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A Simple and Direct Method for Converting Thioamides into Thioesters

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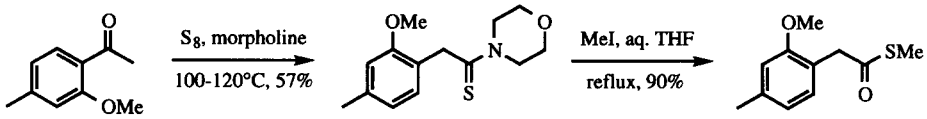
Abstract: Thioamides may be transformed into thioesters through the simple expedient of warming them in an aqueous THF solution containing an alkylating agent. Reactions proceed in high yield and are amenable to multi-gram scale. © 1999 Elsevier Science Ltd. All rights reserved.

Keywords: Thioester, Thioamide, Alkylation.

Thioesters are activated carboxylic acid derivatives which exhibit acylating properties similar to those of acid anhydrides.[1] As such, they have found widespread application in synthetic chemistry as precursors to aldehydes,[2] ketones,[3] acids,[4] esters,[5] lactones,[6] amides,[7] lactams and related heterocycles.[8] Most commonly prepared by the reactions of thiols or their metal salts with acid halides, anhydrides and esters,[1,2] their ability to form stable enolate anions makes them particularly versatile intermediates.[9] In this paper we describe a new route to thioesters from thioamides that is mild, inexpensive and experimentally is easy to perform.

The method was devised to address a need for a reliable, multi-gram synthesis of thioester **3**.[10] As thioamide **2** can be prepared from acetophenone **1** using a Kindler modified Willgerodt reaction, it seemed reasonable to use this as a starting point.[11] Our intention had been to hydrolyse **2** to the corresponding carboxylic acid and then proceed to **3** *via* the acid chloride.[1] However, we found that warming an aqueous THF solution of **2** with methyl iodide gave thioester **3** directly and in high yield.[12]



1 **2** **3**

To explore the scope of the method for preparing thioesters, we decided to seek some further examples (see Table). We can report that the reaction proceeds efficiently with aliphatic and aromatic thioamides and that alkyl iodides, dialkyl sulfates and activated alkyl bromides provide suitable alkylating agents. Alkyl bromides and activated alkyl chlorides also give the reaction but at a much slower rate. Reaction conditions are mild and tolerant of aryl ethers and acetals. When volatile halides are employed, products of ~95% purity can be

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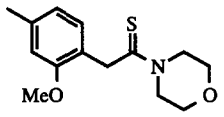
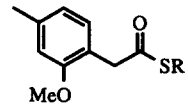
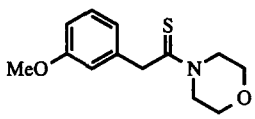
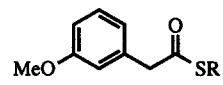
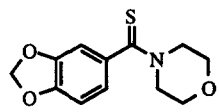
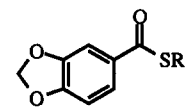
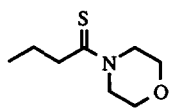
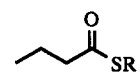
obtained in near quantitative yield after a simple acid wash. (Yields given in the Table refer to samples purified by recrystallisation or chromatography as detailed in the experimental section).

Table: Conversion of Thioamides to Thioesters *via* Alkylation in Aqueous THF at reflux.

Substrate	Alkylating Agent	Reaction Time	Product	R=	Yield† %
 **2**	MeI	18 h		Me	90
	Me_2SO_4	15 h		Me	73
	EtI	44 h		Et	76
	EtBr	45 h		Et	20 (75)
	allyl-Br	20 h		allyl	67
	BnBr	20 h		Bn	82
	$Ph(CH_2)_2Br$	72 h		$Ph(CH_2)_2$	36 (38)
 **4**	MeI	15 h		Me	85
	Me_2SO_4	18 h		Me	72
	EtI	48 h		Et	69
	allyl-Br	24 h		allyl	79
	BnBr	15 h		Bn	66
 **5**	MeI	18 h		Me	77
	Me_2SO_4	17 h		Me	67
	EtI	17 h		Et	96
	allyl-Br	18 h		allyl	94
	allyl-Cl	5 d		allyl	11 (84)
	BnBr	15 h		Bn	81
 **6**	Me_2SO_4	36 h		Me	51
	EtI	72 h		Et	85
	allyl-Br	48 h		allyl	81

† Figures in parentheses refer to % yield of recovered starting material

In conclusion, we have shown that thioamides may be transformed into thioesters through the simple expedient of warming them in an aqueous THF solution containing an alkylating agent. Reactions proceed in high yield *via in situ S*-alkylation and hydrolysis.[12] They are amenable to multi-gram scale and, if volatile alkyl halides are employed, will deliver products of ~95% purity without the need for chromatographic purification.

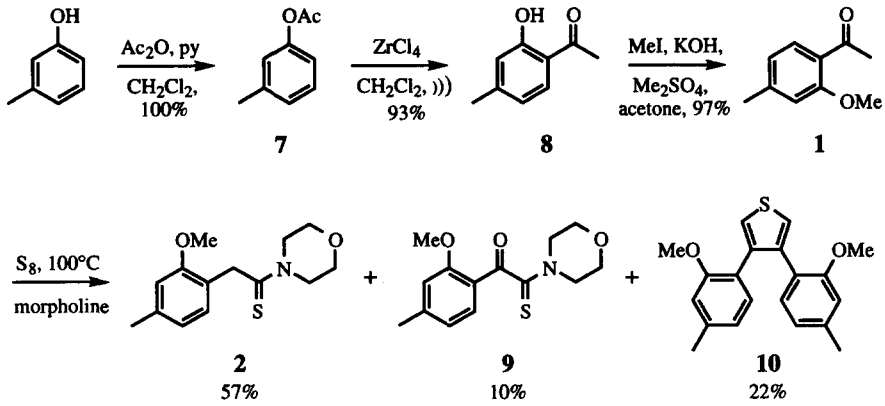
Acknowledgements

The authors thank GlaxoWellcome for their financial support, the EPSRC for the provision of mass spectrometry and database services and Professor John Mellor for his advice and interest in the work.

