THE DEALKYLATION OF TERTIARY AMINES WITH THIOPHOSGENE AND 1-CHLOROETHYL CHLOROTHIONOFORMATE

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Abstract

Thiophosgene and 1-chloroethyl chlorothionoformate react readily with tertiary amines, and give the dialkylamine hydrochloride after hydrolysis of the initial product with water. Benzyl and allyl groups are cleaved in preference to methyl and other alkyl groups. The rection with the isoquinoline alkaloid narcotine occurs particularly easily.

Introduction

The use of cyanogen bromide [1] to achieve the dealkylation of tertiary amines, and thus their conversion to secondary amines, has largely been replaced in recent years by the use of chloroformate esters [2]. The initial difficulties in the hydrolysis of the first formed carbamates (Scheme 1) was overcome to a significant extent by the use of 1-chloroethyl chloroformate [3], vinyl chloroformate [4], 2,2,2-trichloroethyl chloroformate [5], and more recently, phenyl chlorothionoformate [6].

During our study of the application of phenyl chlorothionoformate with various tertiary amines [6,7], it became clear that chlorothionoformates were more reactive than chloroformates, and appeared to form the intermediate salt **1** or **2** essentially immediately. The eventual product, the thiocarbamate **3**, required strong acid or base to achieve hydrolysis, or preferably, prior conversion to the imminium salt **4** which was readily hydrolysed by water [6]. It was felt that a combination of the higher reactivity afforded by the thionoformate group, and the ease of hydrolysis of the chloroethyl group might provide significant synthetic advantages. Accordingly, we set out to prepare the new reagent 1-chloroethyl chlorothionoformate **5**, and to investigate its reactions with tertiary amines.

Key Words: Secondary amines from tertiary aliphatic amines

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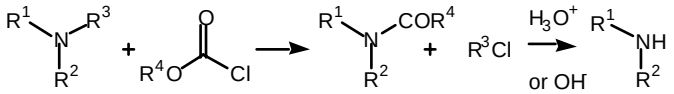
Discussion

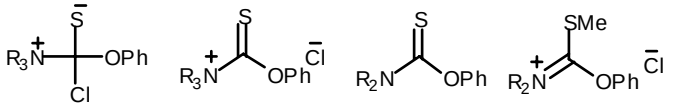
1-Chloroethyl Chlorothionoformate

The procedure used by Olofson to synthesis 1-chloroethyl chloroformate [3] was directly applicable to the synthesis of the chlorothionoformate. In the absence of benzyltributylammonium chloride, the reaction of acetaldehyde with thiophosgene (Scheme 2) was very slow, and could be followed at 25°C by nmr spectroscopy. Addition of 0.05 equivalents of the phase transfer catalyst allowed the reaction to proceed rapidly, and the product **5** was obtained as a yellow liquid in 72% yield by distillation of the product, bp 72^{o} / 760 mm.

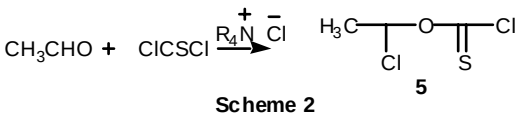
The reaction of amines with **5** was clearly a two-step procedure, as seen by following the reaction of triethylamine with **5** at 25°C in $CDCl_3$ by nmr spectroscopy. The formation of the salt **6** or **7** was



