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Conversion of Thiocarbamates to Carbamates#

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Abstract : Treatment of methyl N-methylthionocarbamate (**2a**) with a catalytic amount of iodine or conc. H_2SO_4 results in the unexpected formation of the isomer, methyl N-methylthiolcarbamate (**3a**) in 90% yield. This has subsequently been transformed into methyl N-methylcarbamate (**4a**), by sodium methoxide. A curious transformation of methyl N-methyldithiocarbamate (**1a**) to (**4a**) on prolonged treatment with sodium methoxide is also discussed.

Introduction

In an earlier paper[1] we had reported a new synthesis of aryl carbamates from alkyl carbamates by trans-esterification. This process is expected to be of industrial importance for the manufacture of carbamate pesticides. This would however, depend upon developing a viable process for the synthesis of the requisite alkyl carbamates. Since the basic objective of the project was to avoid the use of phosgene and methyl isocyanate (MIC), the more obvious methods for the synthesis of alkyl carbamates, such as the reaction of alkyl chloroformates with amines, were ruled out. We had earlier suggested[1] that oxycarbonylation of amines[2] could be a solution to this problem.

Several relatively simple methods are available for the synthesis of alkyl thionocarbamates. The conversion of such thionocarbamates to carbamates would offer an alternate solution to the problem. In this paper, we report our results on such transformations.

There seem to be only two reports in the literature on the conversion of alkyl thionocarbamates (**2**) to alkyl carbamates (**4**). The first depends on the reaction of the thiono compound with a soft electrophile (NO^+) in aqueous solution, followed by a hydrolytic cleavage of the C-S bond and fragmentation to produce the alkyl carbamate.[3] The reported yield is only 38%. In the second method, bakers' yeast has been reported to bring about the conversion of aryl N-alkylthionocarbamates to aryl N-alkylcarbamates in good yields.[4]

We now describe a simple two step method of converting O-alkyl thionocarbamates (**2**) to O-alkyl carbamates (**4**). This proceeds through a preliminary isomerisation to S-alkyl thiolcarbamates (**3**). We also report an unexpected direct conversion of the dithiocarbamate (**1a**) to the carbamate (**4a**) in 36% yield by prolonged reflux with an equivalent amount of sodium methoxide in methanol.

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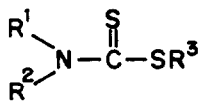
Results and Discussion

N-Methyl thionocarbamate methyl ester (**2a**) was prepared by the oxidative condensation of methyl amine with potassium methyl xanthate.[5]



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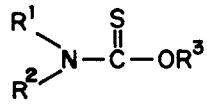

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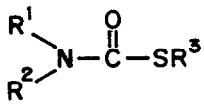

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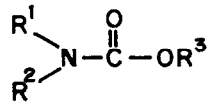

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	R^1	R^2	R^3
a :	H	Me	Me
b :	H	Me	Et
c :	Me	Me	Me
d :	H	Et	Me
e :	Et	Et	Me
f :	H	Cyclohexyl	Me
g :	H	Me	1-naphthyl

A : Isomerisation of O-methyl thionocarbamates (2) to S-methyl thiolcarbamates (3) : Apart from the two methods for the conversion of thionocarbamates to carbamates referred to above, there are several other methods for the transformation of thioamides to amides.[6,7,8,9,10] We have tried to apply some of these methods for the conversion of (**2a**) to (**4a**). However, these attempts have not been successful. Thus treatment of (**2a**) with m-chloroperbenzoic acid[8] did not lead to the desired transformation; the starting material decomposed under these conditions, and no product was isolable. Similarly treatment of (**2a**) with alkali under phase-transfer catalysis[9] gave poor yields (14%) of the desired product (**4a**). Of much greater interest was the fact that DMSO/Iodine (catalytic), a reagent known to transform thiocarbonyl to carbonyl compounds[10], converted (**2a**) to the S-methyl thiolcarbamate (**3a**) in 60% yield. The structure of the product was established by its IR [3300 (NH), 1650 cm^{-1} (-CO-S-)] and ^1H NMR spectra [$CDCl_3$: 2.26 (s, 3H, SCH_3); 2.83 (d, J= 5 Hz, 3H, NCH_3); 6.06 (br, 1H, NH)] and analytical data. Subsequently it was established that DMSO was not necessary to bring about this isomerisation.

