Facile One-Pot Synthesis of S-Alkyl Thio carbamates

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Abstract: We report a novel one-pot two-step synthesis of a variety of S-alkyl thio carbamates. 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 thio carbamates (S-alkyl thioureas) 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 bactericidal,⁵ pesticidal,⁷ 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 thio carbamates; however, these rearrangements are extremely limited in starting substrates.¹² Transition-metal species approaches which incorporate metal catalysts or proceed 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 deacylated with ammonia or potassium hydroxide.¹⁰ It was believed that nucloephilic substitution of trichloroacetyl chloride 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.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 thio carbamates 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 thio carbamates have also been prepared from salts of dithiocarbamic acid, which are prepared by the addition of secondary amines to carbon disulfide (SCS).²¹

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 thio carbamates.

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, nucloephilic substitution resulted, affording the corresponding S-alkyl thio carbamate in high yield. Therefore, we sought to develop an efficient one-pot synthetic approach to S-alkyl thio carbamates, which would allow for direct control of character and degree of substitution. It was likewise desirable to afford a library of thio carbamates 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 deacylated with ammonia or potassium hydroxide.¹⁰ It was believed that nucloephilic substitution of trichloroacetyl chloride

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 halofrom 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 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) afforded 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 CDCl 3 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 a magnetic stirrer 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.

**Trichlorothioacetic Acid S-Hexyl Ester (2a).** FTIR: 3420, 3061, 1705, 1479, 1447, 1095, 1023 cm⁻¹. 1H NMR: 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, 133.8, 130.5, 129.7, 94.9, 31.7, 31.2, 28.5, 28.4, 22.1, 13.9. Bp: 137 °C/1 Torr (lit. 22 bp 104 °C/0.4 Torr).

**Trichlorothioacetic Acid S-Phenyl Ester (2b).** FTIR: 3420, 3061, 1705, 1479, 1447, 1095, 1023 cm⁻¹. 1H NMR δ: 7.46–7.66 (m, 5H). 13C NMR δ: 187.7, 134.7, 130.5, 129.7, 125.9, 94.1. Mp: 55–57 °C (lit. 33 mp 53–55 °C; bp 115–118 °C/1 Torr).

**Trichlorothioacetic Acid S-(4-Chlorobenzyl) Ester (2c).** FTIR: 3029, 2977, 2930, 1776, 1689, 1594, 1487, 1408, 1241, 1181, 1099, 1039, 1019, 952, 781, 745, 694 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 C19H13Cl2O4S: C, 45.0; H, 2.82. Found: C, 45.8; H, 2.96.

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

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**References:**


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: 6.62 (bs, 1H), 6.08 (bs, 1H), 2.45 (t, J = 6, 2H), 1.33–1.59 (m, 4H), 1.27–1.16 (m, 4H), 0.86 (t, J = 7, 3H). ¹³C NMR: 163.6, 39.2, 31.4, 29.2, 28.2, 22.2, 14.0. Mp: 99–102 °C (lit.²⁴ mp 105 °C).

**n-Butylthiocarbamic Acid S-Hexyl Ester (3b).** FTIR: 3308, 2958, 2926, 1651, 1423, 1463, 1372, 1150, 921 cm⁻¹. ¹H NMR: 5.80 (bs, 1NH), 2.26 (t, J = 7, 2H), 1.77–1.54 (m, 4H), 1.40 (s, 9H), 1.35–1.28 (m, 4H), 0.89 (t, J = 6, 3H), 0.90 (t, J = 6, 3H). ¹³C NMR: 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 °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: 6.10 (bs, 2H), 6.03 (t, J = 6, 2H), 2.69 (t, J = 6, 2H). ¹³C NMR: 162.7, 42.1, 38.5, 30.8, 28.7, 27.8, 22.1, 13.8, 12.1. Mp: 64–66 °C. Anal. Calc. for C₁₁H₂₃NOS: 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: 3.05 (q, J = 6, 4H), 2.68 (t, J = 6, 2H), 1.70–1.48 (m, 4H), 1.38 (s, 9H), 1.30–1.15 (m, 4H), 0.89 (t, J = 6, 3H). ¹³C NMR: 162.7, 42.1, 38.5, 30.8, 28.7, 27.8, 22.1, 13.8, 12.1. Mp: 64–66 °C. Anal. Calc. for C₁₁H₂₃NOS: 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, 1547, 1447, 1345, 1071, 1019 cm⁻¹. ¹H NMR (acetone-d₆): 9.97 (bs, 2NH), 7.51 (d, J = 6, 2H), 7.36 (t, J = 6, 2H), 7.23 (d, J = 7, 1H). ¹³C NMR (acetone-d₆): 176.3, 128.9, 127.3, 127.0, 126.8. Mp: 98–100 °C (lit.²⁶ mp 96–98 °C).

**Diethylthiocarbamic Acid S-Phenyl Ester (3f).** FTIR: 2973, 2819, 2775, 2482, 2391, 1657, 1483, 1360, 1210, 1063 cm⁻¹. ¹H NMR (acetone-d₆): 9.39 (bs, 1NH), 7.43 (d, J = 6, 2H), 7.27–7.22 (m, 3H), 2.97 (q, J = 6, 4H), 1.36 (t, J = 6, 3H). ¹³C NMR: 166.7, 135.2, 130.3, 128.9, 128.1, 42.20, 11.1. Mp: 46–49 °C. FTIR and NMR data are in agreement with that previously reported.²⁷

**Thiocarbamic Acid S-(4-Chlorobenzyl) Ester (3g).** FTIR: 3176, 3025, 1657, 1486, 1408, 1328, 1091, 329 cm⁻¹. ¹H NMR: 7.89 (bs, 2NH), 7.41 (d, J = 7, 2H), 7.33 (d, J = 7, 2H), 3.78 (s, 2H). ¹³C NMR: 205.4, 135.3, 131.9, 129.9, 127.5, 104.8. Mp: 130–133 °C (lit.²⁶ mp 137–139 °C).

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


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