EXPERIMENTAL SECTION[13]

PREPARATION OF STARTING MATERIALS

2-[4-Methyl-2-(methyloxy)phenyl]-1-tetrahydro-2*H*-1,4-oxazin-4-yl-1-ethanthione **2**



m-Cresyl acetate **7** was prepared in quantitative yield from *m*-cresol as described by Julia and Chastrette.[14]

2-Hydroxy-4-methyl-acetophenone **8** was prepared as described by Harrowven and Dainty.[15] Thus, to a solution of *m*-cresyl acetate **7** (27.9 g, 186 mmol) in dichloromethane (400 mL) was added $ZrCl_4$ (86.7 g, 372 mmol). The reaction vessel was partially immersed into the water filled bath of a Branson 1200, Bransonic® ultrasound cleaner and irradiated for 24 h (CAUTION: always switch off ultrasonic devices prior to any analysis). The resulting suspension was poured into ice/water (500 mL) and extracted with dichloromethane (4 x 80 mL). The combined organic phases were washed with water (100 mL) and brine (100 mL), dried ($MgSO_4$), evaporated at reduced pressure and purified by column chromatography (silica, 0 to 5% ether in petrol) to give **8** (26.0 g, 173 mmol, 93%) as a pale yellow oil. Spectral and physical characteristics were in accord with previous reports.[16]

2-Methoxy-4-methyl-acetophenone **1** was prepared using a procedure described by Jurd.[17] Thus, a solution of acetophenone **8**, powdered potassium hydroxide (9.1 g, 162 mmol) and dimethyl sulfate (18.7 g, 148 mmol) (21.2 g, 141 mmol) in acetone (400 mL) was stirred at ambient temperature for 15 h then partitioned between brine (300 mL) and ether (100 mL). The aqueous phase was extracted with ether (3 x 100 mL) and the combined organic phases dried ($MgSO_4$), filtered and concentrated *in vacuo* to give a viscous oil. Purification by column chromatography (silica, petrol) gave **1** as a yellow crystalline solid (22.4 g, 137 mmol, 97%). A sample (1.00g) was recrystallised from pentane to give colourless needles (0.88g), **m.p.** 35-37°C: lit. 35-37°C.[14,18] Spectral and physical characteristics were in accord with previous reports.[14,18]

2-[4-Methyl-2-methoxyphenyl]-1-tetrahydro-2*H*-1,4-oxazin-4-yl-1-ethanthione **2** was prepared using a procedure described by Carmack and Spielman.[11] Thus, a mixture of acetophenone **1** (23.3 g, 142 mmol), sulfur (6.8 g, 213 mmol) and morpholine (18.5 g, 213 mmol) was stirred at 100-120°C for 24 h then allowed to cool to ambient temperature. The resulting red oil was purified by chromatography (silica, 10-50% ether/hexanes) to give firstly 3,4-di-[4-methyl-2-methoxyphenyl]-thiophene **10** (5.01 g, 15.4 mmol, 22% after recrystallisation from ether/pentane) as colourless needles; **m.p.** 84-86°C; **IR** (neat) υ_{max} 2934m, 1608m, 1570m, 1537w, 1510s, 1278s, 1258m, 1165m, 1133m, 1036s, 800s cm^{-1}; **UV** (MeOH) λ_{max} (ε) 343 (22000), 308 inf (10000), 235 (14500) nm; **^{1}H NMR** δ_H (300 MHz, $CDCl_3$) 7.58 (2H, d, *J* 7.5 Hz, 2 x Ar*H*), 7.46 (2H, s, 2 x thiophene-*H*), 6.86 (2H, d, *J* 7.5 Hz, 2 x Ar*H*), 6.83 (2H, s, 2 x Ar*H*), 3.95 (6H, s, 2 x OCH_3), 2.41 (6H, s, 2 x $ArCH_3$); **^{13}C NMR** δ_C (75 MHz, $CDCl_3$) 155.8 (2 x *C* (Ar)), 139.1 (2 x *C* (Ar)), 138.5 (2 x *C* (thiophene)), 128.4 (2 x *C*H (Ar)), 125.4 (2 x *C*H (thiophene)), 121.8 (2 x *C*H (Ar)), 121.1 (2 x *C* (Ar)), 112.7 (2 x *C*H (Ar)), 55.7 (2 x OCH_3), 21.7 (2 x $ArCH_3$); **HRMS** (EI) $[M]^+$ found: 324.1182; $C_{20}H_{20}O_2S$ requires 324.1184; **LRMS** (APCI+ve) 325 ($[MH]^+$, 100%), 324

(M^+, 40%); then the title thioamide **2** (21.6 g, 81.5 mmol, 57% after recrystallisation from ethyl acetate/pentane) as colourless crystals; **m.p.** 62-64°C; **CHN** Found: C, 63.2; H, 6.9; N, 5.3; S, 11.7; $C_{14}H_{19}NO_2S$ requires C, 63.4; H, 7.2; N, 5.3; S, 12.1; **IR** (neat) υ_{max} 2920m, 1612m, 1581m, 1506s, 1488s, 1463s, 1287s, 1267s, 1168w, 1032s, 963m, 816w cm^{-1}; **UV** (MeOH) λ_{max} (ε) 279 (13500) nm; **^{1}H NMR** δ_H (300 MHz, $CDCl_3$) 7.29 (1H, d, *J* 7.7 Hz, Ar*H*), 6.76 (1H, d, *J* 7.7 Hz, Ar*H*), 6.69 (1H, s, Ar*H*), 4.37 (2H, app t, *J* 4.9 Hz, OCH_2), 4.24 (2H, s, $ArCH_2$), 3.83 (3H, s, OCH_3), 3.74 (2H, app t, *J* 4.9 Hz, OCH_2), 3.74 (2H, app t, *J* 4.7 Hz, NCH_2), 3.42 (2H, app t, *J* 4.7 Hz, NCH_2), 2.36 (3H, s, $ArCH_3$); **^{13}C NMR** δ_C (75 MHz, $CDCl_3$) 201.7 (*C*=S), 155.7 (*C* (Ar)), 138.5 (*C* (Ar)), 128.5 (*C*H (Ar)), 121.8 (*C*H (Ar)), 121.1 (*C* (Ar)), 111.5 (*C*H (Ar)), 66.6 (OCH_2), 66.4 (OCH_2), 55.6 (OCH_3), 50.8 (NCH_2), 50.3 (NCH_2), 43.4 ($ArCH_2$), 21.7 ($ArCH_3$); **LRMS** (APCI+ve), 266 ($[MH]^+$, 100%); and finally (1-[4-Methyl-2-methoxyphenyl]-2-[tetrahydro-2*H*-1,4-oxazin-4-yl]-2-thioxo-1-ethanone **9** (4.00 g, 14.3 mmol, 10% after recrystallisation from ethyl acetate/pentane) as fine yellow needles; **m.p.** 108-110°C; **CHN** Found: C, 60.2; H, 5.9; N, 5.1; S, 11.4; $C_{14}H_{17}NO_3S$ requires C, 60.2; H, 6.1; N, 5.0; S, 11.5; **IR** (neat) υ_{max} 2857w, 1645s, 1605s, 1572w, 1509s, 1297m, 1276s, 1113s, 1064w, 954m, 806w cm^{-1}; **UV** (MeOH) λ_{max} (ε) 380 (900), 319 (7000), 266 (21000) nm; **^{1}H NMR** δ_H (300 MHz, $CDCl_3$) 7.87 (1H, d, *J* 7.9 Hz, Ar*H*), 6.89 (1H, d, *J* 7.9 Hz, Ar*H*), 6.78 (1H, s, Ar*H*), 4.24 (2H, app t, *J* 5.0 Hz, OCH_2), 3.88 (2H, app t, *J* 5.0 Hz, OCH_2), 3.85 (3H, s, OCH_3), 3.74 (2H, app t, *J* 4.8 Hz, NCH_2), 3.64 (2H, app t, *J* 4.8 Hz, NCH_2), 2.39 (3H, s, $ArCH_3$); **^{13}C NMR** δ_C (75 MHz, $CDCl_3$) 198.6 (*C*=S), 186.7 (*C*=O), 159.4 (*C* (Ar)), 147.4 (*C* (Ar)), 131.9 (*C*H (Ar)), 122.7 (*C*H (Ar)), 121.7 (*C* (Ar)), 113.3 (*C*H (Ar)), 66.4 (OCH_2), 66.1 (OCH_2), 56.2 (OCH_3), 51.8 (NCH_2), 47.0 (NCH_2), 22.3 ($ArCH_3$); **LRMS** (APCI+ve), 280 ($[MH]^+$, 50%) 165 (25%), 111 (100%).

