Primary Alkyl Bromides from Dimethylthiocarbamates

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Abstract: The conversion of primary alkyl dimethylthiocarbamates into alkyl bromides using the Vilsmeier reagent occurs in high yields in the presence of other non-acid sensitive and non-nucleophilic functional groups.

Key words: halogenation, protecting groups, alkyl halides, thiocarbamates, Vilsmeier

Protecting groups are often necessary tools in multistep organic syntheses.[1] Nevertheless, the process of protection and deprotection contributes to the overall inefficiency of a synthetic sequence. Often the liberated functional groups are transformed into other groups. Greater efficiency is possible if the deprotection and subsequent transformation can be performed in a single step.

Alcohols are versatile synthetic intermediates, but because they are ambiphilic, they often require protection to allow reactions at other centers. Alcohols are good precursors for alkyl halides. The thiocarbonyl group is an attractive protecting group for alcohols because of its muted electrophilicity relative to the carbonyl group. Xanthates (dithiocarbonates) are a common class of thiocarbonyl derivatives of alcohols. Barton and co-workers have shown that xanthates can be converted directly into alkyl halides with soft electrophilic reagents.[2] They used excess molecular bromine for the preparation of alkyl bromides. The fact that bromine reacts rapidly with many functional groups limits the synthetic potential of this reaction. Xanthates can also be transformed into alkyl bromides via free-radical methods,[3,4] but again the reactions do not have general utility. Reaction of xanthates with 1-(difluoroiodo)-4-methylbenzene gives alkyl fluorides.[5] Recently we have shown that *O*-ethyl *S*-alkyl dithiocarbonates react with the Vilsmeier reagent to form *S*-alkylchlorothioformates and ethyl chloride.[6] We wondered whether the bromide Vilsmeier reagent would be a reasonable substitute for bromine.

Thiocarbamates are another class of thiocarbonyl-alcohol derivatives that are closely related to xanthates. We chose to examine dimethylthiocarbamates rather than xanthates for two reasons. The first is that dimethylthiocarbamates should show greater chemoselectivity because they are stronger nucleophiles than the xanthates. The second is that the dimethylthiocarbamoyl moiety is a good protecting group for alcohols.[7] It is resistant to many common reagents, and treatment with periodic acid or hydrogen peroxide liberates the alcohol. In this paper we explore using the Vilsmeier reagent to convert dimethylthiocarbamates into alkyl bromides in the presence of other functional groups and alcohol protecting groups.

Dimethythiocarbamates **1a–j** (Scheme 1) were prepared using the methods described by Falck and co-workers.[7] The dimethylthiocarbamoyl group is generated by one of two methods. Method A involves the reaction of an alkoxide with dimethylthiocarbamoyl chloride, while in Method B an alcohol is treated first with thiocarbonyldiimidazole and then dimethylamine. The dimethylthiocarbamates were purified by distillation or column chromatography and characterized by ^{1}H and ^{13}C NMR and high resolution mass spectroscopy. Although Falck and co-workers prepared the seven-carbon-chain homologues of **1a**,**b**,**e–j**, we opted for the six-carbon-chain compounds simply because hexane-1,6-diol is much less expensive than heptane-1,7-diol. We chose to work with the bromide Vilsmeier reagent derived from 4-formylmorpholine, 4-(bromomethylene)morpholin-4-ium bromide (**2**). We have found that it is much more reactive with thiocarbonyls than the more common reagent derived from *N*,*N*-dimethylformamide [*N*-(bromomethylene)-*N*-methylmethanaminium bromide].[6,8]

Our results show that dimethylthiocarbamoyl-protected alcohols can be transformed into alkyl bromides in high yield in the presence of a number of functional groups and other alcohol protecting groups (Table 1). In particular, the highly compatible functional groups include ketone **1c**, ester **1d**, and alkene **1a**, and the fully inert alcohol protecting groups are acetate **1f** and benzyl ether **1g**. In contrast, this method does not work with alcohol **1e** or with tetrahydropyranyl **1h** or *tert*-butyldimethylsilyl **1i** protecting groups. Finally, the reaction works fairly well with aldehyde **1b** and *tert*-butyldiphenylsilyl protecting group **1j**, but each of these gives a small amount of a single byproduct.

