A Novel Synthesis of Thiocarboxylic *S*-Esters from 1-(Acylthio)ethaniminium Halides and Alkyl Halides Using Liquid-Liquid Phase-Transfer Catalysis

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S-Alkyl, *S*-benzyl, and *S*-(2-alkenyl) thiocarboxylates are prepared in good yields by acylation of thioacetamide with acyl halides and reaction of the resultant 1-(acylthio)ethaniminium halides with alkyl halides under liquid-liquid phase-transfer conditions.

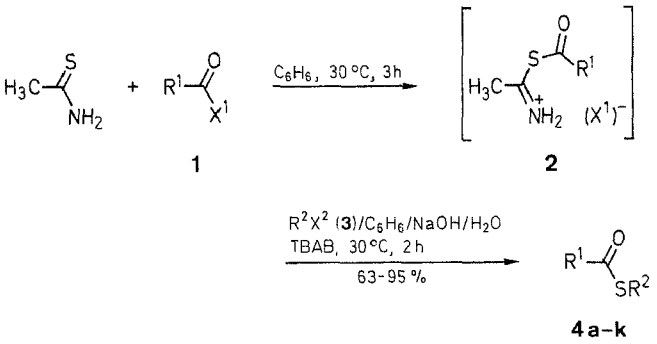
The previously reported[1] reaction of 1-alkylthioethaniminium halides with alkyl halides under phase-transfer catalysis provides a high-yield synthesis of unsymmetrical sulfides.[1] In an

extension of this work, we now report a novel synthesis of thiocarboxylic *S*-esters from 1-(acylthio)ethaniminium halides and alkyl halides under similar conditions.

S-Alkyl thiocarboxylates **(4)** are useful acylating agents in biochemical reactions[2,3] and various procedures for their synthesis have been reported.[4-15] However, most of these preparations use unpleasantly smelling thiols or thioacids. Further, *S*-alkyl thiocarboxylates may be prepared by the hydrolysis of 1-(alkylthio)alkaneiminium halides in acidic media,[16] but this method is not sufficiently general.[17] A method for the preparation of *S*-alkyl thiocarboxylates using 1-(acylthio)alkaniminium halides as the source of thiocarboxylate ion has hitherto not been reported.

In our procedure, the 1-(acylthio)ethaniminium halides **2** are prepared from thioacetamide and acyl halides **1** in benzene at 30 °C (3 hours). Compounds **2** cannot be isolated because they decompose in air (in contrast to the stable 1-(alkylthio) ethaniminium salts which are prepared from thioacetamide and alkyl halides).[1] They are therefore treated, in the mixture of their preparation with alkyl halides **3** using a two-phase system consisting of benzene, aqueous sodium hydroxide, and tetrabutylammonium bromide (TBAB) as a phase-transfer catalyst at 30 °C for 2 hours (Scheme **A**).

The yields of thioesters **4** depend on the structure of the catalyst; they decrease in the order: TBAB > methyltrioctylammonium chloride (MTOAC) > benzyltriethylammonium chloride (BTEAC). For example, the yields of *S*-octyl thiobenzoate **(4f)**, obtained from **2** ($R^1 = C_6H_5$) and **3** ($R^2 = n$-C_8H_{17}), are 87% (TBAB), 71% (MTOAC), and 3% (BTEAC), respectively. This result is consistent with the view that ammonium ions bearing identical, sufficiently long-chain substituents are better than those bearing different substituents.[18] On the other hand, in the absence of a phase-transfer catalyst, the iminium salt **2** ($R^1 = C_6H_5$) did not react with **3** as expected, thiobenzoic acid being obtained in 85% yield. In spite of the fact that thiocarboxylic *S*-esters are easily hydrolyzed in alkaline media,[19] the present method smoothly produced thioesters **4** in good yield.



4	R^1	R^2	4	R^1	R^2
a	n-C_5H_{11}	n-C_8H_{17}	g	C_6H_5	$CH_3CH{=}CHCH_2$
b	n-C_5H_{11}	$C_6H_5CH_2$	h	C_6H_5	$C_6H_5CH_2$
c	n-C_7H_{15}	$C_6H_5CH_2$	i	4-$CH_3OC_6H_4$	n-C_8H_{17}
d	t-C_4H_9	n-C_8H_{17}	j	4-$NO_2C_6H_4$	n-C_8H_{17}
e	C_6H_5	n-C_4H_9	k	$C_6H_5CH{=}CH$	$C_6H_5CH_2$
f	C_6H_5	n-C_8H_{17}			

Scheme A

Table 1. Thiocarboxylic *S*-Esters **4** Prepared[a]