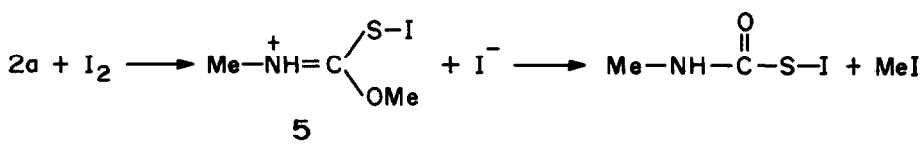
There have been earlier reports of similar conversion of thionocarbamates (**2**) to the corresponding thiolcarbamates (**3**) brought about by boron trifluoride-etherate or p-toluenesulfonic acid [11]; but the yields have not been mentioned. We could confirm this catalytic effect of BF_3-Et_2O or p-TsOH, but in our hands, the yield in this isomerisation was only 30 to 40%. A better yield (90%) was realised when a catalytic amount of conc. sulfuric acid was used in chloroform solution. The Japanese workers have provided evidence for a bimolecular mechanism for this isomerisation, based on cross-over studies.[12] The sulfuric acid catalysed isomerisation was found to be quite general. Table 1 lists the transformations achieved so far. The reason for the high efficiency of the sulfuric acid catalysed process is not clear at present.

Table 1.
Sulfuric acid Catalysed Isomerisation of Thionocarbamates (**2**)
to Thiolcarbamates (**3**)

Starting material	Product	Yield %
2a	**3a**	**90**
2b	**3b**	**80**
2c	**3c**	**85**
2d	**3d**	**89**
2e	**3e**	**75**
2f	**3f**	**80**

The real catalyst in the iodine catalysed isomerisation is perhaps methyl iodide generated in situ by the reaction of (**2a**) with iodine. Some evidence for this has been provided by the isomerisation of (**2a**) with a catalytic amount of CH_3I *in the absence of iodine* in 90% yield. Thus, in the first step, reaction of (**2a**) with iodine presumably gives (**5**) and iodide ion as shown in *scheme 1*. Demethylation of (**5**) by iodide ion generates methyl iodide which then catalyses the isomerisation[13].

Scheme - 1



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B : Conversion of thiolcarbamates (3) to carbamates (4) : The easy availability of S-alkyl thiolcarbamates[14] (**3**) suggested the possibility of using these as intermediates in the conversion of O-alkyl thionocarbamates (**2**) to O-alkyl carbamates or O-aryl carbamates (**4**). This was predicated on the assumption that -SMe is a good leaving group. The results were indeed gratifying. Refluxing (**3a**) with a catalytic amount of sodium methoxide in methanol led to the formation of methyl N-methylcarbamate (**4a**) in 85% yield. Thus, this represents a simple two-step conversion of the thionocarbamate (**2a**) to the carbamate (**4a**). Our initial objective had thus been achieved.

A more desirable goal would be the conversion of (**3a**) directly to aryl carbamates which are of commercial importance as pesticides. We have now achieved moderate success in this objective. The reaction of (**3a**) with 1-naphthol has been carried out employing Lewis acids as well as bases as catalysts. The best yields (about 50%) of Carbaryl (**4g**) were obtained with triethylamine in refluxing acetonitrile; anhydrous zinc chloride in benzene was equally effective.

C : Direct conversion of dithiocarbamates (1) to carbamates (4) : It has been mentioned earlier that methyl N-methyl thionocarbamate (**2a**) was prepared from potassium methyl xanthate. Another standard method of synthesising alkyl thionocarbamates (**2**) is by the action of alkoxides on dithiocarbamates (**1**). We

Table 2.
The reaction of (**1a**) with 0.1 equiv. NaOMe: GC analysis of the reaction mixture

Time (h)	% (**1a**)	% (**2a**)
5	**50**	**50**
7	**30**	**70**
11	**10**	**90**
23	**9**	**91**
29	**9**	**91**
34	**5**	**95**

came across an unexpected transformation when we adopted this method for the synthesis of (**2a**). Methyl N-methyldithiocarbamate (**1a**) (prepared from methylamine and carbondisulfide, followed by S-methylation) was refluxed with sodium methoxide (0.1 equiv.; 10 mol%) in methanol for 11 h. The progress of the reaction was monitored by GC analysis. The results are shown in Table 2. At the end of 11 h, the product was isolated and distilled to yield (**2a**) (yield 90%; purity 90%).

However, when the same reaction was repeated, using 1 equiv. of sodium methoxide, the distilled product showed the presence of a significant amount of the carbamate (**4a**) in the ^{1}H NMR spectrum. In order to

Table 3.
Reaction of (**1a**) with 1 equiv. NaOMe : GC analysis of the reaction mixture.