2-[3-Methoxyphenyl]-1-tetrahydro-2*H*-1,4-oxazin-4-yl-1-ethanethione **4** was prepared as described by Schwenk and Bloch (with slight modification).[19] Thus, a mixture of 3-methoxyacetophenone (9.4 g, 8.6 mL, 62.6 mmol), sulfur (3.0 g, 94.0 mmol) and morpholine (8.17 g, 8.2 mL, 94.0 mmol) was stirred with heating to 90°C for 12 h. The resulting red oil was purified by chromatography (silica, 20-50% ether/petroleum ether) to afford a yellow solid (15.0g) which was recrystallised from ether to give thiomorpholide **4** (11.0 g, 44 mmol, 70%) as colourless, cubic crystals; **m.p.** 81-83°C (ether): lit. 82-84°C (solvent not reported);[19] **CHN** Found: C, 62.2; H, 6.7; N, 5.6; S, 12.8; $C_{13}H_{17}NO_2S$ requires C, 62.1; H, 6.8; N, 5.6; S, 12.8; **IR** (neat) υ_{max} 2957w, 2851w, 1600m, 1256m, 1146w, 1110s, 1034m, 958w, 869w cm^{-1}; **UV** (MeOH) λ_{max} (ε) 280 (12800) nm; **^{1}H NMR** δ_H (300 MHz, $CDCl_3$) 7.24 (1H, app t, *J* 7.8 Hz, Ar*H*), 6.90 (1H, s, Ar*H*), 6.88 (1H, d, *J* 7.8 Hz, Ar*H*), 6.79 (1H, dd, *J* 7.8, 1.5 Hz, Ar*H*), 4.35 (2H, app t, *J* 4.8 Hz, OCH_2), 4.32 (2H, s, $ArCH_2$), 3.80 (3H, s, OCH_3), 3.74 (2H, app t, *J* 4.8 Hz, OCH_2), 3.64 (2H, app t, *J* 5.1 Hz, NCH_2), 3.42 (2H, app t, *J* 5.0 Hz, NCH_2); **^{13}C NMR** δ_C (75 MHz, $CDCl_3$) 199.9 (*C*=S), 160.1 (*C* (Ar)), 137.4 (*C* (Ph)), 130.1 (*C*H (Ar)), 120.1 (*C*H (Ar)), 113.6 (*C*H (Ar)), 112.6 (*C*H (Ar)), 66.5 (OCH_2), 66.3 (OCH_2), 55.4 (OCH_3), 51.0 (NCH_2), 50.8 (NCH_2), 50.3 ($ArCH_2$); **LRMS** (APCI+ve), 252 ($[MH]^+$, 100%).

1,3-Benzodioxol-5-yl-[tetrahydro-2*H*-1,4-oxazin-4-yl]-methanethione **5** was prepared using a procedure described by Carayon-Gentil.[20] Thus, to a solution of piperonal (2.50 g, 16.7 mmol) in dry DMF (5 mL) and under nitrogen was added sulfur (0.80 g, 25.0 mmol) and morpholine (1.59 g, 1.60 mL, 18.3 mmol). The reaction mixture was heated at 55°C for 6 h then cooled. Water (50 mL) was added causing a yellow solid to precipitate. The solid was filtered, washed with petroleum ether and recrystallised from ethanol to give **5** (3.81 g, 15.2 mmol, 91%) as pale yellow crystals; **m.p.** 164-166°C (ethanol); **CHN** Found: C, 57.0; H, 5.0; N, 5.4; S, 12.6; $C_{12}H_{13}NO_3S$ requires C, 57.3; H, 5.2; N, 5.6; S, 12.8; **IR** (neat) υ_{max} 2966w, 2855w, 1604w, 1342w, 1291m, 1251s, 1112m, 1033s, 856w cm^{-1}; **UV** (MeOH) λ_{max} (ε) 287 (13500), 218 (14000) nm; **^{1}H NMR** δ_H (300 MHz, $CDCl_3$) 6.83 (1H, s, Ar*H*), 6.80 (2H, app s, 2 x Ar*H*), 5.98 (2H, s, OCH_2O), 4.40 (2H, br s, OCH_2), 3.87 (2H, br s, OCH_2), 3.66 (4H, br s, 2 x NCH_2); **^{13}C NMR** δ_C (75 MHz, $CDCl_3$) 200.7 (*C*=S), 148.5 (*C* (Ar)), 147.8 (*C* (Ar)), 136.4 (*C* (Ar)), 120.2 (*C*H (Ar)), 108.3 (*C*H (Ar)), 107.7 (*C*H (Ar)), 101.7 (OCH_2O), 66.9 (OCH_2), 66.7 (OCH_2), 52.9 (NCH_2), 50.1 (NCH_2); **LRMS** (APCI+ve), 252 ($[MH]^+$, 100%), 165 ($[MH\text{-morpholine}]^+$, 10%).

