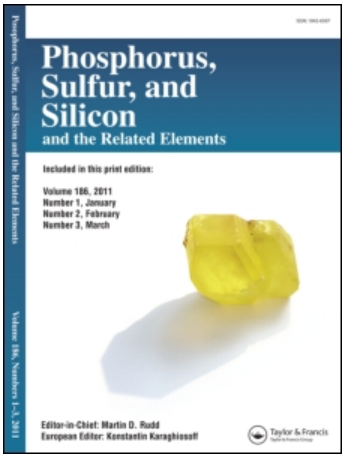

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A FACILE SYNTHESIS OF THIOACIDS BY HYDROLYSIS OF 1-(ACYLTHIO)ETHANIMINIUM CHLORIDES

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A facile method for the preparation of thioacids in moderate to good yields has been developed by hydrolysis of 1-(acylthio)ethaniminium chlorides under a liquid-liquid two phase system consisting of benzene and a sodium hydroxide aqueous solution at room temperature. We have achieved facile preparation of these compounds without use of toxic compounds such as hydrogen sulfide.

Keywords: Acyl halides; acylthioethaniminium salt; thioacetamide; thioacids; thiocarboxylate ions

Many different methods[1–8] for preparing thioacids have been reported and they recently have begun to attract notice because functionalized organic thioacids are useful and efficient acylating agents for amines, amino acids, and peptides in biochemical reactions.[9,10] However, most of these preparations have involved the use of toxic and unpleasantly smelling compounds such as hydrogen sulfide, and have sometime suffered from cumbersome manipulations due to the formation of carboxylic acids or thioacid anhydrides (diacyl sulfides) as by-products. We have achieved the preparation of thioacids without the use of hydrogen sulfide. Herein, we report a novel and facile method for the preparation of thioacids by hydrolysis of 1-(acylthio)ethaniminium halide.

We have previously reported[11] the preparation of thiobenzoic acid by hydrolysis and methanolysis of *N*,*N*-dimethyl-1-(benzoylthio)-methaniminium chloride prepared from *N*,*N*-dimethylthioformamide[12]

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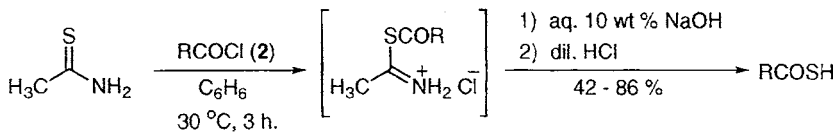
(DMTF) with benzoyl chloride. We also have attempted to apply an aliphatic acyl chloride in this method, but this reaction afforded a carboxylic acid and a methyl carboxylate as the major products together with a small amount of an aliphatic thioacid. This result suggested that the stability of aliphatic acyl chloride/DMTF adducts are relatively low, and the rates of hydrolysis[13] and esterification[14] of aliphatic acyl chlorides are faster than those benzoyl chloride. We also earlier have reported[15] an efficient method for synthesizing thiol esters using 1-(acylthio)ethaniminium halides as s source of thiocarboxylate ions. It was found that when this reaction carried out in the absence of the phasetransfer catalyst and an alkyl halide, the hydrolysis of 1-(acylthio)ethaniminium halide proceeded to produce a thioacid. In an extension of these investigations, this article describes a novel and facile synthesis of thioacids by hydrolysis of 1-(acylthio)ethaniminium chlorides prepared from acylation of thioacetamide under a liquid-liquid two phase system consisting of benzene and a sodium hydroxide aqueous solution. Our facile method for the preparation of thioacids by hydrolysis of 1-(acylthio)ethaniminium chlorides hitherto has not been reported, and a wide range of functionalized thioacids could be prepared.

RESULTS AND DISCUSSION

In our present method, 1-(acylthio)ethaniminium chlorides, **3**, were prepared from thioacetamide, **1**, and acyl chlorides, **2**, in benzene at 30°C for 3 h. The attempts to isolate of **3** were unsuccessful due to their instability in air (this was in contrast to the stable 1-(alkylthio)ethaniminium halides which were prepared from thioacetamide and alkyl halides). It therefore is reasonable to assume that the preparation of thioacids by means of a one-pot reaction would be effective as a synthetic strategy. They were hydrolyzed to give thioacids, **4**, in a liquid-liquid two phase system consisting of benzene and a sodium hydroxide aqueous solution at room temperature for 30 min.

The reactions were carried out under mild conditions, and thioacids, **4**, were obtained in 42–86% yields and the results are summarized in Table I. These reactions also have afforded a small amount of corresponding carboxylic acids as a by-product, formed by direct hydrolysis of remaining acyl chloride as an unreactant, because the formation of **3** would be reversible reaction.[16] The separation of desired **4** and carboxylic acids was easily achieved by using column chromatographic purification. The attempts to increase yields of **4** by using excess thioacetamide, **1**, or an acyl chloride, **2**, to drive the equilibrium were examined. When the reaction of **1** (1.5 eq. and 2.0 eq.) with *n*-octanoyl



1 3 4

4	R	4	R
a	*n*-C_4H_9	**g**	$CH_3(CH_2)_3CH(C_2H_5)$
b	*n*-C_5H_{11}	**h**	*tert*-C_4H_9
c	*n*-C_6H_{13}	**i**	*cyclo*-C_6H_{11}
d	*n*-C_7H_{15}	**j**	C_6H_5
e	*n*-C_8H_{17}	**k**	*p*-$CH_3OC_6H_4$
f	*n*-C_9H_{19}	**l**	*p*-$NO_2C_6H_4$

SCHEME 1

chloride, **2d** (1.0 eq.) produced thiooctanoic acid (**4d**) in 81% and 83% yield respectively. The use of **1** (1.0 eq.) with **2d** (1.5 eq.) in this reaction produced **4d** in 88% yield by GLC calculation, but the reaction also afforded a large amount of *n*-octanoic acid as a by-product. Accordingly, the isolation of **4d** was unsuccessful due to the formation of the by-product in good yield; so it was found that the equimolar reaction of **1** and **2** would be reasonable in this reaction.

