

Facile One-Pot Synthesis of *S*-Alkyl Thiocarbamates

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Abstract: We report a novel one-pot two-step synthesis of a variety of *S*-alkyl thiocarbamates. This method offers a two-directional approach making use of trichloroacetyl chloride, requires no complex starting material, incorporates a variety of substituents, and proceeds in high yields.

S-Alkyl thiocarbamates (*S*-alkyl thiourethanes) are an important class of compounds that have received considerable attention in the literature.^{1,2} Such compounds are of interest due to their numerous biological effects including anesthetic,³ fungicidal,^{2,4} bactericidal,^{5,6} pesticidal,^{7,8} and antiviral.⁹ Despite the aforementioned reasons, these compounds are most noted for their use as commercial herbicides.^{8,10,11}

Many reports illustrate the intramolecular rearrangement of various derivatives to afford *S*-alkyl thiocarbamates; however, these rearrangements are extremely limited in starting substrates.¹² Transition-metal species containing elements such as palladium,¹³ nickel,¹⁴ and rhodium^{13b} have also been employed to promote rearrangement and product formation. There are a variety

of other methods; however, most require the preparation of complex starting materials.¹⁵ Carbon monoxide and elemental sulfur are frequently employed in such preparations; however, these methods involve multistep approaches which incorporate metal catalysts or proceed in low yields.^{10,16} The most widely used method for preparation of these compounds makes use of gaseous carbonyl sulfide (COS), which condenses with a secondary amine, followed by subsequent treatment with base and an alkyl halide.^{8,17} Furthermore, production of many other *S*-alkyl thiocarbamates have received considerable attention in the patent literature.¹⁸

Condensation of a thiol with an isocyanate affords the corresponding thiocarbamate; however, this route was only demonstrated when alkoxy and aroxy-sulfonyl isocyanates were employed.⁶ Moreover, the hydration of a variety of organic thiocyanates has been reported to afford the desired compound in the presence of hydrogen chloride; however, this method is limited to only *N,N*-unsubstituted thiocarbamates.^{19,20} *N,N*-Disubstituted *S*-alkyl thiocarbamates have also been prepared from salts of dithiocarbamic acid, which are prepared by the addition of secondary amines to carbon disulfide (SCS).²⁰ Despite numerous variations, there is no simple comprehensive synthetic approach for the facile preparation of *N*-substituted, *N,N*-disubstituted, and *N,N*-unsubstituted *S*-alkyl thiocarbamates.

While investigating various thiol-protecting groups, we discovered that unique product formation occurs following attempted deprotection of a trichloroacetylalkane thiol adduct with an amine. Rather than achieving deprotection, nucleophilic substitution resulted, affording the corresponding *S*-alkyl thiocarbamate in high yield. Therefore, we sought to develop an efficient one-pot synthetic approach to *S*-alkyl thiocarbamates, which would allow for direct control of character and degree of substitution. It was likewise desirable to afford a library of thiocarbamates through the use of commercially available reagents in a single straightforward, simple, high-yielding process, employing less toxic materials and preferably nongaseous reagents.

The trichloroacetyl protecting group for alcohols and amines can be introduced in high yield and easily cleaved with ammonia or potassium hydroxide.²¹ It was believed that nucleophilic substitution of trichloroacetyl chloride

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SCHEME 1

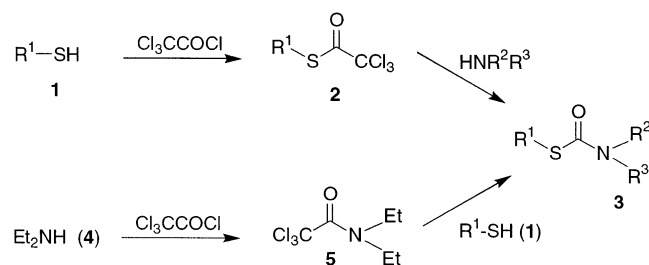


TABLE 1. Summary of Reactions Starting with Thiol (1)

entry	thiol	R ¹	S-ester	R ²	R ³	prod	time (h)	T (°C)	yield (%)
1	1a	<i>n</i> C ₆ H ₁₃ -	2a	H	H	3a	.25	rt	100
2	1a	<i>n</i> C ₆ H ₁₃ -	2a	H	<i>n</i> Bu	3b	.25	rt	87
3	1a	<i>n</i> C ₆ H ₁₃ -	2a	H	<i>t</i> Bu	3c	.25	rt	83
4	1a	<i>n</i> C ₆ H ₁₃ -	2a	Et	Et	3d	1	rt	94
5	1b	Ph-	2b	H	H	3e	12	60	98
6	1b	Ph-	2b	Et	Et	3f	12	60	90
7	1c	<i>p</i> ClPhCH ₂ -	2c	H	H	3g	4	60	99
8	1c	<i>p</i> ClPhCH ₂ -	2c	Et	Et	3h	4	60	91

with a variety of thiols would result in the corresponding thioesters (Scheme 1). Reaction of 1 equiv of thiol (1) with an excess of trichloroacetyl chloride, in a solventless system, afforded an exothermic reaction that proceeded to completion within 45 min or less in all cases. The product was purified by heating the resulting mixture in the same reaction vessel under vacuum to facilitate the removal of excess trichloroacetyl chloride and residual hydrogen chloride, affording the corresponding pure product 2 in quantitative yields.

