49 (s, 1H); 4.25 (q, 2H, J = 7 Hz); 3.65 (s, 2H); 2.3 (td, 2H); 1.25 (t, 3H, J = 7 Hz); 1.25 (m, 4H)	194.26 (C-12); 168.8 (C-6); 166.7 (C-1); 148.2 (C-4); 122.02 (C-2); 104.73 (C-3); 61.33 (C-7); 37.55 (C-5); 33.9 (C-11); 23.2 (C-10); 22.48 (C-9); 14.1 (C-8)
4b	43	—	—[d]	$C_{14}H_{18}O_4$ (250.3)	6.47 (s, 1H); 4.15 (q, 2H, J = 7 Hz); 3.65 (s, 2H); 2.70 (s, 2H); 2.35 (s, 2H); 1.27 (t, 3H, J = 7 Hz); 1.1 (s, 6H)	194.26 (C-12); 168.8 (C-6); 165.8 (C-1); 148.66 (C-4); 120.72 (C-2); 104.4 (C-3); 61.33 (C-7); 51.84 (C-10); 37.29 (C-5); 35.8 (C-11); 33.9 (C-9); 14.03 (C-8); 28.5 (2 CH_3)
5a	—	9	—[d]	$C_{16}H_{17}NO_4$ (287.3)	7.6–7.0 (m, 5H); 5.0 (td, 1H, J = 2 Hz); 4.15 (q, 2H, J = 7 Hz); 3.8 d, 2H, J = 2 Hz); 3.42 (d, 1H, J = 2 Hz); 2.42 (s, 3H); 1.2 (t, 3H, J = 7 Hz)	200.50 (C-9); 171.45 (C-1); 167.37 (C-6); 133.71 (C-3); 129.03 (C-5); 59.71 (C-7); 53.53 (C-4); 29.43 (C-2); 26.96 (C-10); 14.29 (C-8); 129.94, 129.55, 127.60, 127.28 (C_{arom})
5b	—	2	—[d]	$C_{16}H_{17}NO_4$ (287.3)	7.6–7.0 (m, 5H); 5.18 (t, 1H, J = 2 Hz); 4.15 (q, 2H), J = 7 Hz); 3.6 (dd, 2H, J = 2.5 Hz); 2.16 (s, 3H); 1.2 (t, 3H); J = 7 Hz)	204.14 (C-9); 173.15 (C-1); 166.91 (C-6); 158.53 (C-4); 94.47 (C-5); 59.90 (C-7); 59.51 (C-3); 37.42 (C-2); 29.88 (C-10); 14.29 (C-8); 133.58, 129.94, 129.29, 127.60 (C_{arom})
6	—	50	—[d]	$C_{14}H_{21}NO_4$ (267.3)	7.25 (s, 1H); 4.10 (q, 2H, J = 7 Hz); 3.45 (q + s, 4H + 2H); 2.2 (s, 3H); 1.2 (td, 9H)	169.1 (C-6); 148.98 (C-4); 139.23 (C-1); 117.5 (C-2); 107.98 (C-3); 60.75 (C-7); 29.43 (C-5); 14.22 (C-8); 33.98 (CH_3); 170.87, 41.06, 40.80, 12.92 [CO—N(C_2H_5)$_2$]
7	90		127–128 °C	$C_{12}H_{10}O_3$ (202.2)	7.8–7.4 (m, 3H); 7.7–7.5 (m, 2H); 6.7 (d, 1H, J = 5 Hz); 6.3 (d, 1H, J = 5 Hz); 3.3 (s, 2H)	176.04 (C-6); 154.03 (C-1); 146.74 (C-4); 110.8 (C-2); 106.11 (C-3); 35.04 (C-5); 130.92, 128.83, 127.53, 123.89 (C_{arom})

[a] The microanalyses were in satisfactory agreement with the calculated values (C ±0.1, H ±0.3); analyses carried out by C.N.R.S: service central de microanalyse, 43 Bd. du 11 Novembre 1918; 6962 Villeurbanne.

[b] The ^{1}H-N.M.R. spectra were recorded on a Varian T 60 spectrometer.

[c] The ^{13}C-N.M.R. spectra were recorded on a JEOL FX 60 spectrometer; for assignments see small numbers in the respective formulae.

[d] Isolated by chromatography on silica gel.