Scheme 1

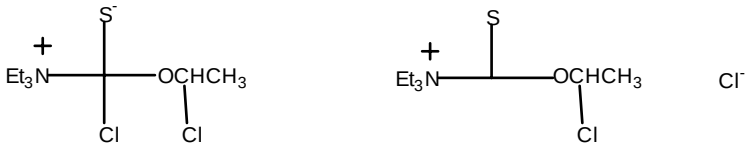


1 **2** **3** **4**

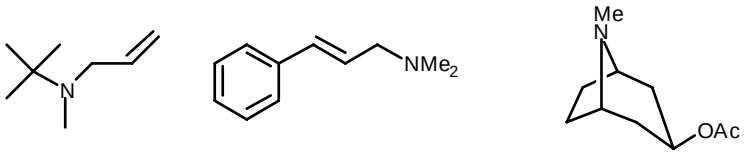


5

Scheme 2



6 **7**



8 **9** **10**

extremely rapid, and then required several hours at 25°C, or more satisfactorily 2h at 80°C, for reaction to be completed. However, in the case of benzylamines, the second, debenzylation, step was also rapid. Thus dimethylbenzylamine was cleanly converted to benzyl chloride and dimethylamine, isolated as the hydrochloride after hydrolysis. Some of the benzyl chloride was converted to the alcohol if it was not isolated before hydrolysis. While we have not studied such an extensive list of amines as we did with phenyl chlorothionoformate [6,7], all our evidence suggests the same relative ease of dealkylation with both of the reagents discussed herein, but at reduced rates. For instance, allyl-t-butylmethylamine (**8**) underwent reaction to the extent of 40% at 80°C with phenyl chlorothionoformate, selectively cleaving the t-butyl group [6], but **8** did not react with either 1-chloroethyl chlorothionoformate or thiophosgene. In addition, cinnamyldimethylamine (**9**) gave about 80% cinnamyl chloride plus dimethylamine, and 20% cinnamyl-methylamine, whereas cinnamyl chloride was the exclusive product with the phenyl ester. With acetyl tropine (**10**) as substrate, selective demethylation was achieved, and O-acetylnortropine was isolated in 80% yield.

Charles and coworkers [8] found that dimethylcyclo-hexylamine reacted with chloroformates predominantly by elimination to give cyclohexene, and we have found that the use of phenyl chlorothionoformate leads not only to cyclohexl cleavage (82%), but also to methyl cleavage (18%). The reaction of dimethylcyclo-

hexylamine with **5** gave only methylcyclohexylamine (15%); the recovery of 85% of the dimethyl-cyclohexylamine as its hydrochloride suggests that **5** is undergoing base catalysed elimination, possibly to the vinyl ester.

1R,9S (-) α-Narcotine (**11**) reacted with **5** within 1h at 20°C to give a single product **12** with retention of configurations at C-1. This conclusion is based on the evidence cited below.

Thiophosgene

The reaction of amines with thiophosgene was faster than with 1-chloroethyl chlorothionoformate. Thus, in the reaction of N-ethylpiperidine at 25°C for 20 minutes, GC/MS analysis after hydrolysis, as discussed below, gave 75% piperidine and 25% N-ethylpiperidine when thiophosgene was used, but only 25% piperidine and 75% N-ethylpiperidine when the chlorothi-onoformate was used. Cinnamyldimethylamine gave dimethylamine (90%), and tropine acetate gave O-acetylnortropine (83%).

α-Narcotine reacted readily with thiophosgene at 20°C in dichloromethane, giving a single compound, as judged by its ^{1}H and ^{13}C nmr spectra, to which was assigned structure **13**, implying retention of configuration in the cleavage of the benzyl group. On treatment with water, this compound formed the hydrochloride **14** very rapidly, and reaction of either **13** or **14** with sodium hydroxide at 20^{o}C after acidification with acetic acid returned α-narcotine. When the free base from **14** was chromatographed on alumina, it gave a ca 1:1 mixture of α- and β-narcotine, **15**, readily separable by chromatography. On the other hand, when **13** was treated with sodium acetate in acetic acid at 20°C for 12 h, the sole product, isolated in 87% yield, was (+)β-narcotine, mp 176^{o} , $[\alpha]_D^{27}$ +99^{o} (lit. [8] 176^{o}, $[\alpha]_D^{27}$ +101^{o}). The rotation of the isolated **15** was the opposite to that reported from the reaction of α-narcotine with base [9], confirming that epimerisation had occurred at C-1 and not C-9. The interpretation of these observations is summarised in Scheme 3.

The key features of the reactions above are that the thiocarbamoyl chloride **13** is extremely readily decomposed with water in a few minutes at 20°C. It can reasonably be supposed that the intramolecular displacement of the chloride, being stereospecific, is an S_N2 reaction, hence the reaction with hydroxide ion must involve opening of the lactone at a rate faster than chloride displacement by the amine, leading to formation of the epoxide, with inversion at C-1. Opening of the epoxide by amine now occurs more rapidly, resulting in a second inversion at C-1, and the reformation of 1R,9S α-narcotine, **11**. Alternatively, if the carbamoyl chloride **13** is treated with sodium acetate in acetic acid, the carbamoyl chloride is converted to the amine without affecting the phthalide, and inversion at C-1 then leads to 1S,9S β-narcotine, **15**.

Hydrolysis of thiocarbamates

Olofson [3] found that the 1-chloroethylcarbamates could be converted to the desired amine hydrochloride by refluxing in methanol, but we have found that the 1-chloroethyl thiocarbamates **16** gave the methyl thiocarbamate **17** in addition to the amine hydrochloride under these conditions, indicative of nucleophilic attack at the thiocarbonyl group as well as the chloroethyl (Scheme 4).