Time (h)	% (**2a**)	% (**4a**)
1	**85**	**3**
2	**81**	**6**
3	**80**	**8**
5	**53**	**20**
8	**46**	**45**
19	**22**	**67**
27	**13**	**84**
31	**10**	**88**
43	**9**	**90**

throw greater light on this curious transformation, the reaction was monitored by GC analysis. The results are shown in Table 3. It is obvious that with increasing duration, the amount of (**2a**) decreases, with a corresponding increase in the desulfurised compound (**4a**). Isolation of the product at the end of 30 h and distillation gave only a 36% yield of practically pure (**4a**). Obviously, other side reactions account for the loss of nearly two-third of the material.

The point of significance for us was, however, the formation of the de-sulfurised product (**4a**) to the extent of 36%. One obvious route for the formation of this would involve the intermediacy of the thionocarbamate (**2a**); the subsequent conversion of this to (**4a**) could take place *via* the isomer (**3a**), or by a direct hydrolytic de-sulfurisation as reported for other thioamides.[9]

In order to verify this, the pure thionocarbamate (**2a**) was subjected to the action of sodium methoxide (1 equiv.) in methanol under GC monitoring as before (Table 4). To our surprise, we found that at the end of 28 h reflux, the product consisted of 75% starting material and only 25% of the carbamate (**4a**). Isolation and distillation yielded the thionocarbamate (**2a**) (recovery 36%; purity 93%). This was thus, in sharp contrast to the results obtained with (**1a**), as the reactant. As with the earlier experiment with (**1a**), other side reactions must be responsible for the loss of nearly two-third of the material.

Table 4.
Reaction of (**2a**) with 1 equiv. NaOMe : GC analysis of the reaction mixture.

Time (h)	% (**2a**)	% (**4a**)
3	**94**	**6**
7	**84**	**15**
17	**84**	**16**
22	**83**	**17**
28	**75**	**25**

The contrasting results obtained under identical conditions with (**1a**) and (**2a**) as the reactants pose an intriguing problem. The only difference between the two reactions is that a considerable amount of methyl mercaptan would be liberated with (**1a**) as the substrate. We therefore focussed our attention on the possible effect of this mercaptan in catalysing the formation of (**4a**). The pure methyl thionocarbamate (**2a**) was refluxed with sodium methoxide (1 equiv.) in methanol, but this time with the *deliberate addition of an equivalent of ethanethiol.* The GC analytical results are presented in Table 5. Isolation and distillation of the product at the end of 28 h gave the carbamate (**4a**) (36% yield; purity 90%).

Table 5.
Reaction of (**2a**) with 1 equiv. NaOMe in presence of 1 equiv. EtSH : GC analysis of the reaction mixture.

Time (h)	% (**2a**)	% (**4a**)
3	**82**	**5**
7	**56**	**21**
17	**28**	**48**
22	**0**	**85**
28	**0**	**78**

The results seem to indicate a possible catalytic role for the thiol; but the exact mechanism is not known yet, and can only be speculated upon.

EXPERIMENTAL

General : Melting points were determined in capillaries and are uncorrected. ^{1}H NMR spectra were recorded on WH-90 FT NMR spectrometer (VARIAN) instrument using tetramethylsilane as internal standard. Chemical shift values are expressed in ppm downfield from the signal for internal Me_4Si. Elemental analysis were performed at the Organic Chemistry Division, National Chemical Laboratory. IR spectra were recorded with a 599-B double beam IR spectrometer. Mass spectra were run on a Finnigan MAT 1020 automated GC/MS instrument. GC experiments were carried out on a HEWLETT Packard Series II 5890 instrument using HP-17 column. For column chromatographic purification under gravity, column grade silica gel (60-120 mesh size) activated at 100°C for 1 h was employed.

Methyl N-methylthionocarbamate (2a) : To a solution of (**1a**) (3.63g, 0.03 mole) in methanol (18 mL), sodium (70 mg, 0.003 mole) was added and the reaction mixture was refluxed . The reaction was completed within 11 h as shown by GC analysis. The reaction mixture was concentrated and diluted with dichloromethane (200 mL), washed with water (50 mL) and dried over Na_2SO_4. Solvent evaporation followed by distillation of the crude product afforded (**2a**) (2.85 g, 90% yield). B.P. 70-72°C at 4 mm. IR : 3300 (NH), 1560 (C=S). ^{1}H NMR ($CDCl_3$) : (cisoid and transoid rotamers) 2.8 and 3.11 (d, J = 5 Hz, 3H, $NHCH_3$), 4.00 and 4.11 (s, 3H, OCH_3), 6.36 and 7.04 (b, 1H, NH). MS (m/z) : 105(100), 74(30). Anal. calcd. for C_3H_7NOS : C, 34.28; H, 6.66; N, 13.33; Found : C, 34.12; H, 6.38; N, 13.12.

