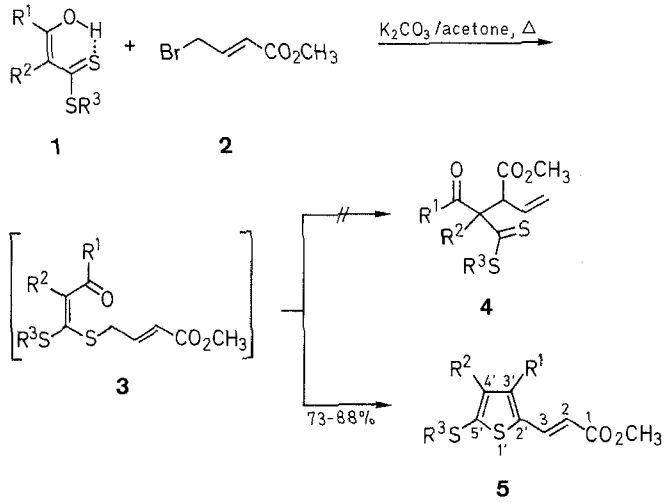
A Novel Route to Methyl 3-(3,4-Disubstituted 5-alkylthio/amino-2-thienyl) propenoates[1]

A. Datta, H. Ila,* H. Junjappa*

Department of Chemistry, North-Eastern Hill University, Shillong 793003, Meghalaya, India

The 3-oxodithioesters **1** and 3-oxothioamides **6** are shown to undergo base catalyzed *S*-alkylation with methyl 4-bromocrotonate followed by intramolecular condensation to give the corresponding methyl 3-(3,4-disubstituted 5-alkylthio/amino-2-thienyl) propenoates **5** and **7** in good yields.

We have recently reported that the aroyl- and acyl(allyl/2-methyl-2-propenyl)ketene dithioacetals undergo facile transformation to the corresponding α-benzylidene and alkylidene-γ-butyrolactones through the intermediacy of α,β-unsaturated esters.[2] The aroyl- and acyl(allyl)ketene dithioacetals were conveniently prepared in a one-pot reaction by *C*-allylation of 3-oxodithioesters via spontaneous 3,3-sigmatropic rearrangement of the intermediate aroyl- and acylketene *S*-allyl dithioacetal to give the 2-allyl-3-oxodithioester followed by its *S*-methylation.[2,3]



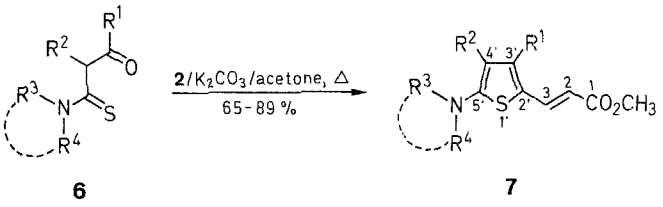
1 2 3 4 5

1–5	R^1	R^2	R^3
a	4-ClC_6H_4	H	CH_3
b	4-$CH_3OC_6H_4$	H	CH_3
c	2-naphthyl	H	CH_3
d	2-thienyl	H	CH_3
e	2-furyl	H	CH_3
f	4-ClC_6H_4	H	C_2H_5
g	CH_3	H	CH_3
h	C_6H_5	CH_3	CH_3

Scheme A

In continuation of these studies, 3-oxodithioesters **1** were reacted with methyl 4-bromocrotonate with a view to synthesize ultimately aroyl- and acyl(1-methoxycarbonyl-2-propenyl) ketene dithioacetals through the intermediate 3-oxodithioesters **4** (Scheme A). However, the expected 3,3-sigmatropic rearrangement was not observed, and the products isolated were characterized as methyl 3-(3,4-disubstituted 5-alkylthio-2-thienyl)propenoates **5**, apparently formed by intramolecular aldol condensation of the intermediate mixed dithioacetals **3**. The results of these studies along with the extension to a similar transformation of 3-oxothioamides **6** to give the corresponding methyl 3-(3,4-substituted 5-amino-2-thienyl)propenoates **7** are reported in this communication.

