Regioselective *C*-alkylation of alkyl 4-hydroxy-2-methylthiophene-3-carboxylates with α-halo ketones

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Regioselective *C*- or *O*-alkylation of alkyl 4-hydroxy-2-methylthiophene-3-carboxylates with α-halo ketones is possible, depending on the solvent nature. A convenient preparative method of *C*-alkylation was proposed and previously not easily accessible β-hydroxythiophene derivatives were synthesized.

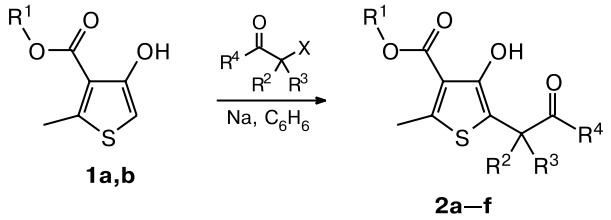
Key words: alkylation, hydroxythiophene, α-halo ketones.

Alkylation of hydroxythiophenes is known[1—3] to often give, in contrast to phenols, mixtures of *O*- and *C*-alkylation products. The direction of the reaction depends on the structure of the starting thiophene, the nature of the alkylating agent and the base, and the polarity of the solvent.[1,3—7] The *C*-alkylation of 2- and 3-hydroxythiophenes with alkyl halides under various conditions was thoroughly studied;[3,5—10] however, information on the use of α-halo ketones in this reaction is lacking. At the same time, both *O*- and *C*-alkylation products of this reaction are of undoubted interest for further functionalization of thiophene derivatives, creation of fused heterocycles on their basis, *etc*.

The goal of the present work was to investigate reactions of β-hydroxythiophenes **1a,b** and their sodium salts with α-halo ketones under various conditions. We found that the reactions of alkyl 4-hydroxy-2-methylthiophene-3-carboxylates **1a,b** with α-halo ketones in benzene at 10 to 25 °C in the presence of sodium metal exclusively yields *C*-alkylation products **2a—f** (Scheme 1).

Depending on the reactivity of α-halo ketone, the reaction duration varies from 30 min to several hours. For instance, the reaction with chloroacetone is completed over 30 min at 10—15 °C, whereas the reaction duration for less reactive phenacyl halides is 8 to 30 h. In the case of α-halo ketones containing the halogen atom at the secondary and tertiary C atom, the reaction proceeds more slowly (as indicated by the hydrogen evolution rate) and the yields of *C*-alkylation products decrease to 46% (for **2b**) and 19% (for **2c**). It should be noted that this reaction is characteristic of α-halo ketones since our attempts to *C*-alkylate hydroxythiophene under these conditions with "common" alkyl halides (ethyl iodide or benzyl bromide) failed. Prolonged heating of the reaction mixture

Scheme 1



R^1 = Me (**1a**), CH_2Me (**1b**)

2	**a**	**b**	**c**	**d**	**e**	**f**
R^1	CH_2Me	Me	CH_2Me	Me	CH_2Me	CH_2Me
R^2	H	Me	Me	H	H	H
R^3	H	H	Me	H	H	H
R^4	Me	Me	Me	Ph	4-BrC_6H_4	4-ClC_6H_4

(15—20 h) results in resinification, with partial recovery of sodium metal and the starting thiophene. Apparently, this is due to a competitive reaction of alkyl halides with sodium. We also studied the reaction of a sodium salt of hydroxythiophene (**3**), which is prepared by the reaction of ester **1** with sodium in benzene or with sodium ethoxide in anhydrous ethanol, with *p*-bromophenacyl bromide in various solvents. It was found that the direction of alkylation strongly depends on the solvent nature. In benzene and ethanol, *C*-alkylation products were exclusively obtained in good yields (75—80%), while in DMF or acetonitrile, this reaction follows another pathway to give *O*-alkylation product **4a** in 60—65% yield (Scheme 2).

O-Alkylation is also the main reaction pathway when hydroxythiophene **1b** reacts with α-halo ketones in DMF or acetonitrile in the presence of potassium carbonate; in