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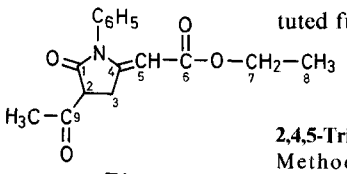

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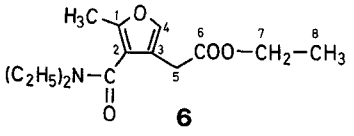

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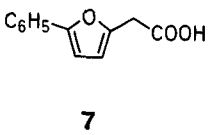

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the carbon-sulphur bond in **3e** can be cleaved by treatment with sodium amalgam in ethanol[6] to give the 2,5-disubstituted furan **7** in 90% yields.

2,4,5-Trisubstituted Furans; General Procedures:

Method A: To a stirred solution of sodium ethoxide [sodium (2.116 g, 0.092 mol) in ethanol (150 ml)] is added the methylene compound **2** (0.092 mol) at −5 °C. The solution turns yellow and, after several minutes a solution of ethyl 3,4-dibromobutenoate[7] (**1**; 10 g, 0.037 mol) in ethanol (15 ml) is added. Stirring is continued for 24 h at room temperature. The mixture is then neutralised by addition of 10% aqueous hydrochloric acid (~10 ml), the solvent is removed under reduced pressure, water (50 ml) is added to the resi-

due, the mixture is extracted with ether (3 × 100 ml), and the extracts dried with magnesium sulphate. Evaporation of the ether gives the crude furans **3** or **4** which are purified by column chromatography on silica gel with chloroform/methanol or by distillation.

Method B: To a stirred solution of dimethylformamide (20 ml), potassium carbonate (4.56 g), and the methylene compound **2** (0.03 mol) is added ethyl 3,4-dibromo-2-butenoate[7] (**1**; 8 g, 0.029 mol) at less than 5 °C. The mixture is stirred for 24 h at room temperature and filtered. The solid is washed several times with ether, the filtrate is combined with the washings and ether (50 ml) is added. Dimethylformamide and residual salts are removed by washing with water and the organic phase is dried with magnesium sulphate. Evaporation of the ether gives the crude furans **3** and **6** which are purified by column chromatography on silica gel with 3:1 petroleum ether/ethyl acetate.

Thus prepared are:

Ethyl 4-ethoxycarbonyl-5-methylfuran-2-acetate **(3a)** from **1** and ethyl acetoacetate; yield: 6.13 g (70%); colourless oil.

Ethyl 4-acetyl-5-methylfuran-2-acetate **(3b)** from **1** and 2,4-pentanedione; yield: 4.25 g (55%); red liquid purified by column chromatography on silica gel with 99:1 chloroform/methanol as eluent.

*Ethyl 4-(*N*-phenylaminocarbonyl)-5-methylfuran-2-acetate* **(3c)** from **1** and *N*-phenylacetoacetamide[8]; yield: 3.80 g (36%); white crystals purified by column chromatography on silica gel with 7:3 petroleum ether/ethyl acetate as eluent. The isomeric pyrrolidones **5a** and **5b** are obtained as a second fraction; they have not been separated.

*Ethyl 4-(*N,N*-diethylaminocarbonyl)-5-methylfuran-2-acetate* **(3d)** and *ethyl 4-(*N,N*-diethylaminocarbonyl)-5-methylfuran-3-acetate* **(6)** from **1** and *N,N*-diethylacetoacetamide[9]; the products are separated by column chromatography on silica gel with 65:35 petroleum ether/ethyl acetate as eluent; yield of **3d:** 0.98 g (10%); of **6:** 5.9 g (50%); yellow liquids.

Ethyl 4-methylsulphonyl-5-phenylfuran-2-acetate **(3e)** from **1** and methyl 2-oxo-2-phenylethyl sulphone[10]; yield: 4.98 g (44%); yellow solid purified by column chromatography on silica gel with 65:35 petroleum ether/ethyl acetate as eluent.

2-Ethoxycarbonyl-4-oxo-4,5,6,7-tetrahydrobenzofuran **(4a)** from **1** and cyclohexane-1,3-dione; yield: 4.65 g (50%); liquid purified by column chromatography on silica gel with 96:4 chloroform/methanol as eluent.

6,6-Dimethyl-2-ethoxycarbonyl-4-oxo-4,5,6,7-tetrahydrobenzofuran **(4b)** from **1** and 5,5-dimethylcyclohexane-1,3-dione; yield: 3.51 g (43%); red liquid purified by column chromatography on silica gel with 99:1 chloroform/methanol as eluent.

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