The formation of compound 2 proceeded rapidly without solvent, with an observed rate of consumption of the thiol in the order of alkyl > benzyl ≫ phenyl. Reaction with the alkanethiol was complete within 15 min, whereas the benzyl thiol required 30 min and the phenyl derivative required approximately 45 min to achieve complete conversion. Lesser reaction times resulted in significantly diminished yields.

The second step involves the displacement of the trichloromethyl group by a haloform displacement upon treatment with an amine. A variety of compounds can be synthesized from a single intermediate (2) by simply altering the amine employed. Ammonium hydroxide, a variety of primary amines, and a secondary amine are used to illustrate the versatility of this method (Table 1). Several solvent systems were also investigated ranging from neat to extremely polar. When concentrated ammonium hydroxide was employed, the water-insoluble product was easily isolated by filtration. When substituted amines were employed in neat, aqueous, and methanolic systems, respectively, the methanolic system afforded the highest yields, while aqueous media afforded only trace product formation due to amine insolubility. Our results indicated that primary amines function best in solventless systems, while secondary amines work best in methanolic solvent systems. Products were purified by simple recrystallization, distillation, or column chromatography.

In an attempt to examine alternative routes, we reversed the order of thiol and amine reagent addition

TABLE 2. Summary of Reactions Starting with Diethylamine (4)

entry	thiol	T (°C)	time (h)	product	yield (%)
1	1d	60	4	3d	59
2	1f	100	8	3f	63
3	1h	80	6	3h	54

as further illustrated in Scheme 1. While this sequence was successful, it did have several limitations. The addition of amine (4) to the solution of trichloroacetyl chloride must be done at a reduced temperature and at a slow rate to prevent amine salt formation (Table 2). Also, the use of a solvent system was necessary to allow control of the rate of reaction. Subsequent treatment of (5) with the corresponding thiol (1) affords compound (3), with a substantially decreased yield combined with a significantly increased reaction time.

Experimental Section

General Methods. Methanol was distilled from calcium hydride under nitrogen. Moisture-sensitive reactions were conducted in oven-dried glassware under a nitrogen atmosphere unless otherwise noted. Analytical thin-layer chromatography was performed on precoated silica gel sheets, and flash column chromatography was accomplished using silica gel, 60 Å (200–400 mesh). External elemental analyses were performed by Atlantic Microlab, Inc., Norcross, GA 30091. All melting points are uncorrected. Unless otherwise noted, ¹H and ¹³C NMR spectra were taken in CDCl₃ at 300 and 75 MHz, respectively, with a TMS internal standard. Chemical shifts are reported in units downfield from TMS. Coupling constants, *J*, are reported in units of hertz (Hz).

General Procedure for Preparation of 2 from 1. A 3.08 g (16.9 mmol) quantity of chilled trichloroacetyl chloride was transferred into a 25 mL round-bottomed flask equipped with magnetic stir bar and a drying tube. After the mixture was warmed to room temperature, the dropwise addition of thiol (1) (8.46 mmol) was made via a syringe over a period of 15 min. The mildly exothermic reaction was stirred for 2 h, followed by distillation (120 °C/5 mmHg) of excess reagent and byproducts, leaving a quantitative yield of the product (2). Additional purification was not necessary for subsequent reactions.

Trichloroacetic Acid S-Hexyl Ester (2a). FTIR: 2961, 2929, 2851, 1693, 1467, 1035, 857, 785, 750, 619 cm⁻¹. ¹H NMR δ: 3.04 (t, *J* = 6, 2H), 2.68 (dt, 2H), 1.48–1.27 (m, 6H), 0.92 δ (t, *J* = 6, 3H). ¹³C NMR δ: 189.3, 94.9, 31.7, 31.2, 28.5, 28.4, 22.4, 13.9 δ. Bp: 137 °C/1 Torr (lit.²² bp 104 °C/0.4 Torr).

Trichloroacetic Acid S-Phenyl Ester (2b). FTIR: 3420, 3061, 1705, 1479, 1447, 1095, 1023 cm⁻¹. ¹H NMR δ: 7.46–7.46 δ (m, 5H). ¹³C NMR δ: 187.7, 134.7, 130.5, 129.7, 125.9, 94.1. Mp: 55–57 °C (lit.²³ mp 53–55 °C; bp 115–118 °C/1 Torr).