A mixture of **1a**, methyl 4-bromocrotonate in acetone and anhydrous potassium carbonate was refluxed for 5–6 hours. The bright yellow solid obtained after work up was characterized as methyl 3-[3-(4-chlorophenyl)-5-methylthio-2-thienyl] propenoate (**5a**) (88% yield) on the basis of spectral and analytical data. The reaction was found to be general, and the corresponding methyl 3-(3,4-substituted-5-alkylthio-2-thienyl)propenoates **5b–h** were obtained in 73–84% overall yields (Scheme **A**). The reaction was further extended to 3-oxothioamides **6a–h**, which, under similar reaction conditions, afforded the corresponding methyl 3-(3,4-substituted 5-amino-2-thienyl)propenoates **7a–h** in 65–88% overall yields (Scheme **B**).



6 7

6, 7	R^1	R^2	R^3 R^4
a	C_6H_5	H	$-(CH_2)_4-$
b	4-ClC_6H_4	H	$-(CH_2)_4-$
c	4-ClC_6H_4	H	$-(CH_2)_2O(CH_2)_2-$
d	C_6H_5	H	C_6H_5 CH_3
e	C_6H_5	CH_3	$-(CH_2)_2O(CH_2)_2-$
f	CH_3	H	$-(CH_2)_4-$
g	2-furyl	H	$-(CH_2)_4-$
h			$-(CH_2)_5-$

Scheme B

The overall transformation is similar to general thiophene synthesis involving *S*-alkylation of dithiotic acids (or their salts) derived from active methylene ketones, nitriles or esters with α-halocompounds (XCH_2Y; Y=CN, COR, CO_2R) followed by intramolecular cyclization.[4,5] However, the present reaction provides a direct one-step entry to a variety of hitherto unknown substituted 3-(2-thienyl)propenoic esters by intramolecular condensation reaction. The known unsubstituted 3-(2-thienyl)propenoic ester is prepared[6] from thiophene 2-carboxaldehyde by classical condensation or Wittig reaction.

The starting 3-oxodithioesters **1** and 3-oxothioamides **6** were prepared according to the earlier reported procedures.[7,8]

Methyl 3-[3,4-Disubstituted 5-alkylthio-2-thienyl]propenoates 5a–h and Methyl 3-[3,4-Disubstituted 5-amino-2-thienyl]propenoates 7a–h; General Procedure:

A suspension of **1** or **6** (5 mmol) and anhydrous K_2CO_3 (5.0 g) in dry acetone (30 mL) is refluxed with stirring for 2 h. The mixture is then cooled and methyl 4-bromocrotonate (**2**; 0.90 g, 5 mmol) is added