Analysis of the product mixtures in those cases where the transformation gives multiple products is revealing. In the case of **1e** there is a direct competition between the primary alcohol and the dimethylthiocarbamate for **2**. Both groups react by nucleophilic addition. The product analysis when **2** is the limiting reagent (0.75 equiv) indicates that the alcohol is four-to-five times more reactive than the dimethylthiocarbamate. The formation of the bromoformate byproduct [$Br(CH_2)_6OCHO$, **9**] results from hydrolysis of the adduct between the alcohol and **2**.

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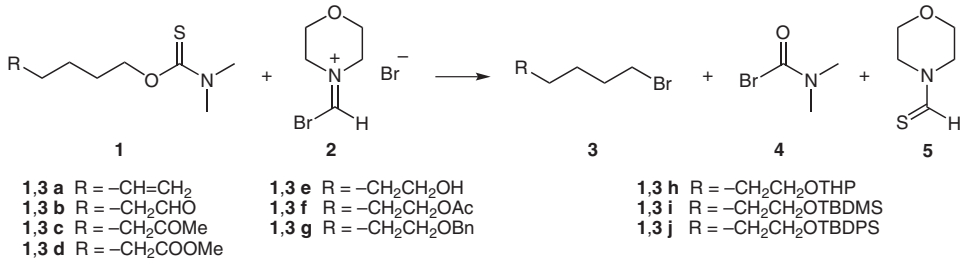
Knowing that the primary alcohol reacts faster than the dimethylthiocarbamate allows for interpretation of the results with the tetrahydropyranyl- and silyl-protected reactants **1h–j**. With **1h** and **1i** the product mixture is mostly **3** and 6-bromohexan-1-ol (**8**). Neither substrate gives much 6-bromohexyl dimethylthiocarbamate (**7**). These results indicate that both protecting groups are being stripped off during the reaction, but at a slower rate than the reaction of **2** with the dimethylthiocarbamate. The reactivity of **2** with the tetrahydropyranyl group is not surprising given that Viehe's salt is reported to convert tetrahydropyranyl-protected alcohols into alkyl halides.[9] In the case of **1i** there may be some direct conversion of the *tert*-butyldimethylsiloxy group into a bromide to account for the relatively larger amount of 1,6-dibromohexane (**6**). The reaction with **1j** gives **3j** as the only brominated product indicating that the protecting group remains intact during the reaction with **2**. The *tert*-butyldiphenylsilyl group is known to be much more resistant to acid than the *tert*-butyldimethylsilyl group.[1]

The results with the aldehyde **1b** are surprising. Here the reaction with the Vilsmeier reagent produces 1,6-dibromohexane (**6**) as a byproduct. In fact, when the normal excess of **2** is used, the dibromide **6** is the major product. Using only a slight excess of **2** maximizes the yield of **3b**. Thus, **3b** is the precursor to the dibromide **6**. However, independent reaction of **3b** with **2** does not give the dibromide **6**. The conversion of the formyl group into a methylene bromide requires a reducing agent. Previous work in our laboratory implicates the involvement of byproduct **5**.[6] Treatment of **5** with oxalyl chloride gives partial oxidation to the halogenated derivative (morpholine-4-carbothioyl chloride). The identity of reducing agent is currently under investigation.

The success of the reaction in the presence of a ketone or an aldehyde is noteworthy because the Vilsmeier reagent is known to react with enols to give chloroformylation.[10]

Secondary dimethylthiocarbamates give elimination byproducts. Reaction with 1-methylhexyl dimethylthiocarbamate gives mostly 2-bromoheptane (64% vs 11% heptenes). However, elimination is the major pathway with cyclohexyl dimethylthiocarbamate (20% cyclohexyl bromide vs 74% cyclohexene).



Scheme 1

Table 1 Conversion of Dimethylthiocarbamates **1a–j** into Alkyl Bromides **3** Using 4-(Bromomethylene)morpholin-4-ium Bromide (**2**)

Reactant	**2** (equiv)	Time (h)	Workup	Product **3**	Yield (%) of **3**	Other Product(s)[a] [Yield (%)]
1a	1.5	2	A	**3a**	88	
1b	1.1	1	B	**3b**	75	$Br(CH_2)_6Br$ (**6**) [5]
	1.5	2.5	A	**3b**	20	**6** [34]
1c	1.5	3	A	**3c**	92	
1d	1.5	1	B	**3d**	95	
1e	1.5	24	A	**3e**	0	**6** [44], $Br(CH_2)_6OCSNMe_2$ (**7**) [50], $Br(CH_2)_6OH$ (**8**) [4]
	0.75	0.5	A		0[b]	**6** [18], **7** [59], **8** [13], $Br(CH_2)_6OCHO$ (**9**) [10]
1f	1.5	2.5	A	**3f**	89	
1g	1.5	1	B	**3g**	96	
1h	1.5	1.5	A	**3h**	14[c]	**6** [5], **7** [3], **8** [27], **9** [23]
1i	1.5	2	A	**3i**	26[d]	**6** [10], **7** [1], **8** [21], TBDMSOH [13]
1j	1.8	2	B	**3j**	81	TBDPSOH [18]