The application of various acyl chlorides to this reaction was examined. It was found that the corresponding thioacids could be prepared in good yield from the linear aliphatic acyl chlorides, trimethylacetyl chloride, and cyclohexanecarbonyl chloride having branches on the α-position of acyl chlorides, but the yield of **4** was decreased by using the acyl chloride with ethyl group on its α-position. In the case of the reaction using *p*-substituted benzoyl chlorides, the yields of **4** were increased by an electron-releasing group on the benzene ring, whereas electron withdrawing groups decreased the yield of **4**. The yields of **4** depended on the structure of thioamides; they decreased in the order: thioacetamide > DMTF > *N*,*N*-dimethylthioacetamide (DMTA). For example, the yields of thiobenzoic acid, obtained from the hydrolyses of corresponding benzoylthioiminium salt were 84% (thioacetamide; **1**), 55% (DMTF), 37% (DMTA) respectively. In hydrolysis using a higher than 10% (w/w) concentration of a sodium hydroxide aqueous solution, the yields of **4** were decreased due to the formation of carboxylic acids as by-products by the decomposition of **3** and **4**. It was found that a 10% (w/w) concentration of sodium hydroxide aqueous solution was reasonable for the hydrolysis of **3**, and this result was in complete contrast to the synthesis of unsymmetrical sulfides. As reported before,[17] 1-alkylthioiminium salt reacted with alkyl halides to form

TABLE I Thioacids **4** Prepared

Product[a] **4**	Yield[b] (%)	b.p. (°C/torr) m.p. (°C) or	HR-MS (FAB-) or Lit. data	IR (neat or KBr) ν_{S-H}	IR (neat or KBr) $\nu_{C=O}$	^{13}C-NMR ($CDCl_3$/TMS): δ [^{1}H-NMR ($CDCl_3$/ TMS): δ]
a	72 (75)	63–64/13	113–140/760[18]	2550	1708	13.6, 21.9, 27,4, 45.6, 197.7
b	71 (77)	77–78/13	98–101/65[18]	2547	1709	13.8, 22.3, 25.0, 30.9, 45.7, 196.6
c	75 (77)	72–73/9	81/11[18]	2551	1709	13.9, 22.4, 25.3, 28.4, 31.4, 45.7, 197.7
d	80 (82)	95–96/3	72/3[19]	2548	1710	14.0, 22.5, 25.3, 28.7, 28.9, 31.5, 45.7, 197.7
e	76 (80)	114–115/13	105/10[18]	2550	1709	14.0, 22.6, 25.3, 28.7, 29.0, 29.2, 31.7, 45.7, 196.6
f	75 (80)	115–116/5	187.1152 ($M - H^+$) Calcd. 187.1157	2546	1710	14.0, 22.6, 25.4, 28.8 × 2, 29.2 × 2, 31.8, 45.8, 195.7 [0.88 (3H, t, $J = 7$ Hz, CH_3), 1.20–1.38 (12H, m, CH_3 $(CH_2)_6$), 1.59–1.72 (2H, m, CH_2CH_2CO), 2.60 (2H, t, $J = 7$ Hz, CH_2CO)]
g	42 (49)	72–73/5	159.0845 ($M - H^+$) Calcd. 159.0844	2547	1709	11.5, 13.8, 22.6, 25.8, 29.3, 32.1, 57.4, 202.0 [0.86–1.01 (6H, m, $CH_3 \times 2$), 1.24–1.37 (4H, m, CH_2CHCH_2), 1.42–1.80 (4H, m, $CH_3CH_2CH_2$), 2.43–2.52 (1H, m, CH)]
h	71 (75)	53–54/11	117.0374 ($M - H^+$) Calcd. 117.0374	2555	1699	27.2, 47.2, 204.8 [1.30 (9H,s, $(CH_3)_3C$)]
i	71 (75)	78–79/8	78–79/7.5[8]	2550	1702	25.4, 25.6, 29.5, 51.9, 201.3
j	72 (76) 84 (86)[c]	85–87/10	82–85/7[8]	2557	1665	127.7, 128.5, 133.7, 136.4, 190.2
k	86 (89)	82–83	82–83[20]	2512	1638	55.3, 113.5, 129.2, 130.0, 163.5, 190.3
l	54 (59)	97–98	94[19]	2550	1669	123.7, 128.0, 141.7, 150.3, 190.3

[a] All products were characterized by ^{1}H-NMR, mass spectra.
[b] Yields were pure isolated **4** based on **2** and in parentheses were calculated by GLC.
[c] C_6H_6COBr was used instead of C_6H_6COCl.

the corresponding unsymmetrical sulfides under liquid-liquid phase transfer conditions; however, this reaction required a 30% (w/w) concentration of sodium hydroxide aqueous solution for the generation of alkanethiolate ions from the salt. These results suggest that the iminium carbon-sulfur linkage of **3** would be weaker than that of 1-alkylthioiminium salt in alkaline solution.

As far as we know, this is the first example of the preparation of thioacids by hydrolysis of acylthioiminium salt. Our method does not use harmful or malodorous compounds such as hydrogen sulfide, and can be applied widely to the synthesis of functionalized thioacids. We expect it to become one of the most convenient syntheses for thioacids without use of hydrogen sulfide.

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