General procedure for the synthesis of thiolcarbamates (3) : To the stirred solution of thionocarbamate (**2**) (0.1 mole) in chloroform (200 mL), conc. sulfuric acid (3 mL) was added and the reaction mixture was refluxed. After cooling, the reaction mixture was washed with water (2x250 mL) and dried over Na_2SO_4. Solvent evaporation gave the crude product which was further purified by distillation to afford pure (**3**).

Methyl N-methylthiolcarbamate (3a) from methyl N-methylthionocarbamate (2a)[15]: Time 20 h; Yield 90%; B.P.70-74°C at 5 mm; IR : 3300 (NH), 1660 (C=O). ^{1}H NMR ($CDCl_3$) : 2.26 (s, 3H, SCH_3); 2.83 (d, J = 5 Hz, 3H, $NHCH_3$); 5.2 (br, 1H, NH). MS (m/z) : 105(100), 58(84). Anal. calcd. for C_3H_7NOS : C, 34.28; H, 6.66; N, 13.33. Found : C, 34.09; H, 6.32; N, 12.82.

Ethyl N-methylthiolcarbamate (3b) from ethyl N-methylthionocarbamate (2b)[5]: Time 20 h; Yield 80%; IR : 3320 (NH), 1660 (C=O); ^{1}H NMR ($CDCl_3$) : 1.28 (t, J = 8 Hz, 3H, Et); 2.86 (d, J = 5 Hz, 3H, $NHCH_3$); 2.93 (q, J = 8 Hz, 2H, SCH_3). MS (m/z): 119(100). Anal. calcd. for C_4H_9NOS : C, 40.33; H, 7.56; N, 11.76. Found: C, 40.64; H, 7.21; N, 11.53.

Methyl N,N-dimethylthiolcarbamate (3c) from methyl N,N-dimethylthionocarbamate (2c)[16] : Time 15 h; Yield 85%; B.P. 180°C; IR : 1660 (C=O). ^{1}H NMR ($CDCl_3$) : 2.26 (s, 3H, SCH_3); 3.03 (s, 6H, 2 NMe); MS (m/z) : 119(50), 72(100). Anal. calcd. for C_4H_9NOS : C, 40.33; H, 7.56; N, 11.76. Found : C, 39.82; H, 7.35; N, 11.49.

Methyl N-ethylthiolcarbamate (3d) from methyl N-ethylthionocarbamate (2d)[17]: Time 4 h; Yield 89%; IR : 3300 (NH); 1670 (C=O). ^{1}H NMR ($CDCl_3$) : 1.16 (t, J = 5 Hz, 3H, CH_3); 2.36 (s, 3H, SCH_3); 3.36 (q, J = 5 Hz, 2H, CH_2); 5.6 (br, 1H, NH). MS (m/z) : 119(12), 72(38), 48(35), 44(55). Anal. calcd. for C_4H_9NOS : C, 40.33; H, 7.56; N, 11.76. Found : C, 40.63; H, 7.21; N, 11.46.

Methyl N,N-diethylthiolcarbamate (3e) from methyl N,N-diethylthionocarbamate (2e)[16]: Time 15 h; Yield 75%; B.P. 190°C; IR : 1660 (C=O); ^{1}H NMR ($CDCl_3$) : 1.16 (t, J = 6 Hz, 6H, 2 NEt), 2.32 (s, 3H, SCH_3), 3.44 (q, J = 6 Hz, 4H, 2 NEt). MS (m/z): 147(35), 100(94), 75(27), 72(100). Anal. calcd. for $C_6H_{13}NOS$: C, 48.97; H, 8.84; N, 9.52. Found : C, 48.34; H, 8.52; N, 9.22.

Methyl N-cyclohexylthiolcarbamate (3f) from methyl N-cyclohexylthionocarbamate (2f)[18] : Time 3 h; Yield 80%; M.P. 112°C; IR : 3300 (NH), 1660(C=O); ^{1}H NMR ($CDCl_3$) : 1.22-2.00 (br m, 11H, C_6H_{11}); 2.33 (s, 3H, SCH_3); 5.22 (b, 1H, NH); MS(m/z) : 173(66), 126(100), 83(47). Anal. calcd. for $C_8H_{15}NOS$: C, 55.49; H, 8.67; N, 8.09. Found : C, 55.06; H, 8.24; N, 8.67.