[a] Product distribution according to GC/MS.
[b] 38% conversion.
[c] 79% conversion.
[d] 95% conversion.

In conclusion, the conversion of **1** into **3** is an attractive method for converting primary alcohols that have been protected as dimethylthiocarbamate directly into bromides. A separate deprotection step is avoided. The reaction is reasonably chemoselective, but it does not work well with acid-sensitive or nucleophilic groups.

Dimethythiocarbamates **1a–j** (Scheme 1) were prepared using the methods described by Falck and co-workers.[7] The bromides **3a–j** are all known compounds, and they show NMR and MS data consistent with their structures. Product yields are listed in Table 1. In those cases where only the alkyl bromide **3** was produced, the purity was greater than 97% by GC/MS.

***O*-Hex-5-enyl Dimethylcarbamothioate (1a)**
Method B[7] using 6-bromohex-1-ene; yield: 69%; bp 93–94 °C/0.4 mbar.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.80 (ddt, *J* = 17.1, 10.2, 6.7 Hz, 1 H), 5.02 (dd, *J* = 17.1, 2.1 Hz, 1 H), 5.97 (dd, *J* = 10.2, 2.1 Hz, 1 H), 4.44 (t, *J* = 6.5 Hz, 2 H), 3.35 (s, 3 H), 3.10 (s, 3 H), 2.10 (td, *J* = 7.9, 6.7 Hz, 2 H), 1.74 (tt, *J* = 6.9, 6.5 Hz, 2 H), 1.50 (tt, *J* = 7.9, 6.9 Hz, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 188.44, 138.52, 114.99, 71.73, 42.85, 37.90, 33.53, 28.45.

HRMS: *m*/*z* [M + Na]$^+$ calcd for $C_9H_{17}NNaOS$: 210.09231; found: 210.09223.

***O*-6-Oxohexyl Dimethylcarbamothioate (1b)**
From CrO_3 oxidation of **1e**,[7] followed by chromatography (silica gel); yield: 44%.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.78 (t, *J* = 1.6 Hz, 1 H), 4.45 (t, *J* = 6.7 Hz, 2 H), 3.36 (s, 3 H), 3.12 (s, 3 H), 2.47 (td, *J* = 7.2, 1.6 Hz, 2 H), 1.76 (m, 2 H), 1.69 (m, 2 H), 1.44 (m, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 202.36, 188.28, 71.42, 43.97, 42.91, 37.95, 28.83, 25.82, 21.97.

HRMS: *m*/*z* [M + Na]$^+$ calcd for $C_9H_{17}NNaO_2S$: 226.08722; found: 226.08707.

***O*-6-Oxoheptyl Dimethylcarbamothioate (1c)**
Method B[7] using 7-hydroxyheptan-2-one (the latter was made from the reaction of ε-caprolactone with MeLi); yield: 30%; bp 145–146 °C/0.4 mbar.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.43 (t, *J* = 6.6 Hz, 2 H), 3.36 (s, 3 H), 3.11 (s, 3 H), 2.45 (t, *J* = 7.4 Hz, 2 H), 2.14 (s, 3 H), 1.74 (m, 2 H), 1.62 (m, 2 H), 1.40 (m, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 208.86, 188.28, 71.56, 43.73, 42.88, 37.94, 30.20, 28.86, 25.80, 23.66.

HRMS: *m*/*z* [M + Na]$^+$ calcd for $C_{10}H_{19}NNaO_2S$: 240.10287; found: 240.10237.

Methyl 6-(Dimethylcarbamothioyloxy)hexanoate (1d)
Method B[7] using methyl 6-hydroxyhexanoate (the latter was made from the reaction of ε-caprolactone with methanolic H_2SO_4); yield: 42%; bp 155–160 °C/0.4 mbar.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.44 (t, *J* = 6.5 Hz, 2 H), 3.67 (s, 3 H), 3.36 (s, 3 H), 3.10 (s, 3 H), 2.33 (t, *J* = 7.5 Hz, 2 H), 1.75 (m, 2 H), 1.68 (m, 2 H), 1.44 (m, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 188.45, 174.07, 71.55, 51.71, 42.86, 37.88, 34.15, 28.70, 25.80, 24.83.