Table. Compounds **5** and **7** Prepared

Product	Yield (%)	mp[a] (°C)	Molecular Formula[b]	IR (KBr)[c] ν (cm^{-1})	^{1}H-NMR ($CDCl_3$/TMS)[d] δ, J (Hz)	MS (70 eV)[e] m/z M^+ (%)
5a	88	99–100	$C_{15}H_{13}ClO_2S_2$ (324.9)	1696, 1609	2.58 (s, 3H, SCH_3); 3.71 (s, 3H, OCH_3); 6.13 (d, 1H, J = 15, H-2); 6.92 (s, 1H, H-4′); 7.21–7.48 (m, 4H$_{arom}$); 7.67 (d, 1H, J = 15, H-3)	326 (45), 324 (89)
5b	80	94	$C_{16}H_{16}O_3S_2$ (320.4)	1711, 1607	2.55 (s, 3H, SCH_3); 3.73 (s, 3H, OCH_3); 3.82 (s, 3H, OCH_3); 6.12 (d, 1H, J = 15, H-2); 6.93 (s, 1H, H-4′); 6.40–7.35 (m, 4H$_{arom}$); 7.73 (d, 1H, J = 15, H-3)	320 (98)
5c	78	82	$C_{19}H_{16}O_2S_2$ (340.4)	1703, 1610	2.52 (s, 3H, SCH_3); 3.66 (s, 3H, OCH_3); 6.09 (d, 1H, J = 15, H-2); 7.01 (s, 1H, H-4′); 7.30–7.92 (m, 8H$_{arom}$, H-3)	340 (45)
5d	81	98	$C_{13}H_{12}O_2S_3$ (296.4)	1709, 1610	2.57 (s, 3H, SCH_3); 3.75 (s, 3H, OCH_3); 6.13 (d, 1H, J = 15, H-2); 7.01 (s, 1H, H-4′); 7.09–7.45 (m, 3H$_{thienyl}$); 7.97 (d, 1H, J = 15, H-3)	296 (51)
5e	79	81	$C_{13}H_{12}O_3S_2$ (280.3)	1709, 1600	2.55 (s, 3H, SCH_3); 3.79 (s, 3H, OCH_3); 6.11 (d, 1H, J = 15, H-2); 6.41–6.60 (m, 2H$_{furyl}$); 7.09 (s, 1H, H-4′); 7.53 (m, 1H$_{furyl}$); 8.29 (d, 1H, J = 15, H-3)	280 (100)
5f	84	70	$C_{16}H_{15}ClO_2S_2$ (338.9)	1712, 1615	1.32 (t, 3H, J = 7, CH_3CH_2S); 2.88 (q, 2H, J = 7, CH_3CH_2S); 3.66 (s, 3H, OCH_3); 6.05 (d, 1H, J = 15, H-2); 6.95 (s, 1H, H-4′); 7.15–7.42 (m, 4H$_{arom}$); 7.55 (d, 1H, J = 15, H-3)	340 (41), 338 (95)
5g	76	69	$C_{10}H_{12}O_2S_2$ (228.3)	1710, 1613	2.22 (s, 3H, CH_3); 2.40 (s, 3H, SCH_3); 3.64 (s, 3H, OCH_3); 5.85 (d, 1H, J = 15, H-2); 6.66 (s, 1H, H-4′); 7.60 (d, 1H, J = 15, H-3)	228 (100)
5h	73	68	$C_{16}H_{16}O_2S_2$ (304.4)	1710, 1611	2.05 (s, 3H, CH_3); 2.49 (s, 3H, SCH_3); 3.61 (s, 3H, OCH_3); 5.92 (d, 1H, J = 15, H-2); 6.96–7.45 (m, 6H$_{arom}$, H-3)	304 (100)
7a	65	99	$C_{18}H_{19}NO_2S$ (313.4)	1707, 1606	1.90–2.10 (m, 4H, CH_2); 3.08–3.43 (m, 4H, NCH_2); 3.68 (s, 3H, OCH_3); 5.72 (s, 1H, H-4′); 5.75 (d, 1H, J = 15, H-2); 7.33 (br s, 5H$_{arom}$); 7.64 (d, 1H, J = 15, H-3)	–
7b	69	127	$C_{18}H_{18}ClNO_2S$ (347.9)	1690, 1599, 1524	1.98–2.15 (m, 4H, CH_2); 3.07–3.50 (m, 4H, NCH_2); 3.60 (s, 3H, OCH_3); 5.58 (s, 1H, H-4′); 5.65 (d, 1H, J = 7, H-2); 7.29 (br s, 4H$_{arom}$); 7.52 (d, 1H, J = 15, H-3)	–
7c	70	152	$C_{18}H_{18}ClNO_3S$ (363.9)	1688, 1600, 1521	3.13–3.34 (m, 4H, NCH_2); 3.70 (s, 3H, OCH_3); 3.65–3.90 (m, 4H, OCH_2); 5.63 (d, 1H, J = 15, H-2); 6.03 (s, 1H, H-4′); 7.20–7.51 (dd, 4H$_{arom}$); 7.66 (d, 1H, J = 15, H-3)	363 (48), 365 (85)
7d	82	168	$C_{21}H_{19}NO_2S$ (349.4)	1689, 1596	3.40 (s, 3H, NCH_3); 3.66 (s, 3H, OCH_3); 5.82 (d, 1H, J = 15, H-2); 6.13 (s, 1H, H-4′); 7.05–7.43 (m, 10H$_{arom}$); 7.73 (d, 1H, J = 15, H-3)	349 (100)
7e	68	132	$C_{19}H_{21}NO_3S$ (343.4)	1703, 1610	1.90 (s, 3H, CH_3); 2.85–3.05 (m, 4H, NCH_2); 3.64 (s, 3H, OCH_3); 3.58–3.85 (m, 4H, OCH_2); 5.97 (d, 1H, J = 15, H-2); 7.08–7.45 (m, 15H$_{arom}$); 7.46 (d, 1H, J = 15, H-3)	343 (30)
7f	70	89	$C_{13}H_{17}NO_2S$ (251.3)	1704, 1605	1.90–2.12 (m, 4H, CH_2); 2.22 (s, 3H, CH_3); 3.12–3.42 (m, 4H, CH_2); 3.62 (s, 3H, OCH_3); 5.42 (s, 1H, H-4′); 5.71 (d, 1H, J = 15, H-2); 7.60 (d, 1H, J = 15, H-3)	251 (94)
7g	77	67	$C_{16}H_{17}NO_3S$ (303.3)	1689, 1596	1.87–2.15 (m, 4H, CH_2); 3.12–3.42 (m, 4H, NCH_2); 3.69 (s, 3H, OCH_3); 5.69 (d, 1H, J = 15, H-2); 5.79 (s, 1H, H-4′); 6.32–6.53 (m, 2H$_{furyl}$); 7.40–7.50 (m, 1H$_{furyl}$); 8.09 (d, 1H, J = 15, H-3)	–
7h	65	134	$C_{21}H_{23}NO_2S$ (353.40)	1699, 1598	1.45–1.86 (m, 6H, piperidine CH_2); 2.48–2.85 (m, 4H, ring CH_2); 2.90–3.10 (m, 4H, NCH_2); 3.78 (s, 3H, OCH_3); 6.10 (d, 1H, J = 15, H-2); 7.13–7.40 (m, 3H$_{arom}$); 7.50–7.67 (m, 1H$_{arom}$); 8.12 (d, 1H, J = 15, H-3)	353 (100)

