Pergamon

Tetrahedron Letters 39 (1998) 4387–4390

TETRAHEDRON LETTERS

The Dealkylation of Tertiary Aliphatic Amines with Phenyl Chlorothionoformate

David S. Millan and Rolf H. Prager*

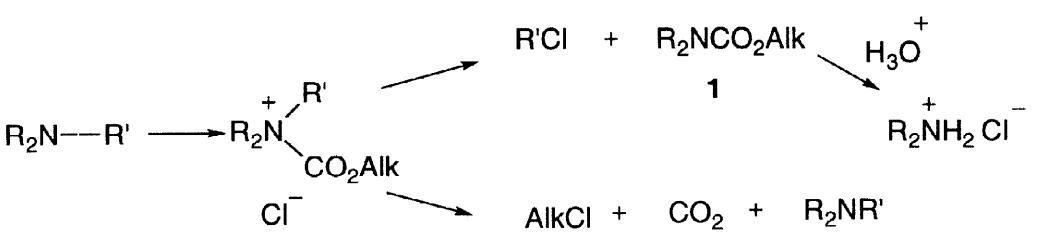
Department of Chemistry, Flinders University of South Australia,

G.P.O Box 2100, Adelaide, Australia 5001.

Received 23 February 1998; revised 7 April 1998; accepted 8 April 1998

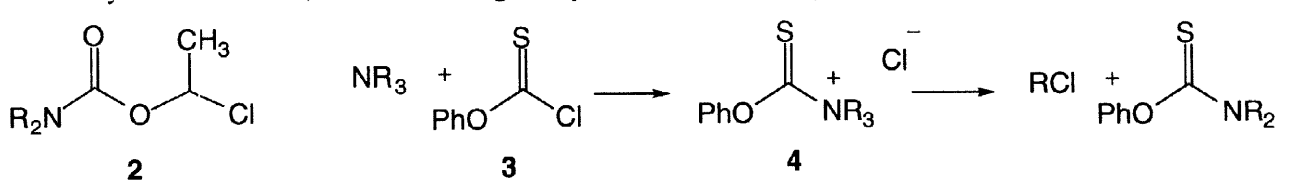
Abstract: Phenyl chlorothionoformate reacts rapidly with aliphatic amines at 20°C to give a thiourethane and an alkyl chloride. The urethanes are readily converted to the secondary amine salt by reaction with dimethyl sulfate, followed by hydrolysis with water. Rates of reaction, and alkyl group cleavage selectivity, are comparable to those reported for 1-chloroethyl chloroformate.

In recent years the classic dealkylation of aliphatic and alicyclic tertiary amines with cyanogen bromide (the von Braun reaction)[1] has been replaced by the use of ethyl chloroformate[2], aryl chloroformate[3] or analogous reagents[4-6], as the method of choice for dealkylation of tertiary amines, although oxidation[7] is an alternative in certain cases. The high activity of cyanogen bromide leads to reduced selectivity, and the cyanamide is difficult to hydrolyse. The disadvantages of the use of alkyl chloroformates are side reactions involving formation of the alkyl chloride and therefore necessitating the use of excess of reagent, and the relatively strong acidic conditions required for hydrolysis of the carbamate **1** (Scheme 1).



Scheme 1

The procedure of Olofson[4] overcomes these difficulties, as the intermediate carbamate **2** can be decomposed by methanol at 70°C. Finally, Montzka[6] reports that treatment of a tertiary amine with 2,2,2-trichloroethyl chloroformate delivers the required secondary amine after reaction with zinc and acetic acid. We have found[8] that the readily available phenyl chlorothionoformate **3** has reactivities similar to that of 1-chloroethyl chloroformate[4], and the resulting dialkyl thiocarbamates may be readily hydrolysed (Scheme 2).



Scheme 2

0040-4039/98/$19.00
PII: S0040-4039(98)00743-6

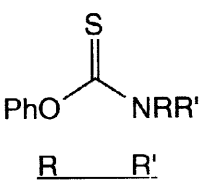
The data in Table 1 supports the rate determining decomposition of the intermediate ammonium species 4, either by an S_N1 process when allyl, benzyl or tertiary groups are present, or more generally, by an S_N2 process.