HRMS: *m*/*z* [M + Na]$^+$ calcd for $C_{10}H_{19}NNaO_3S$: 256.09779; found: 256.09716.

***O*-6-Hydroxyhexyl Dimethylcarbamothioate (1e)**
Method A[7] using hexane-1,6-diol (3.5 equiv) to favor monosubstitution; yield: 57%; bp 143–144 °C/0.4 mbar.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.44 (t, *J* = 6.6 Hz, 2 H), 3.65 (t, *J* = 6.6 Hz, 2 H), 3.36 (s, 3 H), 3.11 (s, 3 H), 1.75 (m, 2 H), 1.59 (m, 2 H), 1.42 (m, 4 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 188.43, 71.77, 62.98, 42.83, 37.88, 32.81, 28.94, 25.98, 25.63.

HRMS: *m*/*z* [M + Na]$^+$ calcd for $C_9H_{19}NNaO_2S$: 228.10287; found: 228.10235.

6-(Dimethylcarbamothioyloxy)hexyl Acetate (1f)
From the reaction of **1e** with Ac_2O and pyridine; yield: 50%; bp 165–169 °C/0.4 mbar.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.44 (t, *J* = 6.6 Hz, 2 H), 4.06 (t, *J* = 6.6 Hz, 2 H), 3.37 (s, 3 H), 3.11 (s, 3 H), 2.05 (s, 3 H), 1.74 (m, 2 H), 1.65 (m, 2 H), 1.42 (m, 4 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 188.39, 171.33, 71.67, 64.58, 42.83, 37.88, 28.86, 28.70, 25.84, 25.82, 21.24.

HRMS: *m*/*z* [M + Na]$^+$ calcd for $C_{11}H_{21}NNaO_3S$: 270.11344; found: 270.11273.

***O*-6-(Benzyloxy)hexyl Dimethylcarbamothioate (1g)**
Method B[7] using 6-(benzyloxy)hexan-1-ol (the latter was made from the reaction of hexane-1,6-diol with BnCl and KOH) followed by chromatography (silica gel); yield: 89%.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.34 (m, 5 H), 4.5 (s, 2 H), 4.43 (t, *J* = 6.6 Hz, 2 H), 3.47 (t, *J* = 6.5 Hz, 2 H), 3.36 (s, 3 H), 3.09 (s, 3 H), 1.73 (m, 2 H), 1.63 (m, 2 H), 1.42 (m, 4 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 188.49, 138.77, 128.54, 127.8, 127.68, 73.12, 71.89, 70.49, 42.85, 37.9, 29.93, 28.98, 26.17, 26.12.

HRMS: *m*/*z* [M + Na]$^+$ calcd for $C_{16}H_{25}NNaO_2S$: 318.14982; found: 318.14971.

***O*-6-(Tetrahydro-2*H*-pyran-2-yloxy)hexyl Dimethylcarbamothioate (1h)**
From the reaction of **1e** with tetrahydropyran and TsOH, followed by chromatography (silica gel); yield; 77%.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.57 (m, 1 H), 4.43 (t, *J* = 6.6 Hz, 2 H), 3.87 (m, 1 H), 3.74 (m, 1 H), 3.50 (m, 1 H), 3.39 (m, 1 H), 3.37 (s, 3 H), 3.11 (s, 3 H), 1.90–1.48 (m, 10 H), 1.43 (m, 4 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 188.45, 99.08, 71.89, 67.67, 62.61, 42.84, 37.9, 30.99, 29.89, 28.96, 26.2, 26.1, 25.71, 19.95.

HRMS: *m*/*z* [M + Na]$^+$ calcd for $C_{14}H_{27}NNaO_3S$: 312.16039; found: 312.15972.