[a] Recorded on Thomas Hoover capillary melting point apparatus.
[b] Satisfactory microanalyses obtained: C ±0.29, H ±0.31, N ±0.28.
[c] Recorded on Perkin-Elmer 983 spectrophotometer.
[d] Recorded on Varian EM 390 Spectrometer.
[e] Recorded on Jeol JMS-D 300 Spectrometer.

dropwise followed by further refluxing with stirring for 6 h. It is then filtered, the residue washed with acetone (25 mL), and the solvent evaporated from the combined filtrate. The crude products thus obtained are purified by column chromatography [silica gel (for **5a–h**) or neutral alumina (for **7a–h**) column using hexane/EtOAc as eluent (20:1)] and recrystallization from $CHCl_3$/hexane (Table).

A. D. thanks CSIR New Delhi for a Senior Research Fellowship. Financial assistance from UGC, New Delhi under the COSSIST program is also acknowledged.

Received: 14 January 1988

(1) Part 74 of the series on Polarized Ketene *S,S*- and *S,N*-Acetals; Part 73: Chakrasali, R.T., Ila, H., Junjappa, H. *Synthesis*, in press.
(2) Datta, A., Ila, H., Junjappa, H. *Tetrahedron* **1987**, *43*, 5367.
(3) Apparao, S., Bhattacharji, S.S., Ila, H., Junjappa, H. *J. Chem. Soc. Perkin Trans. 1* **1985**, 641.
(4) Gronowitz, S., in: *Thiophene and its Derivatives*, Part I, Gronowitz, S. (ed.), John Wiley & Sons, New York, 1985, p. 66–67, and references cited therein.
(5) Dieter, R.K. *Tetrahedron* **1986**, *42*, 3074, and references cited therein.
(6) King, W.J., Nord, F.F. *J. Org. Chem.* **1949**, *14*, 405.
Miller, R.E., Nord, F.F. *J. Org. Chem.* **1950**, *15*, 89.
Schuetz, R.D., Houff, W.H. *J. Am. Chem. Soc.* **1955**, *77*, 1836.
(7) Singh, G., Bhattacharji, S.S., Ila, H., Junjappa, H. *Synthesis* **1982**, 693.
(8) Vishwakarma, J.N., Apparao, S., Ila, H., Junjappa, H. *Indian J. Chem. Sect. B* **1985**, *24*, 466.