A Novel Route to 2-Alkoxy/Aryloxythiophenes via Simmons–Smith Reaction on Acylketene *O,S*-Acetals

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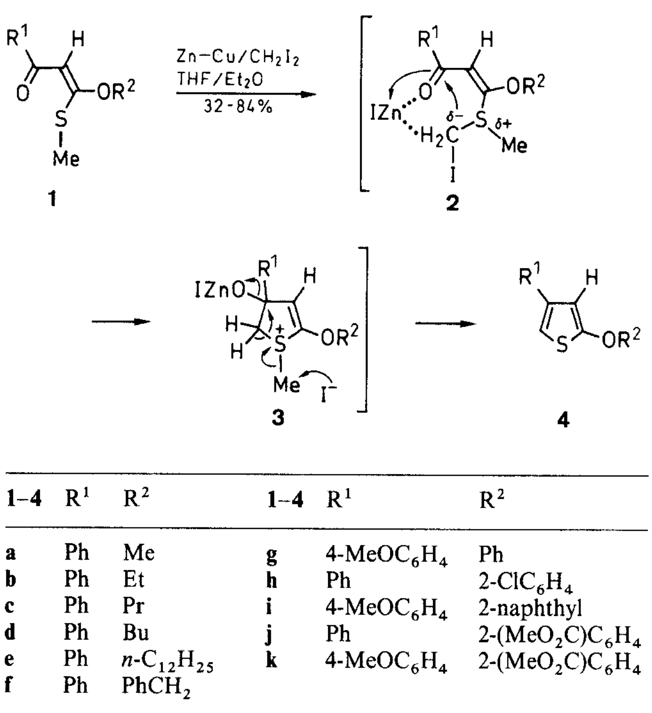
A novel route to 2-alkoxy/aryloxy-4-arylthiophenes **4a–k** and the corresponding 3,4-annulated thiophene **7** has been developed by subjecting the respective acylketene *O,S*-acetals **1a–k** and **6** to Simmons–Smith reaction conditions (zinc–copper/diiodomethane).

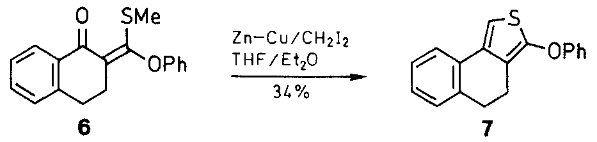
As a part of our interest in the chemistry of α-oxoketene dithioacetals we had recently observed that these acetals under Simmons–Smith reaction conditions yield the corresponding thiophenes in high yields.[1] A reaction pathway involving participation of divalent sulfur with the Simmons–Smith methylene carbenoid species to give the intermediate unstable ylide and its subsequent intramolecular aldol condensation was suggested for the formation of these compounds. We have now extended this reaction to the recently synthesized acylketene *O,S*-acetals[2] and report herein a new route for the synthesis of 2-alkoxy/aryloxythiophenes.



1–4	R^1	R^2	1–4	R^1	R^2
a	Ph	Me	g	4-$MeOC_6H_4$	Ph
b	Ph	Et	h	Ph	2-ClC_6H_4
c	Ph	Pr	i	4-$MeOC_6H_4$	2-naphthyl
d	Ph	Bu	j	Ph	2-$(MeO_2C)C_6H_4$
e	Ph	n-$C_{12}H_{25}$	k	4-$MeOC_6H_4$	2-$(MeO_2C)C_6H_4$
f	Ph	$PhCH_2$			

Scheme 1

In a typical experiment the *O,S*-acetal **1a** was reacted with zinc–copper couple with diiodomethane in refluxing diethyl ether/tetrahydrofuran and the product isolated after workup was characterized as 2-methoxy-4-phenylthiophene (66%) on the basis of spectroscopic and analytical data. The other homologous 2-alkoxythiophenes **4b–e** and 2-benzyloxythiophene **4f** were similarly obtained in 32–72% overall yield. The reaction was found to be equally facile for the synthesis of 2-aryloxythiophenes **4g,h** and 2-(2-naphthyloxy)thiophene **4i** which were obtained in 66–76% yield from the respective *O*-aryl acetals **1g–i**. Similarly, the 2-[2-(methoxycarbonyl)phenoxy]thiophenes **4j,k** and the 3,4-fused derivative **7** could also be synthesized through this route in moderate to good yields.