Accordingly, hydrolysis was readily achieved by refluxing the thiocarbamate with H_2O / THF, when the secondary amine hydrochloride was obtained in good yield.

Experimental Section

Freshly distilled solvents were used throughout, and anhydrous solvents were dried according to Perrin [10]. Melting points were determined on a Reichert hot stage microscope and were uncorrected. ^{1}H(300MHz) and ^{13}C(75.5MHz) n.m.r measurements were determined on a Gemini Varian 300 nuclear magnetic resonance spectrometer in deuterochloroform($CDCl_3$) with tetramethylsilane(TMS) as an internal standard. Infrared spectra were recorded on a Perkin Elmer 1600 FT-infrared spectrophotometer, using fused sodium chloride cells. Solids were measured as nujol mulls and liquids as films. Mass spectra and high resolution mass spectra were recorded on a Kratos MS25RF spectrometer. Radial chromatography was performed with silica gel PF254 coated glass rotors using a Chromatotron 7924T. GCMS analyses were performed on a Varian Saturn 4D instrument, with a J & W DB5 5% phenylmethyl polysiloxane column (30 m x 0.25 mm i.d.).

1-Chloroethyl Chlorothionoformate

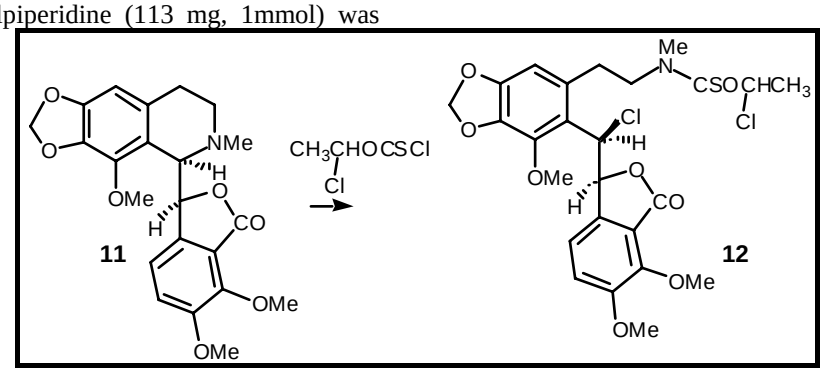
(i) Thiophosgene (11.15 g, 97 mmol) was added dropwise to a stirred mixture of acetaldehyde (3.19 g, 88 mmol) and benzyltributylammonium chloride (1.58 g, 4.4 mmol) at -10^{o}C under nitrogen. After 1h the mixture was distilled to give the title product as an orange-red liquid (10.8g, 72%), bp 72^{o}C. ^{1}H NMR ($CDCl_3$) δ 1.38 (d, J 2.6 Hz, 3H), 5.05 (q, J 2.6 Hz, 1H). ^{13}C NMR ($CDCl_3$) δ 20.43, 98.42, 170.55. d = 1.578 kgL^{-1}.

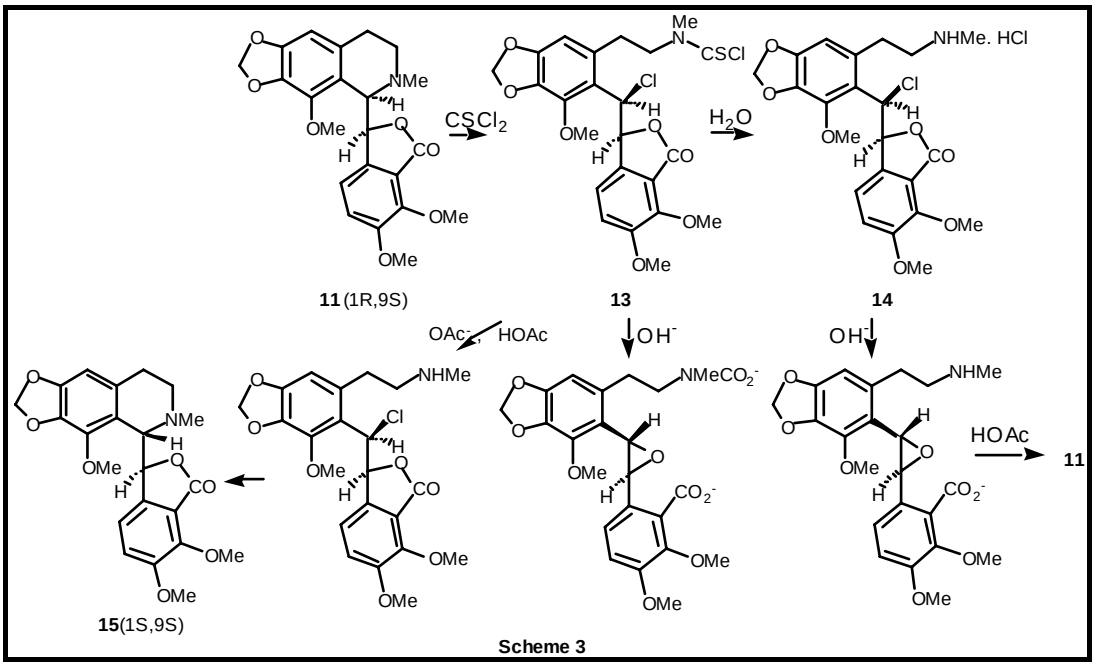
(ii) The nmr spectrum of a mixture of thiophosgene (136 mg, 1 mmol), acetaldehyde (44 mg, 1 mmol) and benzyltributylammonium chloride (7.5 mg, 0.05 mmol) in deuterochloroform (0.5 ml), taken 10 min after mixing, showed that reaction was complete.