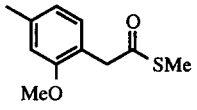
1-[Tetrahydro-2*H*-1,4-oxazin-4-yl]-butanethione **6** (cream solid; m.p. 41-43°C (ethanol). Lit. 40-42°C (ethanol);[21] Lit. 46°C (water)[22]) was prepared in 41% yield from 2-butanone, sulfur and morpholine as described by Viehe *et al.*[21] Physical and spectroscopic characteristics have been reported and were in good agreement.[21,22]

GENERAL PROCEDURE FOR EFFECTING THE CONVERSION OF THIOAMIDES INTO THIOESTERS

A stirred solution of thiomorpholide (1.89 mmol) and alkyl halide (4.47 mmol) in THF (10 mL) and water (1 mL) was refluxed for 18 h. The reaction mixture was then cooled to ambient temperature and partitioned between water (5 mL) and ether (5 mL). The aqueous layer was extracted into ether (3 x 5 mL), the combined organic phases were washed with saturated aqueous sodium thiosulfate (10 mL) and brine (20 mL) then dried ($MgSO_4$), filtered and concentrated *in vacuo*. Purification by column chromatography and/or recrystallisation afforded the thioester.

COMPOUNDS PREPARED USING THE ABOVE PROCEDURE

Methyl 2-[4-methyl-2-methoxyphenyl]ethanethioate

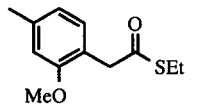


3

2 (20.0 g, 75.4 mmol), MeI (26.8 g, 189 mmol), THF (180 mL), water (20 mL), 18 h. Purification by column chromatography (silica, 0 to 5% ether in petrol) gave thioester **3** (14.2 g, 67.5 mmol, 90%). Alternatively: **2** (0.50 g, 1.88 mmol), Me_2SO_4 (0.60 g, 4.75 mmol), THF (9 mL), water (1 mL), 15 h, gave thioester **3** (0.29 g, 1.38 mmol, 73%) after purification by column chromatography.

Pale yellow oil; **IR** (neat) υ_{max} 3002w, 1688s, 1613w, 1583w, 1509m, 1318w, 1270m, 1039m, 933w, 799w cm^{-1}; **UV** (MeOH) λ_{max} (ε) 278 (3000), 223 (10000) nm; **^{1}H NMR** δ_H (300 MHz, $CDCl_3$) 7.10 (1H, d, *J* 7.4 Hz, Ar*H*), 6.77 (1H, d, *J* 7.4 Hz, Ar*H*), 6.73 (1H, s, Ar*H*), 3.83 (5H, s, ArCH_2 & OCH_3), 2.37 (3H, s, ArCH_3), 2.27 (3H, s, SCH_3); **^{13}C NMR** δ_C (75 MHz, $CDCl_3$) 199.1 (*C*=O), 157.8 (*C* (Ar)), 139.4 (*C* (Ar)), 131.4 (*C*H (Ar)), 121.3 (*C*H (Ar)), 119.5 (*C* (Ar)), 111.8 (*C*H (Ar)), 55.6 (OCH_3), 44.7 (ArCH_2), 21.8 (ArCH_3), 11.9 (SCH_3); **HRMS** (EI) $[M]^+$ found: 210.0724; $C_{11}H_{14}O_2S$ requires 210.0715; **LRMS** (APCI+ve), 211 ($[MH]^+$, 80%), 210 ($[M]^+$, 60%), 135 ($[M\text{-}CH_3SCO]^+$, 100%).

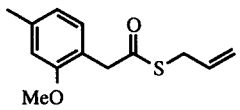
Ethyl 2-[4-methyl-2-methoxyphenyl]ethanethioate



2 (0.50 g, 1.88 mmol), EtI (0.67 g, 4.29 mmol), THF (10 mL), water (1 mL), 44 h. Purification by column chromatography (silica, 0 to 5% ether in petrol) gave thioester (0.32 g, 1.43 mmol, 76%).

Colourless oil; **IR** (neat) υ_{max} 2966m, 2872w, 1682s, 1614m, 1584m, 1509s, 1270s, 1040s, 933m, 717w cm^{-1}; **UV** (MeOH) λ_{max} (ε) 278 (2500), 223 (9500) nm; **^{1}H NMR** δ_H (300 MHz, $CDCl_3$) 7.09 (1H, d, *J* 7.5 Hz, Ar*H*), 6.77 (1H, d, *J* 7.5 Hz, Ar*H*), 6.72 (1H, s, Ar*H*), 3.83 (3H, s, OCH_3), 3.80 (2H, s, ArCH_2), 2.85 (2H, q, *J* 7.5 Hz, SCH_2), 2.37 (3H, s, ArCH_3), 1.23 (3H, t, *J* 7.5 Hz, SCH_2CH_3); **^{13}C NMR** δ_C (75 MHz, $CDCl_3$) 198.8 (*C*=O), 157.7 (*C* (Ar)), 139.3 (*C* (Ar)), 131.3 (*C*H (Ar)), 121.3 (*C*H (Ar)), 119.6 (*C* (Ar)), 111.8 (*C*H (Ar)), 55.6 (OCH_3), 44.9 (ArCH_2), 23.6 (SCH_2), 21.8 (ArCH_3), 14.8 (CH_2CH_3); **HRMS** (EI) $[M]^+$ found: 224.0869; $C_{12}H_{16}O_2S$ requires 224.0871; **LRMS** (APCI+ve), 225 ($[MH]^+$, 75%), 224 ($[M]^+$, 60%), 135 ($[M\text{-}CH_3CH_2SCO]^+$, 55%), 101 (100%).

Allyl 2-[4-methyl-2-methoxyphenyl]ethanethioate

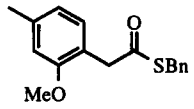


2 (0.50 g, 1.88 mmol), Allyl-Br (0.57 g, 4.71 mmol), THF (10 mL), water (1 mL), 20 h. Purification by column chromatography (silica, 0 to 5% ether in petrol) gave thioester (0.30 g, 1.27 mmol, 67%).