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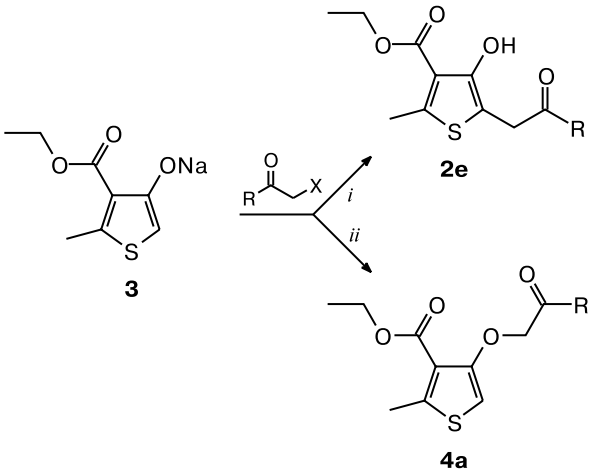
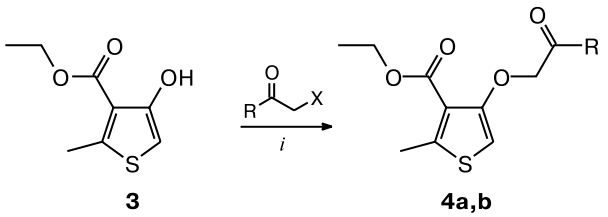
Scheme 2



R = 4-BrC_6H_4

i. C_6H_6 or EtOH; *ii*. MeCN or DMF.

Scheme 3



R = 4-BrC_6H_4 (**4a**), Me (**4b**)

i. MeCN or DMF.

DMF, this reaction affords minimum amounts of by-products (Scheme 3).

The structures of the compounds obtained were proved by ^1H and ^{13}C NMR spectroscopy and mass spectrometry and confirmed by elemental analysis. The ^1H NMR spectra of *C*-alkylation products contain characteristic signals for the OH protons (δ_H 9.10—9.26), while those of *O*-alkylation products show signals for the protons of the thiophene ring (δ_H 5.96—6.03). As expected, a signal for the carbon atom of the CH_2 group of the halo ketone residue is significantly shifted upfield in the ^{13}C NMR spectra of *C*-alkylation products **2** (δ_C 34.8—39.5) compared to an analogous signal for *O*-alkylation products **4** (δ_C 73.8—75.2).

Thus, the convenient preparative method for the *C*-alkylation of β-hydroxythiophenes **1** with α-halo ketones was developed and the possibility of their regioselective *O*- and *C*-alkylation was demonstrated, depending on the solvent nature.

Experimental

^1H and ^{13}C NMR spectra were recorded on Bruker AC-200, Bruker WM-250, and Bruker AM-300 spectrometers in $CDCl_3$. Mass spectra were recorded on a Kratos instrument (EI, 70 eV, direct inlet probe). Melting points were determined on a Boetius

Table 1. Reaction conditions and the physicochemical characteristics of the compounds obtained

Compound	Solvent	Reagent	τ/h	M.p./°C (solvent)*	Yield (%)	Found / Calculated (%)		
						C	H	S
2a	Benzene	Na	0.5	62—64 (hexane)	85	54.52 / 54.53	5.96 / 5.82	13.11 / 13.23
2b	»	»	72	61—63	46	55.87 / 54.53	5.94 / 5.82	12.30 / 13.23
2c	»	»	110	45—47	19	57.45 / 57.76	6.77 / 6.71	11.79 / 11.86
2d	»	»	32	115—116 (heptane—ethyl acetate)	72	62.51 / 62.05	4.90 / 4.86	10.64 / 11.04
2e	»	»	30	131—133 (heptane)	80	50.10 / 50.14	3.99 / 3.94	8.94 / 8.37
2f	»	»	29	113—115 (heptane)	78	57.15 / 56.72	4.72 / 4.46	9.13 / 9.46
4a	DMF—MeCN	K_2CO_3	16	94—95 (ethanol)	82 / 54	50.49 / 50.14	3.91 / 3.94	8.51 / 8.37
4b	DMF—MeCN	K_2CO_3	3	47—48 (hexane)	58 / 32	54.79 / 54.53	5.86 / 5.82	14.02 / 13.23

* The solvent for recrystallization.