added to the nmr tube containing the mixture in (ii)

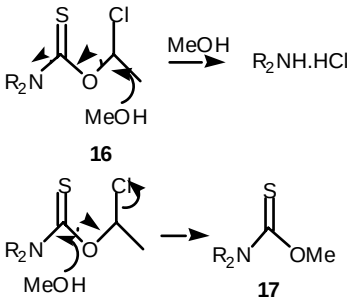
Reactions with 1-Chloroethyl Chlorothionoformate

(i) When N-ethylpiperidine (113 mg, 1mmol) was





Scheme 3



Scheme 4

above, the instantaneous formation of a complex equivalent to **6** or **7** was noted. ($^{H}\delta$ ethyl 1.35, 2 x d, J 7 Hz; 3.13, 2 x q, J 7 Hz; $^{C}\delta$ 98.2, C=S 192) . If the reaction mixture was diluted with a mixture of THF (5 ml) and water (1 ml) after 20 min, and the mixture heated at 60°C for 1h, gc / ms analysis and comparison

with authentic samples showed the presence of piperidine (75%) and N-ethylpiperidine (25%). No evidence for ring opened products could be seen.

When the original solution was heated at 50°C for 12 h, and then worked up as above, reaction was seen to be complete. The 1-chloroethyl piperidinothiocarbamate could be isolated as a stable yellow oil, which showed a single peak by gc / ms. Mass spectrum m/z 209 (8%, M), 207 (22, M), 86 (22), 83 (36), 51 (29), 49 (100).

Decomposition of the reaction mixture above with methanol gave methyl piperidinothiocarbamate (**17**, R_2 = $(CH_2)_5$) as a yellow oil. ^{1}H NMR ($CDCl_3$) δ 4.05 (s, 3H), 3.55 (m, 2H), 3.10 (m, 2H), 2.63 (m, 2H), 2.28 (m, 2H),1.90 (m, 2H).

(ii) A mixture of 1-chloroethyl chlorothionoformate (204 mg) and triethylamine (100 mg) was refluxed in dichloromethane (5 ml) for 12 h. The solvent was removed to give a dark solid (287 mg), shown to be 1-chloroethyl diethylthiocarbamate (**16**, R = Et) by its spectral properties. ^{1}H NMR ($CDCl_3$) δ 1.32 (d, J 5 Hz, 3H) overlapping with 1.34 (t, J 6 Hz, 6H), 3.78 (q, J 6 Hz, 2H), 3.95 (q, J 6 Hz, 2H), 5.04 (q, J 5 Hz, 1H). ^{13}C NMR ($CDCl_3$) δ 8.29 (CH_3), 10.48 (CH_3), 12.53 (CH_3), 49.88 (CH_2), 50. 11 (CH_2), 97.0, 170.55. Reaction with methanol for 2 h at 20°C gave methyl N,N-diethylthiocarbamate (**17**, R = Et) as a pale yellow oil (146 mg, 100%). ^{1}H NMR ($CDCl_3$) δ 1.39 (t, J 6 Hz, 6H), 3.09 (q, J 6 Hz, 2H), 3.16 (q, J 4 Hz, 2H), 3.50 (s,3H).

(iii) *General procedure*: A mixture of dimethylbenzylamine (100 mg) and the chlorothionoformate (159 mg) was refluxed in dichloromethane (2 ml) for 15 h. After removal of solvent, the residue was stirred for 2 h in THF (4 ml) and water (1 ml). Addition of water and extraction with ether gave a 1:1 mixture of benzyl alcohol and benzyl chloride (75 mg), and evaporation of the aqueous phase gave dimethylamine hydrochloride (80 mg). The identity of both fractions was confirmed by their ^{1}H nmr spectra, and gc / ms comparison with authentic samples.