Colourless oil; **IR** (neat) υ_{max} 3007w, 1687s, 1639w, 1613w, 1582w, 1508m, 1269s, 1184m, 1040s, 923m, 798w cm^{-1}; **UV** (MeOH) λ_{max} (ε) 277 (2500), 220 (10000) nm; **^{1}H NMR** δ_H (300 MHz, $CDCl_3$) 7.10 (1H, d, *J* 7.5 Hz, Ar*H*), 6.77 (1H, d, *J* 7.5 Hz, Ar*H*), 6.72 (1H, s, Ar*H*), 5.80 (1H, ddt, *J* 16.9, 9.9, 7.0 Hz, C*H*=CH_2), 5.22 (1H, dd, *J* 16.9, 1.1 Hz, CH=C*H*H), 5.09 (1H, d, *J* 9.9 Hz, CH=CH*H*), 3.83 (3H, s, OCH_3), 3.80 (2H, s, ArCH_2), 3.52 (2H, d, *J* 7.0 Hz, SCH_2), 2.38 (3H, s, ArCH_3); **^{13}C NMR** δ_C (75 MHz, $CDCl_3$) 198.0 (*C*=O), 157.8 (*C* (Ar)), 139.4 (*C* (Ar)),

133.4 (*C*H=CH_2), 131.4 (*C*H (Ar)), 121.3 (*C*H (Ar)), 119.4 (*C* (Ar)), 117.8 (CH=CH_2), 111.8 (*C*H (Ar)), 55.6 (OCH_3), 44.8 (ArCH_2), 32.1 (SCH_2), 21.9 (ArCH_3); **HRMS** (EI) $[M]^+$ found: 236.0871; $C_{13}H_{16}O_2S$ requires 236.0871; **LRMS** (APCI+ve), 237 ($[MH]^+$, 80%), 236 ($[M]^+$, 50%), 135 ($[M\text{-}C_3H_5SCO]^+$, 100%).

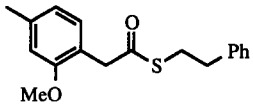
Benzyl 2-[4-methyl-2-methoxyphenyl]ethanethioate



2 (0.50 g, 1.88 mmol), $PhCH_2Br$ (0.81 g, 4.73 mmol), THF (10 mL), water (1 mL), 20 h. Purification by column chromatography (silica, 0 to 5% ether in petrol) and recrystallisation from pentane gave thioester (0.44 g, 1.54 mmol, 82%).

Colourless crystals; **m.p.** 52-54°C (pentane); **CHN** Found: C, 71.2; H, 6.3; S, 11.0; $C_{17}H_{18}O_2S$ requires C, 71.3; H, 6.3; S, 11.2; **IR** (film with trace of $CDCl_3$) υ_{max} 3028w, 1687s, 1612w, 1582w, 1508m, 1320w, 1270m, 1124m, 1040m, 933w, 703m cm^{-1}; **UV** (MeOH) λ_{max} (ε) 277 (3500), 221 inf (18000) nm; **^{1}H NMR** δ_H (300 MHz, CDCl) 7.35-7.20 (5H, m, 5 x Ar*H*), 7.10 (1H, d, *J* 7.5 Hz, Ar*H*), 6.77 (1H, d, *J* 7.5 Hz, Ar*H*), 6.72 (1H, s, Ar*H*), 4.11 (2H, s, PhCH_2), 3.83 (2H, s, ArCH_2), 3.79 (3H, s, OCH_3), 2.38 (3H, s, ArCH_3); **^{13}C NMR** δ_C (75 MHz, $CDCl_3$) 198.1 (*C*=O), 157.8 (*C* (Ar)), 139.4 (*C* (Ar)), 138.0 (*C* (Ph)), 131.4 (*C*H (Ar)), 129.1 (2 x *C*H (Ph)), 128.7 (2 x *C*H (Ph)), 127.3 (*C*H (Ph)), 121.3 (*C*H (Ar)), 119.4 (*C* (Ar)), 111.8 (*C*H (Ar)), 55.5 (OCH_3), 44.8 (ArCH_2), 33.5 (SCH_2), 21.9 (ArCH_3); **LRMS** (APCI+ve), 287 ($[MH]^+$, 25%), 193 ($[BnSCOH+CH_3CN]^+$, 100%), 152 ($[BnSCOH]^+$, 12%), 135 ($[M\text{-}BnSCO]^+$, 20%).

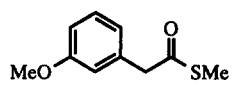
2-Phenylethyl 2-[4-methyl-2-methoxyphenyl]ethanethioate



2 (0.50 g, 1.88 mmol), $PhCH_2CH_2Br$ (0.87 g, 4.70 mmol), THF (10 mL), water (1 mL), 72 h. Purification by column chromatography (silica, 0 to 50% ether in petrol) gave thioester (0.20 g, 0.67 mmol, 36%) and recovered **2** (0.19 g, 38%).

Colourless oil; **IR** (neat) υ_{max} 3027w, 1686s, 1614m, 1584m, 1509s, 1320w, 1271m, 1125m, 1040m, 933w, 698m cm^{-1}; **UV** (MeOH) λ_{max} (ε) 279 (2800), 223 inf (12000) nm; **^{1}H NMR** δ_H (300 MHz, $CDCl_3$) 7.35-7.16 (5H, m, 5 x Ar*H*), 7.09 (1H, d, *J* 7.5 Hz, Ar*H*), 6.77 (1H, d, *J* 7.5 Hz, Ar*H*), 6.71 (1H, s, Ar*H*), 3.83 (5H, app s, ArCH_2 & OCH_3), 3.08 (2H, app dd, *J* 9.2, 5.9 Hz, SCH_2), 2.85 (2H, app dd, *J* 9.2, 5.9 Hz, PhCH_2), 2.38 (3H, s, ArCH_3); **^{13}C NMR** δ_C (75 MHz, $CDCl_3$) 198.6 (*C*=O), 157.7 (*C* (Ar)), 140.4 (*C* (Ar)), 139.3 (*C* (Ph)), 131.3 (*C*H (Ar)), 128.8 (2 x *C*H (Ph)), 128.6 (2 x *C*H (Ph)), 126.6 (*C*H (Ph)), 121.3 (*C*H (Ar)), 119.6 (*C* (Ar)), 111.8 (*C*H (Ar)), 55.6 (OCH_3), 45.0 (ArCH_2), 36.1 (PhCH_2), 30.6 (SCH_2), 21.9 (ArCH_3); **HRMS** (EI) $[M]^+$ found: 300.1180; $C_{18}H_{20}O_2S$ requires 300.1184; **LRMS** (APCI+ve), 301 ($[MH]^+$, 60%), 196 ($[MH\text{-}PhCH_2CH_2]^+$, 40%), 135 ($[M\text{-}PhCH_2CH_2SCO]^+$, 100%).

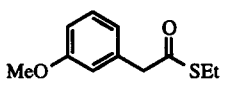
Methyl 2-[3-methoxyphenyl]ethanethioate[23]



4 (0.50 g, 1.99 mmol), MeI (0.71 g, 5.0 mmol), THF (10 mL), water (1 mL), 15 h. Purification by column chromatography (silica, 0 to 5% ether in petrol) gave thioester (0.33 g, 1.68 mmol, 85%). Alternatively: **4** (0.50 g, 1.99 mmol), Me_2SO_4 (0.63 g, 5.0 mmol), THF (10 mL), water (1 mL), 18 h gave thioester (0.28 g, 1.43 mmol, 72%) after purification by column chromatography.