***O*-6-(*tert*-Butyldimethylsiloxy)hexyl Dimethylcarbamothioate (1i)**
Method B[7] using 6-(*tert*-butyldimethylsiloxy)hexan-1-ol (the latter was made from the reaction of hexane-1,6-diol with NaH, then with TMDMSCl) followed by chromatography (silica gel); yield: 99%.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.43 (t, *J* = 6.6 Hz, 2 H), 3.61 (t, *J* = 6.4 Hz, 2 H), 3.37 (s, 3 H), 3.11 (s, 3 H), 1.73 (tt, *J* = 7.4, 6.6 Hz, 2 H), 1.53 (tt, *J* = 7.1, 6.4 Hz, 2 H), 1.39 (m, 4 H), 0.89 (s, 9 H), 0.05 (s, 6 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 188.48, 71.94, 63.32, 42.85, 37.9, 32.97, 29.04, 26.22, 26.07, 25.77, 18.63, –5.00.

HRMS: *m*/*z* [M + Na]$^+$ calcd for $C_{15}H_{33}NNaO_2SSi$: 342.18935; found: 342.18884.

***O*-6-(*tert*-Butyldiphenylsiloxy)hexyl Dimethylcarbamothioate (1j)**

Method B[7] using 6-(*tert*-butyldiphenylsiloxy)hexan-1-ol (the latter was made from the reaction of hexane-1,6-diol with TBDPSCl and *i*-PrNEt$_2$) followed by chromatography (silica gel); yield: 99%.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.66 (m, 4 H), 7.38 (m, 6 H), 4.42 (t, *J* = 6.6 Hz, 2 H), 3.66 (t, *J* = 6.4 Hz, 2 H), 3.36 (s, 3 H), 3.08 (s, 3 H), 1.70 (m, 2 H), 1.57 (m, 2 H), 1.39 (m, 4 H), 1.04 (s, 9 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 188.39, 135.63, 134.14, 129.62, 127.69, 71.81, 63.91, 42.74, 37.79, 32.59, 28.93, 27.04, 25.91, 25.66, 19.39.

HRMS: *m*/*z* [M + Na]$^+$ calcd for $C_{25}H_{37}NNaO_2SSi$: 466.22065; found: 466.22041.

Alkyl Bromides 3; General Procedure

In a typical reaction the Vilsmeier reagent **2** was prepared in situ by adding oxalyl bromide (650 mg, 3 mmol) to 4-formylmorpholine in CH_2Cl_2 (40 mL). The mixture was stirred at 0 °C for 2 h under argon and then the dimethylthiocarbamate **1** (2 mmol) was added and the mixture was allowed to react for the time shown in Table 1. Two different workup procedures were used. Workup A: sat. aq $NaHCO_3$ (3 mL) was added and the CH_2Cl_2 was removed in vacuo. The residue was diluted with petroleum ether (150 mL) and stirred with ice cold 20% aq NH_3 for 5 min. The organic layer was washed with H_2O (5 × 150 mL), dried (Na_2SO_4), and concentrated in vacuo. In Workup B, H_2O was added instead of sat. aq $NaHCO_3$, and the 20% aq NH_3 wash was excluded. The purpose of the ammonia wash was to convert byproduct **4** into a water soluble urea. The multiple H_2O washing removed the morpholine byproduct **5**. Excess Vilsmeier reagent was used to guarantee full conversion since no special precautions were taken with the reagents or solvent.

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References

(1) Greene, T. W.; Wuts, P. G. In *Protective Groups in Organic Synthesis*, 3rd ed.; Wiley: New York, **1999**.
(2) Barton, D. H. R.; Stick, R. V.; Subramanian, R. *J. Chem. Soc., Perkin Trans. 1* **1976**, 2112.
(3) Cristol, S. J.; Seapy, D. G. *J. Org. Chem.* **1982**, *47*, 132.
(4) Barbier, F.; Pautrat, F.; Quiclet-Sire, B.; Zard, S. Z. *Synlett* **2002**, 811.
(5) Koen, M. J.; Le Guyader, F.; Motherwell, W. B. *J. Chem. Soc., Chem. Commun.* **1995**, 1241.
(6) Gade, A. M.; Abelt, C. J. *Synthesis* **2007**, 2097.
(7) Barma, D. K.; Bandyopadhyay, A.; Capdevila, J. H.; Falck, J. R. *Org. Lett.* **2003**, *5*, 4755.
(8) Fikse, M. A.; Bylund, W. E.; Holubowitch, N. E.; Abelt, C. J. *Synthesis* **2006**, 4118.
(9) Schlama, T.; Gouverneur, V.; Mioskowski, C. *Tetrahedron Lett.* **1997**, *38*, 3517.
(10) Jones, G.; Stanforth, S. P. *Org. React.* **2000**, *56*, 355.