Table 1. Dealkylation of Tertiary Amines with **3**

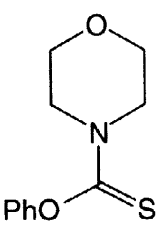
	Amine	Conditions	Product	% Yield
1.	Triethylamine	CH_2Cl_2, 1h, 20 °C	**5** + EtCl	93[a]
2.	N,N-Diethylbenzylamine	CH_2Cl_2, 1h, 20 °C	**5** + BzCl	97[a]
3.	N-Methylmorpholine	CH_2Cl_2, 1h, 20 °C	**6** + MeCl	73[a]
4.	N,N-Dimethylcinnamylamine	CH_2Cl_2, 1h, 20 °C	**7** + cinnamyl chloride	71[a]
5.	Quinuclidine	CH_2Cl_2, 1h, 20 °C	**8**	95[a]
6.	Tropine	CH_2Cl_2, 1h, 20 °C	**9** (66[b])+ **10** (34[b])	>95[c]
7.	Tropine acetate	CH_2Cl_2, 1h, 20 °C	**11**+ MeCl	>95[a]
8.	Bicuculline	CH_2Cl_2, 1h, 20 °C	**12** (eryth/threo, 3:1)	87[a]
9.	N,N-Dimethyl *t*-butylamine	CH_2Cl_2, 2h, 45 °C	**7** + *t*-BuCl	36[a](76[c])
10.	N,N-Dimethylaniline	neat, 24h, 130°	**13** + MeCl	75[a]

[a] Isolated yield, chromatographically pure [b] Relative ratio of products in mixture

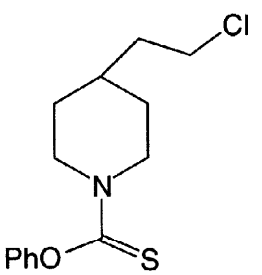
[c] Crude yield



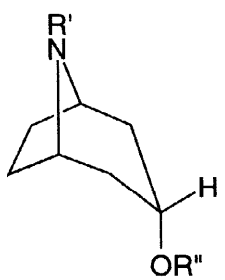
	R	R'
5	Et	Et
7	Me	Me
13	Me	Ph



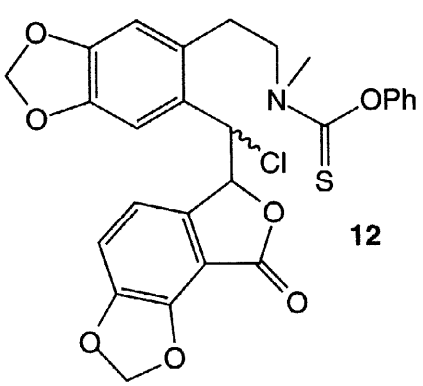
6



8



	R'	R"
9	Me	C(S)OPh
10	C(S)OPh	H
11	C(S)OPh	$COCH_3$



12

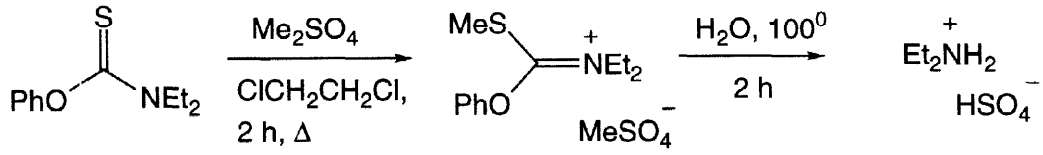
The relative reactivity of phenyl or ethyl chloroformates and phenyl chlorothionoformate can be seen in the competition reactions below (eq. 1-2).

$$NEt_3 + PhOCOCl + PhOCSCl \xrightarrow{20^0} \underset{(74\%)}{PhOC(S)NEt_2} + \underset{(26\%)}{PhOC(O)NEt_2} \quad (1)$$

$$NEt_3 + EtOCOCl + PhOCSCl \xrightarrow{20^0} \underset{(97\%)}{PhOC(S)NEt_2} \quad (2)$$

Whereas cyanogen bromide reacts with N-methylmorpholine to open the ring[9], the chlorothionoformate **3** reacts with exclusive cleavage of the methyl group, as observed with 1-chloroethyl chloroformate[4]. Cleavage at benzylic and tertiary centres adjacent to nitrogen is preferred with chloroformates[5]. We have likewise found that allylic and benzyl groups are cleaved faster than methyl, while N,N-dimethyl *t*-butylamine cleaves only at the *t*-butyl carbon suggesting the reaction occurs by an S_N1 mechanism. Tropine has been efficiently converted to nortropine with vinyl chloroformate[5] but the reaction was unsuccessful with ethyl chloroformate[10] without protection of the hydroxyl group. With one equiv. of **3**, tropine was converted to a 2:1 mixture of the tropine thiocarbonate **9** and the demethylated thiourethane **10**, but when tropine acetate was used, demethylation occurred smoothly. Phenyl chlorothionoformate **3** ring opened quinuclidine to give the thiourethane **8**. As is the case with all chloroformates, dimethylaniline was difficult to dealkylate, requiring 24 hours at 130 °C, in the absence of a solvent. The alkaloid bicuculline gave a mixture of epimers **12** in high yield. When the reaction was followed by NMR spectroscopy, it was clear that epimerisation occurred during the dealkylation step: the epimeric products were configurationally stable, suggesting the reaction occurs by an S_N1 mechanism. Similar reactions with phenyl chloroformate[11] and vinyl chloroformate[5] gave instead the corresponding enol lactone.