Colourless oil; **IR** (neat) υ_{max} 3002w, 2835w, 1686s, 1600s, 1585s, 1258s, 1150m, 1051s, 758m cm^{-1}; **UV** (MeOH) λ_{max} (ε) 276 (1800), 220 inf (7500) nm; **^{1}H NMR** δ_H (300 MHz, $CDCl_3$) 7.27 (1H, m, Ar*H*), 6.89 (1H, d, *J* 7.5 Hz, Ar*H*), 6.87-6.82 (2H, m, 2 x Ar*H*), 3.82 (3H, s, OCH_3), 3.81 (2H, s, ArCH_2), 2.29 (3H, s, SCH_3); **^{13}C NMR** δ_C (75 MHz, $CDCl_3$) 197.8 (*C*=O), 159.9 (*C* (Ar)), 135.2 (*C* (Ar)), 129.8 (*C*H (Ar)), 122.0 (*C*H (Ar)), 115.3 (*C*H (Ar)), 113.1 (*C*H (Ar)), 55.4 (OCH_3), 50.5 (ArCH_2), 12.1 (SCH_3); **HRMS** (EI) $[M]^+$ found: 196.0548; $C_{10}H_{12}O_2S$ requires 196.0558; **LRMS** (APCI+ve), 196 (M^+, 5%), 121 ($[M\text{-}CH_3SCO]^+$, 100%). These data were in broad agreement with those reported previously.[23]

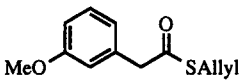
Ethyl 2-[3-methoxyphenyl]ethanethioate



4 (0.50 g, 1.99 mmol), EtI (0.78 g, 5.0 mmol), THF (10 mL), water (1 mL), 48 h. Purification by column chromatography (silica, 0 to 5% ether in petrol) gave thioester (0.29 g, 1.38 mmol, 69%).

Colourless oil; **IR** (neat) υ_{max} 2966w, 2835w, 1688s, 1600m, 1585m, 1259s, 1150m, 1051m, 759m, 690w cm^{-1}; **UV** (MeOH) λ_{max} (ε) 276 (2000), 219 inf (8500) nm; **^{1}H NMR** δ_H (300 MHz, $CDCl_3$) 7.26 (1H, dd, *J* 8.6, 7.7 Hz, Ar*H*), 6.92-6.81 (3H, m, 3 x Ar*H*), 3.82 (3H, s, OCH_3), 3.79 (2H, s, $ArCH_2$), 2.88 (2H, q, *J* 7.5 Hz, SCH_2), 1.24 (3H, t, *J* 7.5 Hz, CH_2CH_3); **^{13}C NMR** δ_C (75 MHz, $CDCl_3$) 197.6 (*C*=O), 159.9 (*C* (Ar)), 135.3 (*C* (Ar)), 129.8 (*C*H (Ar)), 122.1 (*C*H (Ar)), 115.3 (*C*H (Ar)), 113.1 (*C*H (Ar)), 55.4 (OCH_3), 50.7 ($ArCH_2$), 23.8 (SCH_2), 14.7 (CH_2CH_3); **HRMS** (EI) $[M]^+$ found: 210.0706; $C_{11}H_{14}O_2S$ requires 210.0715; **LRMS** (APCI+ve), 211 ($[MH]^+$, 20%), 210 (M^+, 60%), 162 ($[M-CH_3CH_2SCO+CH_3CN]^+$, 100%), 101 (60%).

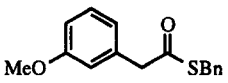
Allyl 2-[3-methoxyphenyl]ethanethioate



4 (0.50 g, 1.99 mmol), Allyl-Br (0.60 g, 4.96 mmol), THF (10 mL), water (1 mL), 24 h. Purification by column chromatography (silica, 0 to 5% ether in petrol) gave thioester (0.35 g, 1.58 mmol, 79%).

Pale yellow oil; **IR** (neat) υ_{max} 3084w, 2835w, 1690s, 1637m, 1600s, 1585s, 1259s, 1151m, 924m, 759m cm^{-1}; **UV** (MeOH) λ_{max} (ε) 276 (2400), 221 inf (10000) nm; **^{1}H NMR** δ_H (300 MHz, $CDCl_3$) 7.27 (1H, m, Ar*H*), 6.89 (1H, d, *J* 7.8 Hz, Ar*H*), 6.86 (1H, d, *J* 6.3 Hz, Ar*H*), 6.84 (1H, s, Ar*H*), 5.80 (1H, ddt, *J* 16.9, 9.9, 7.0 Hz, CH=CH_2), 5.23 (1H, dd, *J* 16.9, 1.1 Hz, CH=C*H*H), 5.10 (1H, br d, *J* 9.9 Hz, CH=CH*H*), 3.82 (3H, s, OCH_3), 3.81 (2H, s, $ArCH_2$), 3.54 (2H, d, *J* 7.0 Hz, SCH_2); **^{13}C NMR** δ_C (75 MHz, $CDCl_3$) 196.8 (*C*=O), 159.9 (*C* (Ar)), 135.0 (*C* (Ar)), 133.0 (CH=CH_2), 129.8 (*C*H (Ar)), 122.1 (*C*H (Ar)), 118.2 (CH=CH_2), 115.3 (*C*H (Ar)), 113.1 (*C*H (Ar)), 55.4 (OCH_3), 50.6 ($ArCH_2$), 32.3 (SCH_2); **HRMS** (EI) $[M]^+$ found: 222.0718; $C_{12}H_{14}O_2S$ requires 222.0715; **LRMS** (APCI+ve), 222 (M^+, 10%), 112 (50%), 100 (100%).

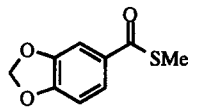
Benzyl 2-[3-methoxyphenyl]ethanethioate



4 (0.50 g, 1.99 mmol), $PhCH_2Br$ (0.85 g, 4.97 mmol), THF (10 mL), water (1 mL), 15 h. Purification by column chromatography (silica, 0 to 5% ether in petrol) gave thioester (0.36 g, 1.32 mmol, 66%).