Trichloroacetic acid S-(4-Chlorobenzyl) Ester (2c). FTIR: 3029, 2977, 2930, 1776, 1689, 1594, 1487, 1408, 1241, 1198, 1099, 1039, 1011, 852, 781, 745, 690 cm⁻¹. ¹H NMR δ: 7.31–7.25 (m, 4H), 4.18 δ (s, 2H). ¹³C NMR δ: 188.5, 133.8, 133.6, 130.3, 129.1, 94.4, 35.3. Anal. Calcd for C₉H₆Cl₃O₂S: C, 35.56; H, 1.99. Found: C, 35.89; H, 1.96.

General Procedure for Preparation of 3 from 2. A solution of trichloroacetic ester (2) (1.90 mmol) in 10 mL of methanol was prepared in a 50 mL round-bottomed flask equipped with magnetic stirring bar, thermometer, and N₂ inlet.

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After the mixture was stirred for 5 min at rt, 3.80 mmol of the corresponding amine was rapidly added. The reaction was rapidly stirred at the indicated temperature for 24 h (see Table 1). The reaction was worked up by concentration to dryness on the rotary evaporator followed by distillation employing the short-path distillation head to remove excess reagent and byproducts. Additional purification was made by either recrystallization or flash column chromatography for the aryl compounds. Yields ranged from 70 to 97%.

Thiocarbamic Acid S-Hexyl Ester (3a). FTIR (neat): 3366, 3326, 3247, 2971, 2943, 2589, 1653 cm^{-1} . ^1H NMR δ : 6.62 (bs, 1NH), 6.08 (bs, 1NH), 2.65 (t, $J = 7$, 2H), 1.63–1.59 (m, 4H), 1.27–1.16 (m, 4H), 0.86 δ (t, $J = 7$, 3H). ^{13}C NMR δ : 163.6, 39.2, 31.4, 29.2, 28.2, 22.2, 14.0. Mp: 99–102 $^{\circ}\text{C}$ (lit.²⁴ mp 105 $^{\circ}\text{C}$).

n-Butylthiocarbamic Acid S-Hexyl Ester (3b). FTIR: 3308, 2958, 2926, 1651, 1523, 1463, 1463, 1372, 1150, 921 cm^{-1} . ^1H NMR δ : 8.20 (bs, 1NH), 3.03 (t, $J = 6$, 2H), 2.69 (t, $J = 6$, 2H), 1.82–1.65 (m, 2H), 1.62–1.57 (m, 4H), 1.47–1.29 (m, 6H), 0.96 (t, $J = 6$, 3H), 0.90 δ (t, $J = 6$, 3H). ^{13}C NMR δ : 164.3, 44.7, 39.5, 38.8, 30.9, 29.2, 27.9, 22.2, 19.5, 13.7, 13.2. Mp: 142–148 $^{\circ}\text{C}$ dec. FTIR and NMR data are in agreement with that previously reported.²⁵

t-Butylthiocarbamic Acid S-Hexyl Ester (3c). FTIR (neat): 2958, 2922, 2858, 1667, 1450, 1265 cm^{-1} . ^1H NMR δ : 5.80 (bs, 1NH), 2.268 (t, $J = 7$, 2H), 1.77–1.54 (m, 4H), 1.40 (s, 9H), 1.32–1.29 (m, 4H), 0.89 δ (t, $J = 6$, 3H). ^{13}C NMR δ : 163.0, 67.0, 52.4, 39.1, 31.4, 31.3, 29.0, 22.7, 14.0. Mp: 212–124 $^{\circ}\text{C}$. Anal. Calcd for $\text{C}_{11}\text{H}_{23}\text{NOS}$: C, 60.78; H, 10.66; N, 6.44. Found: C, 60.84; H, 10.37; N, 6.79.

Diethylthiocarbamic Acid S-Hexyl Ester (3d). FTIR: 2969, 2819, 2794, 1646, 1487, 1372, 1205, 1094, 1011 cm^{-1} . ^1H NMR δ : 3.05 (q, $J = 6$, 4H), 2.68 (t, $J = 6$, 2H), 1.70–1.48 (m, 2H), 1.43 (t, $J = 6$, 6H), 1.41–1.35 (m, 2H), 1.30–1.15 (m, 4H), 0.89 δ (t, $J = 6$, 3H). ^{13}C NMR δ : 162.7, 42.1, 38.5, 30.8, 28.7, 27.8, 22.1, 13.8, 12.1. Mp: 64–66 $^{\circ}\text{C}$. Anal. Calcd for $\text{C}_{11}\text{H}_{23}\text{NOS}$: C, 60.78; H, 10.66; N, 6.44. Found: C, 60.98; H, 10.36; N, 6.68.

