Pseudoesters and Derivatives; XVII[1]. Synthesis of 4-Alkylamino- and 4-Alkylthio-5-methoxyfuran-2(5*H*)-ones

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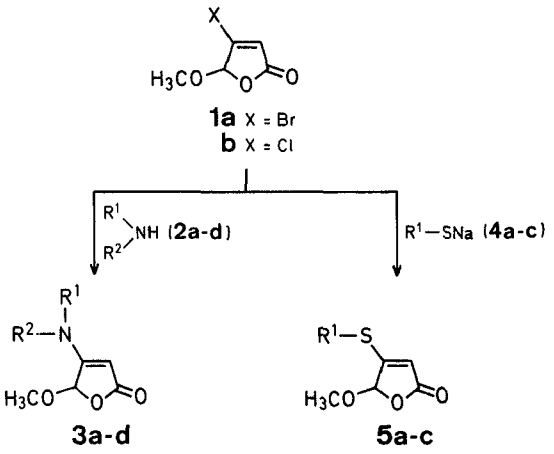
5-Alkoxyfuran-2(5*H*)-ones, which may be considered as cyclic pseudoesters of 4-oxobut-2-enoic acid, are useful intermediates in organic syntheses, especially when they bear extra functional groups. The preparation of 5-methoxyfuran-2(5*H*)-one is readily achieved by sensitised photooxygenation of furan or furfural using methanol as solvent[2]. The reaction involves 1,4-cycloaddition of singlet oxygen to the furan ring[3,4] and rearrangement of the primary endoperoxide to the 4-oxobut-2-enoic acid[5,6], which is converted into the corresponding pseudoester, 5-methoxyfuran-2(5*H*)-one, in the presence of methanol. The application of this procedure to the synthesis of 3- or 4-substituted 5-methoxyfuran-2(5*H*)-ones is limited because of the difficult accessibility of the starting 3-substituted furans and the lack of regioselectivity of the process[6].

We have previously reported that the halogen addition to 5-alkoxyfuran-2(5*H*)-ones followed by HX elimination under different experimental conditions, affords a regioselective synthesis of the 3- and 4-halogenated alkoxyfuranones[7,8]. These, and especially the 4-halogenated furanones **1a, b** appeared to be suitable substrates for the introduction of other functional groups into the furanone nucleus by nucleophilic substitution of the halogen. Recently[9] we described the substitution of methyl 3-bromo-4,4-dimethoxybut-2-enoates by oxygen, nitrogen- and sulphur-containing nucleophiles and the reactions in most cases are suitable for preparative purposes. However, only one example has been reported[10] in which a direct substitution of the halogen by a thiolate ion is achieved in the chlorofuranone **1b**. Moreover, our previous results[11] indicated that reaction of **1a** with the methoxide ion as nucleophile yielded only a small amount of the expected 4-methoxy-substituted furanone, the opening of the lactone ring being the main initial reaction.

We describe here a general synthesis of the title compounds, in which the reactions of the halogenated furanones **1a, b** with primary and secondary amines **(2)** and sodium thiolates **(4)** have been carried out in tetrahydrofuran or carbon tetrachloride in order to prevent the opening of the lactone ring. Under these conditions, **1a** and **1b** afforded the substitution products **3a–d** and **5a–c** in very good yields.



The substitution with thiolates **4** has also been effected using methanol as solvent and, generally, the reactions are faster than in carbon tetrachloride or tetrahydrofuran. We found, however, that when chlorofuranone **1b** reacts with 2-propanethiolate the expected substitution product **5c** is only obtained in 29% yield, the main reaction being the ring opening to give the normal aldehyde-ester, followed by conjugate addition of thiolate to the —CH=CX—CHO system and subsequent HX elimination yielding methyl (*Z*)-2-isopropylthio-4-oxobut-2-enoate and its cyclic isomer, 3-isopropylthio-5-methoxyfuran-2(5*H*)-one. Similar results have been reported in the reaction of halofuranone **1a** with methoxide[10].

4-Alkylamino-5-methoxyfuran-2(5*H*)-ones (3a–d); General Procedure: To a solution of 4-bromo- **(1a)** or 4-chloro-5-methoxyfuran-2(5*H*)-one **(1b)** (4 mmol) in tetrahydrofuran or carbon tetrachloride (40 ml), the amine **2** (8 mmol) is added at room temperature. Disappearance of the halogenated substrate is monitored by G.L.C. After removal of salts and solvent, the residue is purified by column chromatography on silica gel (Merck 60, 70–230 mesh ASTM) using benzene/methanol (4 : 1) as eluent and/or crystallisation from cyclohexane.