Colourless oil; **IR** (neat) υ_{max} 3060w, 2834w, 1686s, 1600s, 1584s, 1314w, 1151s, 875w, 758m, 700s cm^{-1}; **UV** (MeOH) λ_{max} (ε) 277 (2400) nm; **^{1}H NMR** δ_H (300 MHz, $CDCl_3$) 7.32-7.23 (6H, m, 5 x Ph*H* + Ar*H*), 6.89 (1H, d, *J* 7.7 Hz, ArH), 6.86 (1H, d, *J* 7.7 Hz, Ar*H*), 6.84 (1H, s, Ar*H*), 4.13 (2H, s, $ArCH_2$), 3.84 (2H, s, SCH_2), 3.82 (3H, s, OCH_3); **^{13}C NMR** δ_C (75 MHz, $CDCl_3$) 196.8 (*C*=O), 159.9 (*C* (Ar)), 137.4 (*C* (Ph)), 135.0 (*C* (Ar)), 129.8 (*C*H (Ar)), 129.0 (2 x *C*H (Ph)), 128.8 (2 x *C*H (Ph)), 127.5 (*C*H (Ph)), 122.1 (*C*H (Ar)), 115.3 (*C*H (Ar)), 113.2 (*C*H (Ar)), 55.4 (OCH_3), 50.4 ($ArCH_2$), 33.8 (SCH_2); **HRMS** (EI) $[M]^+$ found: 272.0873; $C_{16}H_{16}O_2S$ requires 272.0871; **LRMS** (APCI+ve), 273 ($[MH]^+$, 30%), 272 (M^+, 50%), 162 ($[M-PhCH_2SCO+CH_3CN]^+$, 100%).

Methyl 1,3-benzodioxole-5-carbothioate

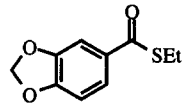


5 (0.40 g, 1.59 mmol), MeI (0.56 g, 3.94 mmol), THF (10 mL), water (1 mL), 18 h gave crude thioester (0.31 g, 1.58 mmol, 99%). Purification by recrystallisation from ethanol gave thioester (0.24 g, 1.22 mmol, 77%). Alternatively **5** (0.40 g, 1.59 mmol), Me_2SO_4 (0.50 g, 3.97 mmol), THF (10 mL), water (1 mL), 17 h gave thioester (0.21 g, 1.07 mmol, 67%) after purification.

Colourless needles; **m.p.** 68-70°C (ethanol); **CHN** Found: C, 55.1; H, 3.8; S, 16.5; $C_9H_8O_3S$ requires C, 55.1; H, 4.1; S, 16.3; **IR** (film with trace of $CDCl_3$) υ_{max} 3037w, 2930w, 1654s, 1611w, 1503m, 1270m, 1092s, 927s, cm^{-1};

UV (MeOH) λ_{max} (ε) 310 (16000), 279 (11500), 225 (27500) nm; **^{1}H NMR** δ_H (300 MHz, $CDCl_3$) 7.61 (1H, dd, *J* 8.2, 1.6 Hz, Ar*H*), 7.43 (1H, d, *J* 1.6 Hz, Ar*H*), 6.84 (1H, d, *J* 8.2Hz, Ar*H*), 6.05 (2H, s, OCH_2O), 2.45 (3H, s, SCH_3); **^{13}C NMR** δ_C (75 MHz, $CDCl_3$) 190.9 (*C*=O), 152.1 (*C* (Ar)), 148.2 (*C* (Ar)), 131.8 (*C* (Ar)), 123.3 (*C*H (Ar)), 108.2 (*C*H (Ar)), 107.3 (*C*H (Ar)), 102.1 (OCH_2O), 12.0 (SCH_3); **LRMS** (APCI+ve), 197 ([MH]$^+$, 30%), 111 (100%).

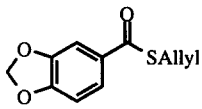
Ethyl 1,3-benzodioxole-5-carbothioate



5 (0.40 g, 1.59 mmol), EtI (0.62 g, 3.97 mmol), THF (10 mL), water (1 mL), 17 h. Purification by column chromatography (silica, 0 to 5% ether in petrol) gave thioester (0.32 g, 1.52 mmol, 96%).

Colourless oil; **IR** (neat) υ_{max} 2969w, 2930w, 1659s, 1612m, 1503m, 1355m, 1254s, 1092m, 1039s, 851m, cm^{-1}; **UV** (MeOH) λ_{max} (ε) 309 (9500), 281 (7500), 226 (18000) nm; **^{1}H NMR** δ_H (300 MHz, $CDCl_3$) 7.61 (1H, dd, *J* 8.2, 1.6 Hz, Ar*H*), 7.43 (1H, d, *J* 1.6 Hz, Ar*H*), 6.84 (1H, d, *J* 8.2 Hz, Ar*H*), 6.05 (2H, s, OCH_2O), 3.05 (2H, q, *J* 7.4 Hz, SCH_2CH_3), 1.33 (3H, t, *J* 7.4 Hz, CH_2CH_3); **^{13}C NMR** δ_C (75 MHz, $CDCl_3$) 190.5 (*C*=O), 152.0 (*C* (Ar)), 148.1 (*C* (Ar)), 131.9 (*C* (Ar)), 123.3 (*C*H (Ar)), 108.1 (*C*H (Ar)), 107.3 (*C*H (Ar)), 102.1 (OCH_2O), 23.7 (SCH_2), 15.0 (CH_2CH_3); **HRMS** (EI) [M]$^+$ found: 210.0342; $C_{10}H_{10}O_3S$ requires 210.0351; **LRMS** (APCI+ve), 252 ([MH+CH_3CN]$^+$, 100%), 211 ([MH]$^+$, 100%), 142 (25%), 111 (40%).

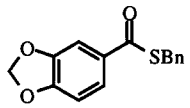
Allyl 1,3-benzodioxole-5-carbothioate



5 (0.40 g, 1.59 mmol), Allyl-Br (0.48 g, 3.97 mmol), THF (10 mL), water (1 mL), 18 h. Purification by column chromatography (silica, 0 to 5% ether in petrol) gave thioester (0.33 g, 1.49 mmol, 94%).