Table 2. Spectral characteristics of the compounds obtained

Compound	^{1}H NMR ($CDCl_3$, δ, *J*/Hz)	^{13}C NMR ($CDCl_3$, δ)	MS, *m/z*, $[M]^+$
2a	1.41 (t, 3 H, $OCH_2\underline{Me}$, *J* = 7.22); 2.22 (s, 3 H, $CO\underline{Me}$); 2.61 (s, 3 H, $\underline{Me}_{thioph}$); 3.72 (s, 2 H, $C\underline{H}_2CO$); 4.41 (q, 2 H, $OC\underline{H}_2Me$, J_2 = 7.22); 9.13 (s, 1 H, O<u>H</u>)	14.30 ($OCH_2\underline{Me}$); 16.99 ($\underline{Me}_{thioph}$); 29.11 ($CO\underline{Me}$); 39.51 ($\underline{C}H_2CO$); 61.09 ($O\underline{C}H_2Me$); 103.94 ($\underline{C}$—CH_2); 115.69 ($\underline{C}$—Me); 146.53 ($\underline{C}$—$COOCH_2Me$); 152.12 (C—OH); 166.42 ($\underline{C}OOCH_2Me$); 205.24 ($Me\underline{C}$=O)	242
2b	1.40 (d, 3 H, $CH\underline{Me}$, *J* = 6.56); 2.20 (s, 3 H, $CO\underline{Me}$); 2.64 (s, 3 H, $\underline{Me}_{thioph}$); 3.95 (s, 3 H, $O\underline{Me}$); 4.15 (q, 1 H, $C\underline{H}Me$, J_1 = 6.56); 9.10 (s, 1 H, O<u>H</u>)	16.76 ($\underline{Me}CH$); 17.04 ($\underline{Me}_{thioph}$); 28.16 ($\underline{Me}CO$); 43.55 ($Me\underline{C}H$); 51.88 (MeO); 111.87 ($\underline{C}_{thioph}$—CHMe); 115.88 ($\underline{C}$—Me); 146.47 ($\underline{C}$—COOMe); 151.31 (C—OH); 166.86 ($\underline{C}OOMe$); 207.98 ($Me\underline{C}$=O)	242
2c	1.35 (t, 3 H, $OCH_2\underline{Me}$, *J* = 6.94); 1.45 (s, 6 H, $C\underline{Me}_2$); 2.12 (s, 3 H, $CO\underline{Me}$); 2.62 (s, 3 H, $\underline{Me}_{thioph}$); 4.38 (q, 2 H, $OC\underline{H}_2Me$, J_1 = 6.94); 9.16 (s, 1 H, O<u>H</u>)	14.30 ($\underline{Me}CH_2O$); 17.02 ($\underline{Me}_{thioph}$); 24.88 ($C\underline{Me}_2CO$); 25.18 ($\underline{Me}CO$); 48.55 ($\underline{C}Me_2CO$); 61.14 ($Me\underline{C}H_2O$); 116.60 ($\underline{C}$—CMe_2); 116.94 ($\underline{C}$—Me); 144.62 ($\underline{C}$—$COOCH_2Me$); 150.82 (C—OH); 166.48 ($\underline{C}OOCH_2Me$); 210.11 ($CMe_2\underline{C}$=O)	270
2d	2.60 (s, 3 H, $\underline{Me}_{thioph}$); 3.92 (s, 3 H, MeO); 4.35 (s, 2 H, $C\underline{H}_2CO$); 7.48 (t, 2 H, $C\underline{H}_{benz}$, *J* = 7.21); 7.52 (t, 1 H, $C\underline{H}_{benz}$, *J* = 7.21); 8.10 (d, 2 H, $C\underline{H}_{benz}$); 9.17 (s, 1 H, O<u>H</u>)	17.02 ($\underline{Me}_{thioph}$); 34.85 ($\underline{C}H_2$); 51.87 ($\underline{Me}OCO$); 104.52 ($\underline{C}_{thioph}$—CH_2); 115.48 ($\underline{C}_{thioph}$—COOMe); 128.64; 128.71; 133.41 (CH_{benz}); 136.12 ($\underline{C}_{benz}$—CO); 147.14 ($\underline{C}_{thioph}$Me); 151.93 (C—OH); 167.17 ($\underline{C}OOMe$); 196.57 (C=O)	290
2e	1.41 (t, 3 H, $OCH_2\underline{Me}$, *J* = 7.22); 2.61 (s, 3 H, $\underline{Me}_{thioph}$); 4.27 (s, 2 H, $C\underline{H}_2CO$); 4.39 (q, 2 H, $C\underline{H}_2Me$, *J* = 7.22); 7.60 (d, 2 H, CH_{benz}, *J* = 8.53); 7.94 (d, 2 H, CH_{benz}, *J* = 8.53); 9.26 (s, 1 H, OH)	14.33 ($\underline{Me}CH_2$); 17.05 ($\underline{Me}_{thioph}$); 34.90 ($\underline{C}H_2CO$); 61.16 ($Me\underline{C}H_2O$); 103.98 ($\underline{C}_{thioph}$—CH_2); 115.65 ($\underline{C}_{thioph}$—$COOCH_2Me$); 128.63 (C_{benz}—Br); 130.18, 132.00 (CH_{benz}); 134.69 ($\underline{C}_{benz}$—CO); 147.12 ($\underline{C}_{thioph}$—Me); 151.99 (C—OH); 166.55 ($\underline{C}$—OCH_2Me); 195.68 (C=O)	384, 382
2f	1.39 (t, 3 H, $OCH_2\underline{Me}$, *J* = 7.36); 2.61 (s, 3 H, Me); 4.28 (s, 2 H, CH_2); 4.38 (q, 2 H, $OC\underline{H}_2Me$, *J* = 7.36); 7.43 (d, 2 H, CH_{benz}, *J* = 8.09); 8.03 (d, 2 H, CH_{benz}, *J* = 8.09); 9.21 (s, 1 H, OH)	14.31 ($\underline{Me}CH_2$); 17.00 ($\underline{Me}_{thioph}$); 34.91 ($\underline{C}H_2CO$); 61.13 ($Me\underline{C}H_2O$); 104.06 ($\underline{C}_{thioph}$—CH_2); 115.66 ($\underline{C}_{thioph}$—$COOCH_2Me$); 128.98, 129.13, 129.58, 130.07 (CH_{benz}); 134.32 ($\underline{C}_{benz}$—CO); 139.83 (C_{benz}—Cl); 147.08 ($\underline{C}_{thioph}$—Me); 151.98 (C—OH); 166.52 ($\underline{C}$—OCH_2Me); 195.45 (C=O)	338, 336
4a	1.31 (t, 3 H, $CH_2\underline{Me}$, *J* = 7.28); 2.58 (s, 3 H, $\underline{Me}_{thioph}$); 4.29 (q, 2 H, $C\underline{H}_2Me$, *J* = 7.28); 5.11 (s, 2 H, $OC\underline{H}_2CO$); 6.03 (s, 1 H, $C\underline{H}_{thioph}$); 7.57 (d, 2 H, CH_{benz}, *J* = 8.32); 7.93 (d, 2 H, CH_{benz}, *J* = 8.32)	14.31 ($\underline{Me}CH_2$); 16.99 ($\underline{Me}_{thioph}$); 60.42 ($Me\underline{C}H_2$); 73.83 ($O\underline{C}H_2CO$); 96.53 (CH_{thioph}); 120.53 ($\underline{C}$—$COOCH_2Me$); 129.16 (C_{benz}—Br); 130.27, 132.05 (CH_{benz}); 133.34 ($\underline{C}_{benz}$—CO); 148.28 ($\underline{C}_{thioph}$—Me);154.90 ($\underline{C}$—OCH_2CO); 162.87 ($\underline{C}OOCH_2Me$); 206.29 ($OCH_2\underline{C}$=O)	242
4b	1.39 (t, 3 H, $CH_2\underline{Me}$, *J* = 7.26); 2.35 (s, 3 H, $\underline{Me}CO$); 2.64 (s, 3 H, $\underline{Me}_{thioph}$); 4.35 (q, 2 H, $C\underline{H}_2Me$, *J* = 7.26); 4.45 (s, 2 H, $C\underline{H}_2$); 5.96 (s, 1 H, CH_{thioph})	14.41 ($\underline{Me}CH_2$); 16.96 ($\underline{Me}_{thioph}$); 26.72 ($\underline{Me}CO$); 60.39 ($Me\underline{C}H_2$); 75.19 ($O\underline{C}H_2CO$); 95.51 (CH_{thioph}); 120.37 ($\underline{C}$—$COOCH_2Me$); 148.45 ($\underline{C}$—Me); 154.86 ($\underline{C}_{thioph}$—OCH_2); 162.88 ($\underline{C}OOCH_2Me$); 206.12 ($OCH_2\underline{C}$=O)	384, 382