Table 1. Preparation of 4-Alkylamino- **(3a–d)** and 4-Alkylthio-5-methoxyfuran-2(5*H*)-ones **(5a–c)**

Product No.	R^1	R^2	Reaction Conditions Solvent/Time	Yield [%] from **1a**	Yield [%] from **1b**	m.p. [°C] (c-C_6H_{12})	Molecular formula[a]	
3a	$-(CH_2)_4-$		THF/15 min	85	85	107–109°	$C_9H_{13}NO_3$	(183.2)
3b	$-(CH_2)_5-$		THF/90 min	96	89	78–79°	$C_{10}H_{15}NO_3$	(197.2)
3c	C_2H_5	C_2H_5	THF/96 h	84	84	43–44°	$C_9H_{15}NO_3$	(185.2)
3d	$C_6H_5CH_2$	H	THF or CCl_4/48 h	85	85	115–116°	$C_{12}H_{12}NO_3$	(219.2)
5a	C_2H_5	—	CH_3OH/10 min	83	70	41–43°[b]	$C_7H_{10}O_3S$	(174.2)
			THF or CCl_4/90 min	80	72			
5b	$C_6H_5CH_2$	—	CH_3OH/10 min	97	56	60–61°	$C_{12}H_{12}O_3S$	(236.2)
			THF or CCl_4/60 min	97	90			
5c	i-C_3H_7	—	CH_3OH/10 min	95	29[c]	oil[d]	$C_8H_{12}O_3S$	(188.2)
			THF or CCl_4/90 min	88	88			

[a] Satisfactory microanalyses obtained: C ±0.31, H ±0.30, N ±0.26, S ±0.24.

[b] Purification by sublimation at 80–85 °C/14 torr also possible.

[c] Also obtained from reaction mixture are:
methyl (*Z*)-2-isopropylthio-4-oxo-2-butenoate;
^{1}H-N.M.R. (CCl_4): $\delta = 1.30$ (d); 3.6 (m); 3.88 (s); 6.80 (d); 10.23 ppm (d),
and 3-isopropylthio-5-methoxyfuran-2(5*H*)-one;
^{1}H-N.M.R. (CCl_4): $\delta = 1.1$ (m); 3.5 (m); 3.53 (s); 5.73 (d); 6.53 ppm (d).

[d] Isolated by preparative T.L.C. on silica gel eluting with 100:7 benzene/ethyl acetate.

4-Alkylthio-5-methoxyfuran-2(5*H*)-ones (5a–c); General Procedure:
To a solution of **1a** or **1b** (2 mmol) in tetrahydrofuran, carbon tetrachloride, or methanol (20 ml), sodium thiolate **4** (2.2 mmol) is added. The mixture is stirred at room temperature until the starting material is consumed. Disappearance of furanones **1** is followed by G.L.C. or T.L.C. After evaporation of the solvent the residue is extracted with ether (2 × 40 ml) and the crude 4-alkylthiofuranone **5** is purified by column chromatography on silica gel (Merck 60, 70–230 mesh ASTM) using benzene/ethyl acetate as eluent and/or crystallisation.

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Table 2. Spectral Data of 4-Alkylamino- **(3a–d)** and 4-Alkylthio-5-methoxyfuran-2(5*H*)-ones **(5a–c)**

Compound	I.R. [cm^{-1}][a] $\nu_{C=O}$	$\nu_{C=C}$	^{1}H-N.M.R. ($CDCl_3$/$TMS_{int.}$)[b] δ [ppm]	M.S.[c] m/e (M^+)
3a	1790–1720	1625	5.70 (s, 1H, 5-H); 4.48 (s, 1H, 3-H); 3.49 (s, 3H, OCH_3); 3.3 (m, 4H, CH_2N); 2.0 (m, 4H, CH_2)	183
3b	1785–1720	1625	5.72 (s, 1H, 5-H); 4.61 (s, 1H, 3-H); 3.48 (s, 3H, OCH_3); 3.3 (m, 4H, CH_2N); 1.7 (m, 6H, CH_2)	197
3c	1780–1740	1620	5.72 (s, 1H, 5-H); 4.55 (s, 1H, 3-H); 3.47 (s, 3H, OCH_3); 3.27 (q, 4H, CH_2N, $J = 7.5$ Hz); 1.19 (t, 6H, CH_3)	185
3d	1770–1720	1625	7.3 (m, 5H_{arom}); 5.62 (s, 1H, 5-H); 5.57 (br. s, NH); 4.67 (s, 1H, 3-H); 4.29 (d, 2H, CH_2, $J = 6.0$ Hz); 3.47 (s, 3H, OCH_3)	219
5a	1755	1580	5.74, 5.72 (2s, 2H, 5-H, 3-H); 3.52 (s, 3H, OCH_3); 2.95 (q, 2H, CH_2S, $J = 7.5$ Hz); 1.41 (t, 3H, CH_3)	174
5b	1760	1575	7.3 (m, 5H_{arom}); 5.79, 5.72 (2s, 2H, 5-H, 3-H); 4.13 (s, 2H, $CH_2C_6H_5$); 3.49 (s, 3H, OCH_3)	236
5c	1760	1575	5.76, 5.70 (2s, 2H, 5-H, 3-H); 3.52 (s, 3H, OCH_3); 3.4 [m, 1H, $CH(CH_3)_2$]; 1.43 (d, 6H, CH_3, $J = 6.9$ Hz)	188

[a] Perkin-Elmer 257 spectrometer. Compounds **3a–d** and **5a, b** as Nujol mulls and compound **5c** as a liquid film.

[b] Varian EM-390 spectrometer.

[c] Hitachi Perkin-Elmer RMU-6MG spectrometer.

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