Thiocarbamic Acid S-Phenyl Ester (3e). FTIR: 3648, 3623, 3068, 2984, 1687, 1574, 1475, 1435, 1071, 1019 cm^{-1} . ^1H NMR (acetone- d_6) δ : 9.97 (bs, 2NH), 7.51 (d, $J = 6$, 2H), 7.36 (t, $J = 6$, 2H), 7.23 δ (d, $J = 7$, 1H). ^{13}C NMR (acetone- d_6) δ : 176.3, 128.9, 127.3, 127.0, 127.0, 126.8. Mp: 98–100 $^{\circ}\text{C}$ (lit.²⁶ mp 96–98 $^{\circ}\text{C}$).

Diethylthiocarbamic Acid S-Phenyl Ester (3f). FTIR: 2973, 2819, 2775, 2482, 2391, 1657, 1483, 1360, 1210, 1063 cm^{-1} . ^1H NMR δ : 9.39 (bs, 1NH), 7.43 (d, $J = 6$, 2H), 7.27–7.22 (m, 3H), 2.97 (q, $J = 6$, 4H), 1.38 δ (t, $J = 6$, 6H). ^{13}C NMR 168.7, 133.2, 130.3, 128.9, 128.1, 42.20, 11.1. Mp: 46–49 $^{\circ}\text{C}$. FTIR and NMR data are in agreement with that previously reported.²⁷

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Thiocarbamic Acid S-(4-Chlorobenzyl) Ester (3g). FTIR: 3176, 3025, 1657, 1486, 1408, 1328, 1091, 329 cm^{-1} . ^1H NMR δ : 7.89 (bs, 2NH), 7.41 (d, $J = 7$, 2H), 7.33 (d, $J = 7$, 2H), 3.78 δ (s, 2H). ^{13}C NMR δ : 205.4, 135.3, 131.9, 129.9, 127.5, 40.8. Mp: 130–133 $^{\circ}\text{C}$ (lit.²⁸ mp 137–139 $^{\circ}\text{C}$).

Diethylthiocarbamic Acid S-(4-Chlorobenzyl) Ester (3h). FTIR: 3017, 2977, 2819, 1657, 1491, 1368, 1206, 1091, 1015 cm^{-1} . ^1H NMR δ : 7.28 (d, $J = 6$, 2H), 7.15 (d, $J = 6$, 2H), 3.67 (s, 2H), 3.07 (q, $J = 6$, 4H), 1.40 δ (t, $J = 6$, 6H). ^{13}C NMR δ : 168.0, 134.8, 131.7, 129.6, 127.3, 42.1, 36.3, 10.2 δ . Mp: 161–164 $^{\circ}\text{C}$. FTIR and NMR data are in agreement with that previously reported.^{27,29}

2,2,2-Trichloro-N,N-diethylacetamide (5). A solution of 1.00 g diethylamine (13.67 mmol) in 20 mL methanol was prepared in a 50 mL two-necked round-bottomed flask equipped with a stirring bar, thermometer, nitrogen inlet, condenser, and septum. After the mixture was cooled to 0 $^{\circ}\text{C}$ and stirred for 10 min, 4.97 g of trichloroacetyl chloride (27.34 mmol) was added dropwise via syringe over a 45 min, followed by stirring under the indicated conditions. The reaction was worked up by concentration to dryness through a short path still head, diluting the residual product with CH_2Cl_2 (30 mL), and washing with water (3 \times 10 mL). The organic layer was dried over MgSO_4 and concentrated under reduced pressure. The crude product was purified by flash column chromatography (hexane/EtOAc) to afford the desired product (5) in a 45% yield. FTIR: 2989, 2937, 1708, 1519, 1455, 1364, 1268, 12114, 912, 821, 733, 682 cm^{-1} . ^1H NMR δ : 3.77 (q, $J = 6$, 4H), 1.15 δ (t, $J = 6$, 6H). ^{13}C NMR δ : 160.3, 93.1, 52.8, 25.4 δ . Bp: 79 $^{\circ}\text{C}/2$ Torr (lit.³⁰ bp 109 $^{\circ}\text{C}/\text{Torr}$).

General Procedure for Preparation of 3 from 5. A solution of 1.00 g of compound 5 (4.58 mmol) in 15 mL of freshly distilled THF was prepared in a 50 mL round-bottomed flask. After the mixture was stirred at rt for 15 min, thiol (1) (6.86 mmol) was added dropwise via syringe over 15 min. The reaction was refluxed for 4 h followed by 12 h of stirring under nitrogen. The reaction mixture was diluted with CH_2Cl_2 (30 mL) and washed with water (3 \times 10 mL). The organic layer was dried over MgSO_4 and concentrated under reduced pressure to afford a brown oil. Subsequent purification ensued employing flash column chromatography to afford the desired product (3).

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