Colourless oil; **IR** (neat) υ_{max} 3081w, 2904m, 1661s, 1613s, 1503s, 1355s, 1256m, 1098s, 850s, 729m cm^{-1}; **UV** (MeOH) λ_{max} (ε) 310 (10000), 280 (7000), 227 (16000) nm; **^{1}H NMR** δ_H (300 MHz, $CDCl_3$) 7.61 (1H, dd, *J* 8.3, 1.6 Hz, Ar*H*), 7.42 (1H, d, *J* 1.6 Hz, Ar*H*), 6.85 (1H, d, *J* 8.3 Hz, Ar*H*), 6.05 (2H, s, OCH_2O), 5.90 (1H, ddt, *J* 16.9, 9.9, 7.0 Hz, C*H*=CH_2), 5.32 (1H, dd, *J* 16.9, 1.2 Hz, CH=C*H*H), 5.15 (1H, br d, *J* 9.9 Hz, CH=CH*H*), 3.72 (2H, d, *J* 7.0 Hz, SCH_2); **^{13}C NMR** δ_C (75 MHz, $CDCl_3$) 189.7 (*C*=O), 152.0 (*C* (Ar)), 148.2 (*C* (Ar)), 133.4 (*C*H=CH_2), 131.6 (*C* (Ar)), 123.5 (*C*H (Ar)), 118.2 (CH=CH_2), 108.2 (*C*H (Ar)), 107.4 (*C*H (Ar)), 102.1 (OCH_2O), 32.1 (SCH_2); **HRMS** (EI) [M]$^+$ found: 222.0341; $C_{11}H_{10}O_3S$ requires 222.0351; **LRMS** (APCI+ve), 223 ([MH]$^+$, 100%), 149 ([M-SAllyl]$^+$, 10%), 111 (90%), 101 (90%).

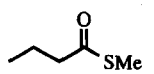
Benzyl 1,3-benzodioxole-5-carbothioate



5 (0.40 g, 1.59 mmol), BnBr (0.68 g, 3.98 mmol), THF (10 mL), water (1 mL), 15 h gave crude thioester (0.45 g, 1.65 mmol, 104%). Purification by recrystallisation from ethanol gave thioester (0.35 g, 1.29 mmol, 81%).

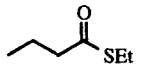
Colourless flakes; **m.p.** 86-88°C (ethanol); **CHN** Found: C, 66.2; H, 4.5; S, 11.57; $C_{15}H_{12}O_3S$ requires C, 66.2; H, 4.4; S, 11.8; **IR** (neat) υ_{max} 2910w, 1656s, 1600w, 1502m, 1265s, 1040m, 970m, 806m, 707m cm^{-1}; **UV** (MeOH) λ_{max} (ε) 311 (12000), 280 (8500), 226 (22000) nm; **^{1}H NMR** δ_H (300 MHz, $CDCl_3$) 7.62 (1H, dd, *J* 8.2, 1.6 Hz, Ar*H*), 7.44 (1H, d, *J* 1.6 Hz, Ar*H*), 7.42-7.24 (5H, m, 5 x Ar*H*), 6.84 (1H, d, *J* 8.2 Hz, Ar*H*), 6.06 (2H, s, OCH_2O), 4.31 (2H, s, SCH_2); **^{13}C NMR** δ_C (75 MHz, $CDCl_3$) 189.7 (*C*=O), 152.2 (*C* (Ar)), 148.2 (*C* (Ar)), 137.7 (*C* (Ar)), 131.5 (*C* (Ph)), 129.1 (2 x *C*H (Ph)), 128.8 (2 x *C*H (Ph)), 127.5 (*C*H (Ph)), 123.6 (*C*H (Ar)), 108.2 (*C*H (Ar)), 107.4 (*C*H (Ar)), 102.1 (OCH_2O), 33.6 (SCH_2); **LRMS** (APCI+ve), 273 ([MH]$^+$, 20%), 149 ([M-SCH_2Ph]$^+$, 10%), 111 (100%).

Methyl butanethioate



6 (0.40 g, 2.31 mmol), Me_2SO_4 (0.33 g, 2.61 mmol), THF (10 mL), water (1 mL), 36 h. Purification by column chromatography (silica, 0-5% ether in petrol) gave thioester (0.14 g, 1.19 mmol, 51%) as a colourless oil identical in all respects to a commercial sample of the title compound.

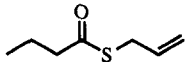
Ethyl butanethioate[24]



6 (0.40 g, 2.31 mmol), EtI (0.49 g, 3.14 mmol), THF (10 mL), water (1 mL), 72 h. Purification by column chromatography (silica, 0-4% ether in petrol) gave thioester (0.26 g, 1.97 mmol, 85%).

Colourless oil; **IR** (neat) υ_{max} 2967s, 2876m, 1690s, 1456m, 1417w, 1370w, 1266w, 1115m, 990m, 757s cm^{-1}; **UV** (MeOH) λ_{max} (ε) 232 (2000) nm; **^{1}H NMR** δ_H (300 MHz, $CDCl_3$) 2.87 (2H, q, *J* 7.4 Hz, SCH_2), 2.57 (2H, t, *J* 7.4 Hz, CH_2CO), 1.69 (2H, sextet, *J* 7.4 Hz, CH_2CH_3), 1.25 (3H, t, *J* 7.4 Hz, SCH_2CH_3), 0.95 (3H, t, *J* 7.4 Hz, $CH_2CH_2CH_3$); **^{13}C NMR** δ_C (75 MHz, $CDCl_3$) 199.8 (*C*=O), 46.1 (SCH_2), 23.2 (CH_2CO), 19.3 (CH_2CH_3), 14.9 (SCH_2CH_3), 13.6 ($CH_2CH_2CH_3$); **LRMS** (APCI+ve), 133 ([MH]$^+$, 100%), 124 (40%).

2-Propenyl butanethioate



6 (0.40 g, 2.31 mmol), Allyl-Br (0.42 g, 3.47 mmol), THF (10 mL), water (1 mL), 48 h. Purification by column chromatography (silica, 0-10% ether in petrol) gave thioester (0.27 g, 1.88 mmol, 81%).

Colourless oil; **IR** (neat) υ_{max} 2966m, 2876w, 1694s, 1638w, 1459m, 1421w, 1232w, 1114m, 989m, 921m cm^{-1}; **UV** (MeOH) λ_{max} (ε) 231 (3800) nm; **^{1}H NMR** δ_H (300 MHz, $CDCl_3$) 5.81 (1H, ddt, *J* 16.9, 9.9, 7.0 Hz, CH=CH_2), 5.23 (1H, dd, *J* 16.9, 1.3 Hz, =C*H*H), 5.11 (1H, brd, *J* 9.9 Hz, =CH*H*), 3.54 (2H, d, *J* 7.0 Hz, SCH_2), 2.54 (2H, t, *J* 7.4 Hz, CH_2CO), 1.71 (2H, sextet, *J* 7.4 Hz, CH_2CH_3), 0.97 (3H, t, *J* 7.4 Hz, CH_3); **^{13}C NMR** δ_C (75 MHz, $CDCl_3$) 199.0 (C=O), 133.4 (=CH), 117.9 (=CH_2), 46.0 (SCH_2), 31.8 (CH_2CO), 19.3 (CH_2CH_3), 13.6 (CH_3); **LRMS** (APCI+ve), 145 ([MH]$^+$, 30%), 124 (100%), 100 (80%).

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