microscope stage and are given uncorrected. The reaction completion was checked by TLC data (Silufol UV-254, light petroleum (60—80 °C)—AcOEt (6 : 1) as the eluent). Acros silica gel (C.A.S.-7631-86-9) (0.060—0.200 μm) was used for column chromatography. Alkyl 4-hydroxy-2-methylthiophene-3-carboxylates **1a,b** were prepared according to a known procedure.[11] Commercially accessible Merck, Acros, and Aldrich chemicals (1-chloroacetone, 2-bromo-1-phenylethanone, 2-bromo-1-(4′-chlorophenyl)ethanone, 2-bromo-1-(4′-bromophenyl)ethanone, 3-chlorobutan-2-one, 3-hydroxy-3-methylbutan-2-one) and anhydrous (99.9%) methanol, acetonitrile, DMF, and benzene were used. 3-Chloro-3-methylbutan-2-one was prepared from 3-hydroxy-3-methylbutan-2-one according to a known procedure.[12]

***C*-Alkylation of alkyl 4-hydroxy-2-methylthiophene-3-carboxylates with α-halo ketones (general procedure).** Sodium metal (0.01 mol) was added to a solution of compound **1** (0.01 mol) in 5 mL of anhydrous benzene. Then, a solution of the corresponding α-halo ketone (0.011 mol) in 3 mL of anhydrous benzene was added dropwise with stirring at 10—15 °C. The reaction mixture was stirred at ~20 °C until the starting hydroxythiophene disappeared completely. After the reaction was completed (TLC), the solvent was removed and the residue was chromatographed on silica gel in light petroleum (60—80 °C)—ethyl acetate (6 : 1). The characteristics of the products obtained are given in Tables 1 and 2.