Product	X^1 in **1**	X^2 in **3**	Yield[b] (%)	mp (°C)[c] or bp (°C)/Torr	Molecular Formula[d] or Lit. Data	Exact Mass[e] (20 eV) m/z (M^+)	IR (neat)[f] $\nu_{C=O}$ (cm^{-1})	^{13}C-NMR ($CDCl_3$/TMS)[g] δ
a	Cl	Br	89	104–105/7	$C_{14}H_{28}OS$ (244.4)	244.1495	1686	13.9, 14.1 (CH_3); 22.4, 22.7, 25.5, 28.8, 29.2, 29.7, 31.2, 31.9, 44.2 (CH_2); 199.5 (C=O)
b	Cl	Br	86	136–137/4	$C_{13}H_{18}OS$ (222.3)	222.1099	1680	13.6 (CH_3); 22.0, 25.0, 30.8, 32.8, 43.4 (CH_2); 126.8, 128.2, 128.5, 137.5 (C_6H_5); 198.1 (C=O)
c	Cl	Br	86	158–159/4	$C_{15}H_{22}OS$ (250.3)	250.1391	1690	14.0 (CH_3); 22.5, 25.5, 28.8, 31.5, 33.1, 43.7 (CH_2); 127.1, 128.5, 128.7, 137.7 (C_6H_5); 198.6 (C=O)
d	Cl	Br	83	110–111/5	$C_{13}H_{26}OS$ (230.35)	230.1717	1672	14.0, 27.3 (CH_3); 22.6, 28.4, 28.8, 29.1, 29.5, 31.8 (CH_2); 46.2 (–C–); 206.4 (C=O)
e	Br	Br	91	127–128/8	125/5[4]	194.0761	1660	13.7 (CH_3); 22.1, 28.7, 31.7 (CH_2); 127.1, 128.5, 133.1, 137.2 (C_6H_5); 191.5 (C=O)
f	Br	Br	87	188–189/8	$C_{15}H_{22}OS$ (250.3)	250.1372	1659	14.1 (CH_3); 22.7, 29.1, 29.2, 29.7, 31.9 (CH_2); 127.2, 128.5, 133.0, 137.3 (C_6H_5); 191.5 (C=O)
g	Br	Cl	88	116–117/4	$C_{11}H_{12}OS$ (192.2)	192.0616	1660	17.6 (CH_3); 31.1 (CH_2); 125.5, 129.2 (C=C); 127.0, 128.3, 133.0, 136.9 (C_6H_5); 191.1 (C=O)
h	Br	Br	82	38–39 (hexane/C_6H_6)	36–38[20]	228.0627	1665 (KBr)	33.2 (CH_2); 127.2, 128.5, 128.9, 133.3, 136.7, 137.4 ($2C_6H_5$); 191.0 (C=O)
i	Cl	Br	95	oil	$C_{16}H_{24}O_2S$ (280.4)	280.1495	1656	14.0 (CH_3); 55.3 (OCH_3); 22.6, 28.8, 28.9, 29.1, 29.7, 31.8 (CH_2); 113.5, 129.2, 130.0, 163.5 (C_6H_4); 190.3 (C=O)
j	Cl	Br	63	oil	$C_{15}H_{21}NO_3S$ (295.3)	295.1277	1662	14.0 (CH_3); 22.5, 28.8, 29.1, 29.2, 29.5, 31.7 (CH_2); 123.7, 128.0, 141.7, 150.3 (C_6H_4); 190.3 (C=O)
k	Cl	Br	93	67–69 (hexane/C_6H_6)	70[21]	254.0745	1668 (KBr)	33.2 (CH_2); 124.6, 127.2, 128.3, 128.6, 128.9, 134.0, 137.6 ($2C_6H_5$); 130.6, 140.8 (C=C); 189.0 (C=O)

[a] Reactions were carried out at 30 °C and at the molecular ratio 1:1:1:0.03 for thioacetamide, acid halide, alkyl halide, and TBAB as phase-transfer catalyst.
[b] Yield of pure isolated **4**, based on thioacetamide.
[c] Uncorrected, measured with a Yanagimoto apparatus.
[d] Satisfactory microanalyses obtained: C ±0.1, H ±0.04, S ±0.2.
[e] Recorded on a Hitachi M-80B spectrometer.
[f] Recorded on a Shimazu IR-435 infrared spectrophotometer.
[g] Obtained on a JEOL FX-100 spectrometer.

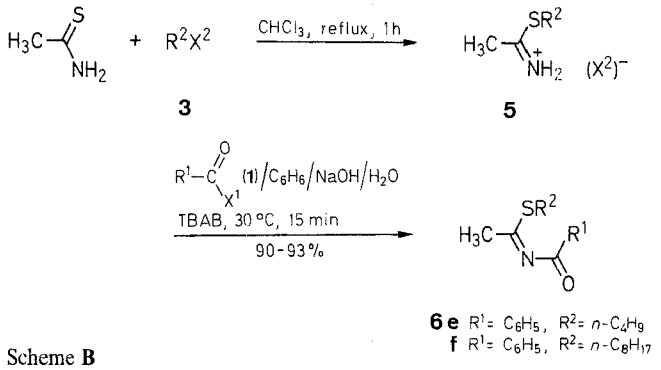
Table 2. Alkyl *N*-Acylethanimidothioates **6** Prepared[a]