Scheme 2

Among the various routes[3–10] available for the synthesis of 2-alkoxythiophenes, the most commonly adopted one involves coupling of 2-halothiophenes with the respective carbinol in the presence of copper catalysts (CuBr, Cu_2O, Cu bronze etc.). However the reaction requires preconstructed halothiophenes which are themselves not easy to synthesize. Besides, the method suffers from several limitations[3] i.e. drastic conditions, prolonged reaction time leading to decomposition of catalyst and reductive dehalogenation of starting halothiophenes. The 2-aryloxythiophenes are excellent precursors for the synthesis of thiophene analogs of xanthones[5,9] which are reported to be formed in poor yields through coupling of 2-bromothiophene with phenols (or ethyl salicylate).[5] The present method therefore provides a simple direct route for the synthesis of hitherto unreported thiophenes in good yields (Table) through acylketene *O,S*-acetals having built-in alkoxy/aryloxy groups.

The probable mechanism of the formation of alkoxy/aryloxythiophenes **4a–k** is shown in Scheme 1.

Melting points were determined on a Thomas-Hoover capillary melting point apparatus and are uncorrected. IR spectra were obtained on a Perkin-Elmer 297 spectrophotometer, ^1H NMR spectra on a Varian EM-390 (90 MHz) spectrometer. Mass spectra were recorded on a Jeol JMS D-300 spectrometer. Elemental analysis were performed on a Heraeus CHN-O-Rapid Elemental Analyzer.

2-Alkoxy/Aryloxythiophenes; General Procedure:

To a well stirred suspension of Zn–Cu couple (4.0 g, 30 mmol) in dry Et_2O (25 mL), under N_2 atmosphere, a small crystal of I_2 and CH_2I_2 (6.70 g, 25 mmol) were added and the mixture was refluxed for 45 min. A solution of the appropriate acylketene *O,S*-acetal (10 mmol) in dry THF (15 mL) was added to the mixture which was further refluxed with stirring for 5–8 h (monitored by TLC). The solvent was removed under reduced pressure and the residue was diluted with $CHCl_3$ (150 mL) and H_2O (200 mL). The extract was filtered to remove metal-based residues and the residue was washed with $CHCl_3$ (2 × 25 mL). The $CHCl_3$ layer was separated and washed with sat. aq NH_4Cl (2 × 50 mL), H_2O (2 × 100 mL), dried (Na_2SO_4) and concentrated to give the crude thiophenes which were purified by column chromatography over silica gel using hexane as eluent.

