

## The Dealkylation of Tertiary Aliphatic Amines with Phenyl Chlorothionoformate

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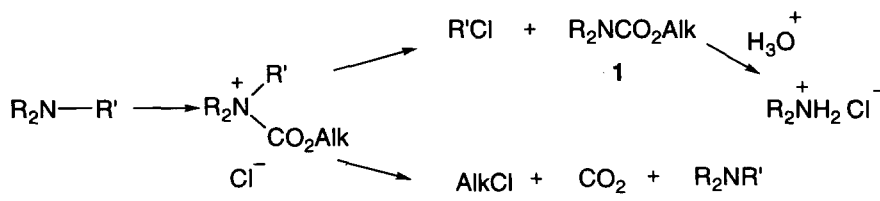
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Received 23 February 1998; revised 7 April 1998; accepted 8 April 1998

**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.

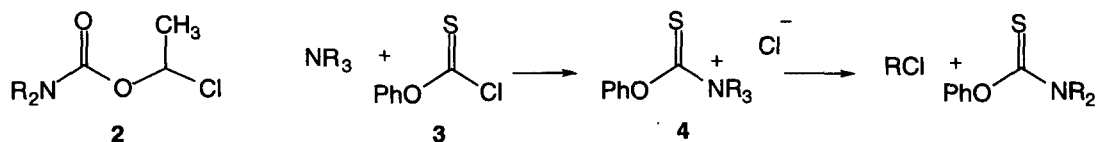
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In recent years the classic dealkylation of aliphatic and alicyclic tertiary amines with cyanogen bromide (the von Braun reaction)<sup>1</sup> has been replaced by the use of ethyl chloroformate<sup>2</sup>, aryl chloroformate<sup>3</sup> or analogous reagents<sup>4,6</sup>, as the method of choice for dealkylation of tertiary amines, although oxidation<sup>7</sup> 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<sup>4</sup> overcomes these difficulties, as the intermediate carbamate **2** can be decomposed by methanol at 70°C. Finally, Montzka<sup>6</sup> 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<sup>8</sup> that the readily available phenyl chlorothionoformate **3** has reactivities similar to that of 1-chloroethyl chloroformate<sup>4</sup>, and the resulting dialkyl thiocarbamates may be readily hydrolysed (Scheme 2).



Scheme 2

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.

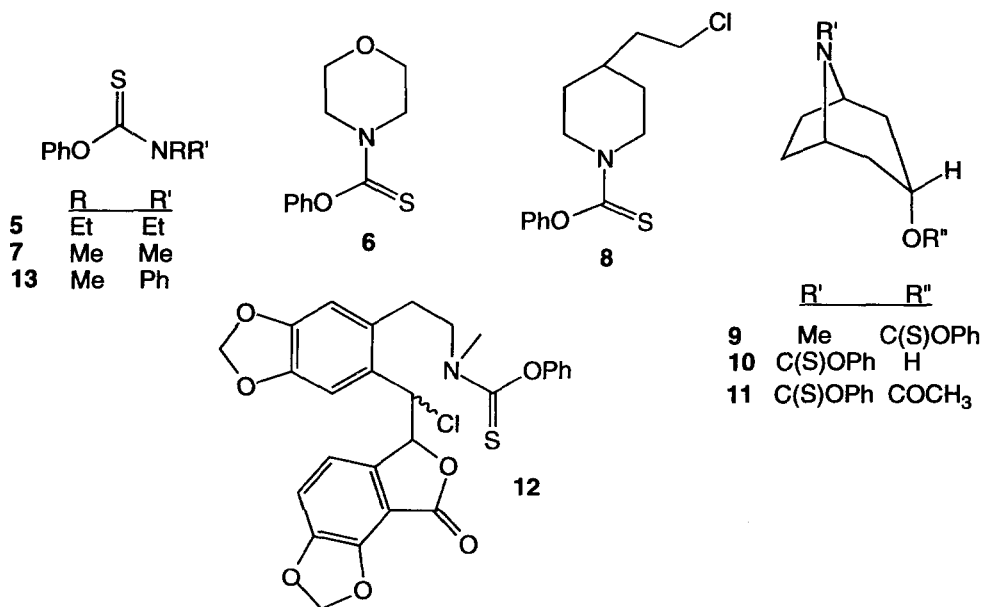
Table 1. Dealkylation of Tertiary Amines with **3**

	Amine	Conditions	Product	% Yield
1.	Triethylamine	$\text{CH}_2\text{Cl}_2$ , 1h, 20 °C	<b>5</b> + EtCl	93 <sup>a</sup>
2.	N,N-Diethylbenzylamine	$\text{CH}_2\text{Cl}_2$ , 1h, 20 °C	<b>5</b> + BzCl	97 <sup>a</sup>
3.	N-Methylmorpholine	$\text{CH}_2\text{Cl}_2$ , 1h, 20 °C	<b>6</b> + MeCl	73 <sup>a</sup>
4.	N,N-Dimethylcinnamylamine	$\text{CH}_2\text{Cl}_2$ , 1h, 20 °C	<b>7</b> + cinnamyl chloride	71 <sup>a</sup>
5.	Quinuclidine	$\text{CH}_2\text{Cl}_2$ , 1h, 20 °C	<b>8</b>	95 <sup>a</sup>
6.	Tropine	$\text{CH}_2\text{Cl}_2$ , 1h, 20 °C	<b>9</b> (66 <sup>b</sup> ) + <b>10</b> (34 <sup>b</sup> )	>95 <sup>c</sup>
7.	Tropine acetate	$\text{CH}_2\text{Cl}_2$ , 1h, 20 °C	<b>11</b> + MeCl	>95 <sup>a</sup>
8.	Bicuculline	$\text{CH}_2\text{Cl}_2$ , 1h, 20 °C	<b>12</b> (eryth/threo, 3:1)	87 <sup>a</sup>
9.	N,N-Dimethyl <i>t</i> -butylamine	$\text{CH}_2\text{Cl}_2$ , 2h, 45 °C	<b>7</b> + <i>t</i> -BuCl	36 <sup>a</sup> (76 <sup>c</sup> )
10.	N,N-Dimethylaniline	neat, 24h, 130 <sup>0</sup>	<b>13</b> + MeCl	75 <sup>a</sup>

<sup>a</sup> Isolated yield, chromatographically pure

<sup>b</sup> Relative ratio of products in mixture

<sup>c</sup> Crude yield



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



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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.
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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%).