Using the procedure in (iii) above, cinnamyldimethylamine was converted to cinnamyl chloride (80%) and cinnamylmethylamine (20%). Tropine acetate gave O-acetylnortropine (80%), identical with an authentic sample. Dimethylcyclohexylamine gave a mixture of the hydrochlorides of dimethylcyclohexylamine (85%) and methylcyclohexylamine (15%). Allyl-t-butylmethylamine was recovered (100%) as its hydrochloride even after 16 h at 80°C in dichloroethane.

Reaction with Thiophosgene

(i) When N-ethylpiperidine (113 mg, 1mmol) was added to the nmr tube containing the mixture in (ii) above, the instantaneous formation of a complex was noted. (^{H}δ ethyl 1.35, 2 x d, J 7 Hz; 3.13, 2 x q, J 7 Hz; ^{C}δ C=S 192). Would show the reaction mixture was diluted with a mixture of THF (5 ml) and water (1 ml) after 1h at 10°C, and the mixture heated at 60°C for 1h, gc / ms analysis (columnn temp 50°C) and comparison with authentic samples would show the presence of piperidine (50%) and N-ethylpiperidine (50%). No evidence for ring opened products could be seen. After 20 min at 25°C, the yield of piperidine was 75%, and after 24 h at 25°C, reaction was complete.

(ii) Preparative reactions were carried out as in (iii) above. Again allyl-t-butylmethylamine failed to react, even at 80°C.

Reaction of α-Narcotine with Thiophosgene

A mixture of α-narcotine (800 mg; generated from the commercially available hydrochloride by reaction with sodium carbonate) , thiophosgene (0.3 ml) and dichloromethane (3 ml) was stirred at 20°C for 20 h. After removal of the solvent, the oily residue was treated with a solution of acetic acid saturated with sodium acetate (6 ml) for 20 h, and then extracted with dichloromethane (2x 10 ml). The combined extract was washed with aqueous sodium carbonate, water, and dried. Evaporation gave off-white crystals, (700 mg, 87%) of (+) β-narcotine, mp 176-177^o $[\alpha]_D^{27}$ +99^o (lit. [9]176^o, $[\alpha]_D^{27}$ +101^o). ^{1}H NMR ($CDCl_3$) δ 7.02 (d, J 9 Hz,1H), 6.30 (s, 1H), 6.20 (d, J 9 Hz, 1H), 5.92 (s, 2H), 5.61, (d, J 4.5 Hz, 1H), 4.43 (d, J 4.5 Hz, 1H), 4.10 (s, 3H), 3.98 (s, 3H), 3.87 (s, 3H), 2.70 (m, 2H), 2.55 (s, 3H), 2.40 (m, 2H). ^{13}C NMR ($CDCl_3$) δ 27.5, 45.5, 49.0, 59.4, 61.5, 62.2, 81.0, 100.5, 102.3, 117.5, 118.0, 119.5, 135.0, 136.0, 140.6, 141.0, 148.4, 152.2, 170.0. υ_{max} 1758, 1628 cm^{-1}.

Acknowledgements

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References

1. Hageman, H. A. *Organic Reactions*, **7**, 198-262, (1953).
2. Cooley, J. H. and Evain, E. J. *Synthesis*, 1-7, (1989).
3. Olofson, R. A., Martz, J. T., Senet, J. P., Piteau, M. and Malfroot, T. *J. Org. Chem.*, **49**, 2081-82, (1984).
4. Olofson, R. A., Schnur, R. C., Bunes, L. and Pepe, J. P. *Tetrahedron Lett.*, **18**, 1567-70, (1977).
5. Montzka, T. A., Matiskella, J. D. and Partyka, R. A. *Tetrahedron Lett.*, **14**, 1325-27, (1974).
6. Millan, D. S. and Prager, R. H. *Ibid.*, **39**, 4387-90, (1998).
7. Millan, D. S. and Prager, R. H. *Aust. J. Chem.*, accepted

for publication, (1999).
8. Kapnang, H., and Charles, G. *Tetrahedron Lett.*, **24**, 3233-36, (1983).
9. Marshall, M. A., Pyman, F. L. and Robinson, R. *J. Chem. Soc*., 1315-20, (1934).
10. Perrin, D. D., Armarego, W. L. F. and Perrin, D. R. Purification of Laboratory Chemicals, 1st Ed., Pergamon Press, Oxford, (1966).