Table. 2-Alkoxy/Aryloxythiophenes **4a–k** and **7** Prepared

Product[a]	Yield (%)	mp (°C)	IR (CCl_4/KBr) ν_{max} (cm^{-1})	^1H NMR ($CDCl_3$/TMS) δ, J (Hz)	MS (70 eV) m/z (%)
4a	66	40–41	1620, 1600, 1507, 1465, 1218	3.84 (s, 3H, OCH_3), 6.55 (d, 1H, H-3, $J = 1.5$), 6.68 (d, 1H, H-5, $J = 1.5$), 7.22–7.69 (m, 5H_{arom})	190 (M^+, 19)
4b	72	viscous liquid	1600, 1580, 1549, 1502, 1465, 1388	1.37 (t,, 3H, $OCH_2C\underline{H}_3$, $J = 6$), 4.09 (q, 2H, $OC\underline{H}_2CH_3$, $J = 6$), 6.45 (d, 1H, H-3, $J = 1.5$), 6.63 (d, 1H, H-5, $J = 1.5$), 7.12–7.64 (m, 5H_{arom})	204 (M^+, 62), 176 (100)
4c	58	35–36	1562, 1520, 1481, 1203	1.97 (t, 3H, $OCH_2CH_2C\underline{H}_3$, $J = 6$), 1.75 (sext, 2H, $OCH_2C\underline{H}_3$, $J = 6$), 3.98 (t, 2H, $OC\underline{H}_2CH_2CH_3$, $J = 6$), 6.54 (d, 1H, H-3, $J = 1.5$), 6.67 (d, 1H, H-5, $J = 1.5$), 7.23–7.67 (m, 5H_{arom})	218 (M^+, 39), 176 (100)
4d	72	43–44	1622, 1602, 1570, 1522, 1481, 1396	0.88 [t, 3H, $OCH_2(CH_2)_2C\underline{H}_3$, $J = 7$], 1.17–1.88 [m, 4H, $OCH_2(C\underline{H}_2)_2CH_3$], 4.02 [t, 2H, $OC\underline{H}_2(CH_2)_2CH_3$, $J = 7$], 6.58 (d, 1H, H-3, $J = 1.5$), 6.69 (d, 1H, H-5, $J = 1.5$), 7.27–7.79 (m, 5H_{arom})	232 (M^+, 24), 176 (100)
4e	59	34–35	1559, 1518, 1478, 1196	0.89 [br t, 3H, $OCH_2(CH_2)_{10}C\underline{H}_3$, $J = 6$], 1.13–1.41 [m, 20H, $OCH_2(C\underline{H}_2)_{10}CH_3$], 4.10 [t, 2H, $OC\underline{H}_2(CH_2)_{10}CH_3$, $J = 6$], 6.62 (d, 1H, H-3, $J = 1.5$), 6.76 (d, 1H, H-5, $J = 1.5$), 7.31–7.75 (m, 5H_{arom})	344 (M^+, 43), 176 (100)
4f	32	82–83	1562, 1518, 1472, 1400, 1201	5.08 (s, 2H, $C\underline{H}_2C_6H_5$), 6.62 (d, 1H, H-3, $J = 1.5$), 6.70 (d, 1H, H-5, $J = 1.5$), 7.19–7.73 (m, 5H_{arom})	266 (M^+, 14), 175 (15), 91 (100)
4g	66	97–98	1619, 1608, 1583, 1486, 1255, 1214	3.78 (s, 3H, OCH_3), 6.76–7.0 (m, 4H, H-3, H-5 and H_{arom}), 7.03–7.57 (m, 7H_{arom})	283 (M^+, 100), 206 (46)
4h	62	46–47	1598, 1562, 1484, 1238	6.80–6.93 (m, 2H, H-3 and H-5), 7.07–7.63 (m, 9H_{arom})	286, 288 (M^+, 100, 30), 252 (51)
4i	76	149	1621, 1530, 1478, 1310, 1276	3.80 (s, 3H, OCH_3), 6.73–7.0 (m, 4H, H-3, H-5 and H_{arom}), 7.33–7.59 (m, 6H_{arom}), 7.64–7.83 (m, 3H_{arom})	332 (M^+, 100)
4j	78	59–60	1748, 1626, 1508, 1472, 1320, 1240	3.88 (s, 3H, OCH_3), 6.82–6.97 (m, 2H, H-3 and H-5), 7.10–7.63 (m, 8H_{arom}), 7.96 (d, 1H_{arom}, $J = 9$)	310 (M^+, 100), 279 (9), 190 (55)
4k	84	69	1721, 1602, 1500, 1482, 1442, 1298, 1217	3.78 (s, 3H, OCH_3), 3.82 (s, 3H, CH_3OCO), 6.62–6.98 (m, 4H, H-3, H-5 and H_{arom}), 7.02–7.24 (m, 2H_{arom}), 7.26–7.53 (m, 3H_{arom}), 7.73–7.96 (s, 1H_{arom})	340 (M^+, 17), 399 (100), 205 (20), 135 (13)
7	34	viscous liquid	1620, 1510, 1238	2.51–2.98 (m, 4H, CH_2), 6.97–7.19 (m, 3H, H-5 and H_{arom}), 7.20–7.49 (m, 6H_{arom}), 7.68 (d, 1H_{arom}, $J = 4.5$)	278 (M^+, 50), 201 (4), 185 (14)

[a] New compounds, satisfactory microanalyses obtained: C ± 0.29, H ± 0.23.

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