Isomerisation of methyl N-methylthionocarbamate (2a) to methyl N-methylthiolcarbamate (3a) with catalytic methyl iodide : A mixture of methyl N-methylthionocarbamate (**2a**, 525 mg, 0.005 mole) in 1 mL benzene and methyl iodide (0.032 mL, 5 mmole) was heated in a sealed tube at 80°C for 15 h. Aqueous work-up followed by chromatography afforded pure methyl N-methylthiolcarbamate (**3a**, 460 mg, 88% yield).

Methyl N-methylcarbamate (4a) Method A : A catalytic amount of sodium (230 mg, 0.01 mole) was added to the solution of (**3a**) (10.5 g, 0.1 mole) in methanol (60mL) and refluxed for 20 h. The reaction mixture was concentrated and diluted with dichloromethane (500 mL). The organic layer was washed with water (50 mL), and dried over Na_2SO_4. Concentration and distillation afforded pure (**4a**) (7.5g, 85% yield). B.P.60-64°C at 5 mm. IR : 3300 (NH), 1700 (C=O); ^{1}H NMR ($CDCl_3$) : 2.8 (d, J = 5 Hz, 3H, $NHCH_3$); 3.6 (s, 3H, OCH_3). MS(m/z) : 89(17), 74(46), 58(100). Anal. calcd. for $C_3H_7NO_2$: C, 40.45; H, 7.86; N, 15.73. Found : C, 40.13; H, 7.24; N, 15.46.

Method B : Sodium (690 mg, 0.03 mole) was added to the solution of (**1a**) (3.63 g, 0.03 mole) in methanol (18 mL) and refluxed for 30 h. The reaction mixture was concentrated and diluted with dichloromethane (100 mL). The organic layer was washed with water (20 mL) and dried over Na_2SO_4. Concentration and distillation of the crude product afforded (**1a**) (960 mg, 36% yield).

Method C : Sodium (690 mg, 0.03 mole) was added to the solution of (**2a**) (3.15 g, 0.03 mole) in methanol (18 mL). Ethanethiol (2.2 mL, 0.03 mole) was then added at room temperature and stirred for 30 min. The reaction mixture was heated to reflux for 28 h. The progress of the reaction was monitored by GC analysis. Work-up as described in method B gave pure (**4a**) (160 mg, 36% yield).

1-Naphthyl N-methylcarbamate (Carbaryl) (4g) Method A : Anhydrous zinc chloride (0.5g,0.0036 mole) was added to the solution of (**3a**) (1.579 g, 0.015 mole) and 1-naphthol (1.44g, 0.01 mole) in benzene (10 mL) and refluxed for 21 h. The reaction mixture was evaporated and diluted with dichloromethane (200 mL). The organic layer was washed with water (3x10 mL), 5% cold NaOH solution (10 mL), water (20 mL) and dried over Na_2SO_4. Solvent evaporation afforded a brown colored solid, which was purified by recrystallisation (n-hexane-benzene) to give Carbaryl (**4g**), (1.0g, 50% yield). M.P. 141°C IR : 3300 (NH), 1715 (C=O). ^{1}H NMR ($CDCl_3$) : 2.86 (d, J = 5 Hz, 3H, $NHCH_3$); 5.14 (br, 1H, NH); 7.17-8.00 (m, 7H, aromatic). Anal. calcd. for $C_{12}H_{11}NO_2$: C, 71.64; H, 5.47; N, 6.96. Found : C, 71.42; H, 5.41; N, 6.42.

Method B : To a solution of 1-naphthol (1.44 g, 0.01 mole) in acetonitrile (200 mL), Et_3N (0.3 mL, 0.002 mole) was added and the reaction mixture was heated to 90°C. To this hot solution, the thiolcarbamate (**3a**) (1.36 g., 0.013 mole) in acetonitrile (30 mL) was added portionwise over a period of 4 h and the heating continued for a further period of 8 h. The reaction mixture was evaporated under reduced pressure and diluted with dichloromethane (200 mL). The organic layer was washed with water (3x20 mL), dried over Na_2SO_4. Solvent evaporation afforded a brown solid (1.4 g), which was further purified by recrystallisation (n-hexane : benzene) to give Carbaryl (1.0g)(**4g**) (50% yield).

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