Hydrolysis[12] of the thiourethanes can be carried out directly with acid (5M HCl, 80°C, 16 h.), or alkali (5M NaOH, 80 °C, 16 h.), but was achieved under mild conditions if, for example the urethane **5** was first methylated, and the imminium salt **14** could then be hydrolysed by refluxing in water (Scheme 3). The mild hydrolysis, approaching the ease of hydrolysis of 1-chloroethylurethanes[4], and the readily availability of phenyl chlorothionoformate **3** suggests that the herein described dealkylation of amines will be a useful alternative to presently used procedures.



5 **14**

Scheme 3

REFERENCES AND NOTES

1. Hageman, H.A. *Organic Reactions* **1953**, 7, 198-262.
2. Gadamer, J.; Knoch., F. *Arch. Pharm.* **1921**, 259, 135-135; Flynn, E.H.; Murphy, H.W.; McMahon, R.E. *J. Am. Chem. Soc.* **1955**, 77, 3104-3106; Campbell, J.A. *J. Org. Chem.* **1957**, 22, 1259-1260.
3. Hobson, J.D.; McCluskey, J.G. *J. Chem. Soc.* (C) **1967**, 2015-2017; Pfaffli, P.; Hauth, H. *Helv. Chim. Acta.* **1973**, 56, 347-355.

4. 1-Chloroethyl chloroformate: Olofson, R.A.; Martz, J.T.; Senet, J.-P.; Piteau, M.; Malfroot, T. *J. Org. Chem.* **1984**, 49, 2081-2082.
5. Vinyl chloroformate: Olofson, R.A.; Schnur, R.C.; Bunes, L.; Pepe, J.P. *Tetrahedron Lett.* **1977**, 1567-1570.
6. 2,2,2-Trichloroethyl chloroformate: Montzka, T.A.; Matiskella, J.D.; Partyka, R.A. *Tetrahedron Lett.* **1974**, 1325-1327.
7. Potassium permanganate: Willstatter, R. *Ber. Dtsch. Chem. Ges.* **1896**, 29, 1575-1584; Werner, G.; Hackel, R.; Mohammad, N.; Seiler, N.; Stoor, K.-H. *Liebigs Ann. Chem.* **1967**, 708, 210-217.
Potassium ferricyanate: Findlay, S.P. *J. Am. Chem. Soc.* **1953**, 75, 3204-3208.
Oxygen: Beckwith, A.L.J.; Eichinger, P.H.; Mooney, B.A.; Prager, R.H. *Aust. J. Chem.* **1983**, 36, 719-739; Kovtum, G.A.; Aleksandrov, A.L. *Izv. Akad. Nauk. SSSR, Ser. Chim.* **1974**, 1274-1279; (*Chem . Abstr.* **1974**, 81, 177130r).
Nitrous acid: Wegler, R.; Frank, W. *Ber. Dtsch. Chem. Ges.* **1936**, 69, 2071-2077; *Ber. Dtsch. Chem. Ges.* **1937**, 70, 1279-1287.
8. Dealkylation procedure: To a solution of triethylamine (0.12g; 0.17mL; 1.19mmol) in dichloromethane (10mL) was added phenyl chlorothionoformate (0.20g; 0.16mL; 1.19mmol) and the solution was stirred under nitrogen for 1 h. The solvent was removed under reduced pressure to give a colourless oil which was chromatographed on silica to give O-phenyl diethylthiocarbamate, **5** (0.23g; 93%).
Satisfactory analytical and spectral data were obtained for all new compounds.
9. Von Braun, J.; Kohler, Z. *Ber. Dtsch. Chem. Ges.* **1918**, 51, 255-265.
10. Kraiss, G.; Nador, K. *Tetrahedron Lett.* **1971**, 57-58.
11. Klotzer, W., Teitel, S., Brossi, A. *Helv. Chim. Acta.* **1972**, 55, 2228-2232.
12. Hydrolysis procedure: The thiourethane **5** (0.2g; 0.96mmol) and dimethyl sulfate (0.24g; 0.18mL; 1.91mmol) were refluxed under nitrogen for 2 h. in dichloromethane (10mL). The solvent was removed under reduced pressure affording the imminium salt **14**. The salt **14** (0.1g; 0.28mmol) was dissolved in water (5mL) and the solution refluxed for 2 h. Excess water was evaporated under reduced pressure to give diethylamine hydrogen sulfate as a spectroscopically pure orange oil (0.038g; >95%).