***O*-Alkylation of 4-hydroxy-2-methylthiophene-3-carboxylates with α-halo ketones (general procedure).** Potassium carbonate (1.38 g, 0.01 mol) was added to a solution of compound **1b** (1.86 g, 0.01 mol) in 10 mL of the corresponding solvent (see Table 1). Then a solution of the corresponding α-halo ketone (0.01 mol) in 3 mL of the same solvent was added dropwise with stirring at 10—25 °C. The reaction mixture was stirred at ~20 °C until the starting hydroxythiophene disappeared completely.

After the reaction was completed (TLC), the mixture was poured into ice and the product was extracted with ethyl acetate, washed with saturated $NaHCO_3$ and water, and dried. The solvent was removed and the residue was chromatographed on silica gel in light petroleum (60—80 °C)—AcOEt (6 : 1). The properties of esters **4a,b** are given in Tables 1 and 2.

Synthesis of ethyl 4-hydroxy-2-methylthiophene-3-carboxylate, sodium salt (3). Sodium metal (0.23 g, 0.01 mol) was added to a solution of hydroxythiophene **1b** (1.86 g, 0.01 mol) in 15 mL of anhydrous benzene. The reaction mixture was stirred at ~20 °C until the starting hydroxythiophene disappeared completely. After the reaction was completed (TLC), the solvent was removed and the residue was dried by distillation with anhydrous benzene to give salt **3** (2.04 g, 98%), m.p. 230—235 °C (decomp.). ^{1}H NMR (DMF-d_7), δ: 1.15 (t, 3 H, $CH_2C\underline{H}_3$, J = 6.62 Hz); 2.31 (s, 3 H, Me_{thioph}); 4.08 (q, 2 H, $C\underline{H}_2CH_3$, J = 6.62 Hz); 5.12 (br.s, 1 H, CH_{thioph}).

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References

1. S. Gronowitz and A.-B. Hörnfeldt, in *The Chemistry of Heterocyclic Compounds: Thiophene and Its Derivatives*, Ed. S. Gronowitz, Wiley, New York, 1986, Vol. **44**, Part 2, Ch. 1.
2. B. Capon and F. C. Kwok, *J. Am. Chem. Soc.*, 1989, **111**, 5346.
3. J. Scramstad, A. Lunde, H. Hope, V. Bjørnstad, and P. Frøyen, *J. Chem. Soc., Perkin Trans. 2*, 2000, 1453.
4. G. A. Hurter and H. McNab, *J. Chem. Soc., Chem. Commun.*, 1990, 375.
5. Y. Zhang, A.-B. Hörnfeldt, and S. Gronowitz, *J. Heterocycl. Chem.*, 1993, **30**, 129.
6. G. A. Hunter, *Diss. Abstr. Int. B*, 1992, **52**, 5827; *Chem. Abstr.*, 1993, **118**, 124340k.
7. R. Lantz and A.-B. Hörnfeldt, *Chem. Scripta*, 1976, **10**, 126.
8. A. Merz and C. Rem, *J. Prakt. Chem. (Chem-Ztg.)*, 1996, **338**, 672.
9. (a) E. B. Pedersen and S.-O. Lawesson, *Tetrahedron*, 1971, **27**, 3861; (b) E. B. Pedersen and S.-O. Lawesson, *Tetrahedron*, 1972, **28**, 2479.
10. (a) B. Cederlund and A.-B. Hörnfeldt, *Chem. Scripta*, 1975, **8**, 140; (b) B. Cederlund and A.-B. Hörnfeldt, *Acta Chem. Scand.*, 1971, **25**, 3546; (c) B. Cederlund and A.-B. Hörnfeldt, *Acta Chem. Scand.*, 1971, **25**, 3657; (d) B. Cederlund and A.-B. Hörnfeldt, *Acta Chem. Scand.*, 1971, **25**, 3324.
11. E. Benary and A. Baravian, *Chem. Ber.*, 1915, **48**, 593.
12. R. Justoni, *Chim. Ind. (Italy)*, 1942, **24**, 195; *Chem. Abstr.*, 1944, **38**, 3610.

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