Product 6	Yield[b] (%)	bp (°C/Torr)	Molecular Formula[c] or Lit. Data	IR (neat)[d] $\nu_{C=O}$ (cm^{-1})	^{1}H-NMR ($CDCl_3$/TMS)[e] δ, J(Hz)	^{13}C-NMR ($CDCl_3$/TMS)[f] δ
e	90	143–145/4	$C_{13}H_{17}NOS$ (235.3)	1635	0.94 [t, 3H, J = 7.4, $(CH_2)_3CH_3$]; 1.45 [qt, 2H, J = 7.4, $(CH_2)_2CH_2CH_3$]; 1.69 (tt, 2H, J = 7.4, $CH_2CH_2C_2H_5$); 2.19 (s, 3H, $=CCH_3$); 3.03 (t, 2H, J = 7.4, $SCH_2C_3H_7$); 7.43–7.97 (m, $5H_{arom}$)	13.7, 23.5 (CH_3); 22.1, 30.5, 30.8 (CH_2); 128.5, 129.4, 132.9, 133.6 (C_6H_5); 171.2, 177.9 (C=O, C=N)
f	93	181–182/4	$C_{17}H_{25}NOS$ (291.4)	1633	0.87 [t, 3H, J = 7.2, $(CH_2)_7CH_3$]; 1.26 [br, 8H, $(CH_2)_4$]; 1.41 [qt, 2H, J = 7.2, $(CH_2)_6CH_2CH_3$]; 1.71 (tt, 2H, J = 7.2, $CH_2CH_2C_6H_{13}$); 2.19 (s, 3H, $=CCH_3$); 3.03 (t, 2H, J = 7.2, $SCH_2C_7H_{15}$); 7.43–7.96 (m, $5H_{arom}$)	14.1, 23.7 (CH_3); 22.6, 28.8, 29.0, 29.1, 30.9, 31.8 (CH_2); 128.4, 129.4, 132.9, 133.5 (C_6H_5); 171.2, 178.3 (C=O, C=N)

[a] Reactions were carried out at 30 °C for 15 min and at the molecular ratio 1 : 1 : 0.03 for thioiminium salt **5**, **1**, and TBAB. X^1 (in **1**) = X^2 (in **3**) = Br.
[b] Yield of pure isolated product, based on **5**.
[c] Satisfactory microanalyses obtained: C ± 0.2, H ± 0.02, N ± 0.1, S ± 0.2.
[d] Recorded on a Shimazu IR-435 infrared spectrophotometer.
[e] Obtained on a JEOL GX-400 spectrometer.
[f] Obtained on a JEOL FX-100 spectrometer.

In the case of the reaction using *p*-substituted benzoyl halides **1**, the yields of **4** are increased by an electron-releasing group on the benzene ring, whereas electron withdrawing groups decrease the yield of **4**.

We also attempted to prepare thioesters **4** by the reaction of 1-(alkylthio)ethaniminium halides **5** (obtained from *S*-alkylation of thioacetamide with alkyl halides **3**) with acyl halides **1**. However, this reaction afforded *N*-(acyl)thioimidates **6** as the major products together with a small amount of **4** (Scheme **B**, Table 2). This result shows that the C–S bond of **2** is easily cleaved to generate the thioacylate ion, while the C–S bond of **5** is stable under these conditions.



Scheme **B**

As far as we know, the present synthesis of thiocarboxylic *S*-esters **4** from 1-(acylthio)ethaniminium halides **2** and alkyl halides **3** is the first example of this type of reaction. The method does not use unpleasantly smelling alkanethiols or thioacids and it can be applied to the synthesis of a wide range of thiocarboxylic *S*-esters under mild conditions.

S-Alkyl, S-Benzyl, and S-(2-Alkenyl) Thiocarboxylates 4; General Procedure:

A mixture of thioacetamide (1.83 g, 30 mmol) and an acyl halides **1** (30 mmol) in benzene (50 mL) is stirred at 30 °C for 3 h under N_2. Then, the alkyl halide **3** (30 mmol), TBAB (0.29 g, 0.9 mmol), and 10% (w/w) aqueous NaOH (50 g) are added and the mixture is vigorously stirred for 2 h at 30 °C. The organic layer is separated, washed with H_2O (3 × 50 mL), dried (Na_2SO_4), and evaporated. The residual product is column-chromatographed on silica gel with hexane/EtOAc (4:1) as eluent to afford the pure thioesters **4**.

Alkyl N-Acylethanimidothioates 6; General Procedure:

A mixture of the freshly prepared 1-(alkylthio)ethaniminium salt[1] **5** (10 mmol), the acyl halide **1** (10 mmol), TBAB (97 mg, 0.3 mmol), benzene (50 mL), and 30% (w/w) aqueous NaOH (50 g) is vigorously stirred under N_2 at 30 °C for 15 min. The organic layer is separated, washed with H_2O (3 × 50 mL), dried (Na_2SO_4), and evaporated. The residue is distilled under reduced pressure to afford the pure product **6**.

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