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2,2,2-TRICHLOROETHYL CHLOROFORMATE: A GENERAL REAGENT FOR DEMETHYLATION OF TERTIARY METHYLAMINES

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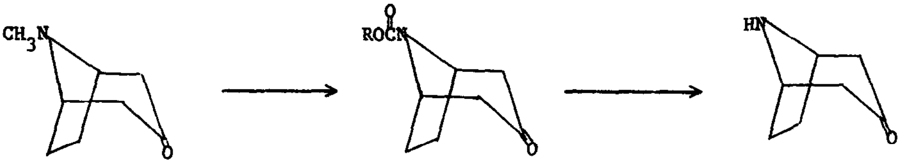
The dealkylation of tertiary amines using cyanogen bromide (von Braun reaction) has found many applications in both synthetic chemistry and degradative structural analysis of alkaloids.[1] The use of chloroformate esters such as ethyl chloroformate or phenyl chloroformate has often been found to be superior to cyanogen bromide in this type of reaction because of their increased selectivity producing cleaner reaction products.[2-6] One of the major problems with the use of ethyl chloroformate has been the extreme difficulty encountered in the hydrolysis of the intermediate carbamates. These often require the use of strong base or acid hydrolysis for long periods of time. The use of phenyl chloroformate partially overcomes this limitation though a strong base such as potassium hydroxide may still be required.[4,5]

2,2,2-Trichloroethanol and its derivatives have found wide application as protecting groups that are easily removed by zinc reduction under a variety of conditions.[7-10] We have found that the reaction of tertiary methylamines with 2,2,2-trichloroethyl chloroformate affords the corresponding demethylated trichloroethyl carbamate derivatives in excellent yields.[11] These carbamates are generally highly crystalline easily purified compounds which are easily cleaved by reduction with zinc in acetic acid or methanol. The following examples demonstrate the utility of this method.

The reaction of tropinone (I) with 10% excess of 2,2,2-trichloroethyl chloroformate in refluxing benzene with a small amount of potassium carbonate gave N-2,2,2-trichlorocarbethoxynortropinone (IIa, mp 79.0-80.0°, 95% yield by glpc analysis). The reduction of this carbamate with zinc in 90% acetic acid at room temperature gave nortropinone (III, 62% yield recrystallized hydrochloride, mp 190-199° decomp.). N-Carbethoxynortropinone (IIb) has been prepared in good yield but fails to undergo direct hydrolysis to nortropinone (III) with either acid or base because of decomposition.[2,3] Acetyltropine (IV) was similarly converted to noracetyltropine (VI, oxalate mp 176-178°, 75%) through the trichloroethylcarbamate (V, mp 93.0-94.0°, 91%).

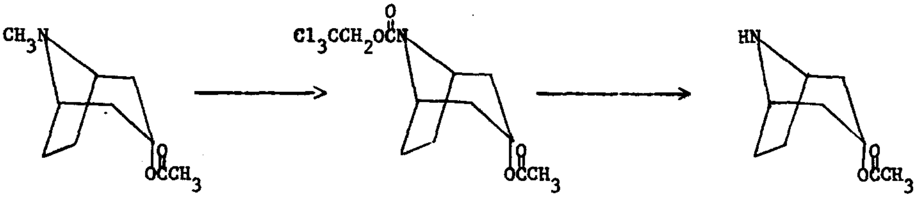


I

II a. R = Cl_3CCH_2-

b. R = CH_3CH_2-

III



IV

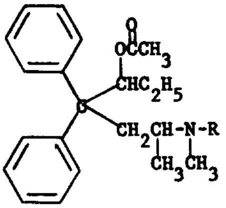
V

VI

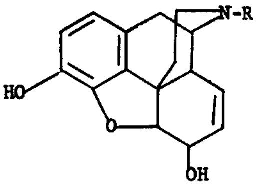
Acetylmethadol (VII) was converted to noracetylmethadol (VIII) in 60% overall yield using this technique. The use of ethyl chloroformate was not satisfactory in this case because the carbamate X proved to be extremely difficult to hydrolyze. After 65 hours of reflux with potassium hydroxide in n-propanol only 75% of the carbamate had been hydrolyzed with considerable decomposition.

The N-demethylation of morphine (XI) has been carried out in 75% yield. The trichlorocarbethoxynormorphine (XII, mp 196-198°, 95% yield) was prepared in chloroform using a procedure similar to that used by P. S. Portoghese for N-carbophenoxynormorphine.[5] The reduction of XII using zinc in 90% acetic acid gave normorphine (XIII, 79% yield, mp 270° decomp.).

The use of 2,2,2-trichloroethyl chloroformate followed by zinc reduction provides a valuable supplementary technique for the N-demethylation of tertiary methylamines. This method is particularly useful for compounds containing groups sensitive to either acidic or basic hydrolytic conditions.



VII. R = CH_3
VIII. R = H
IX. R = $CO_2CH_2CCl_3$
X. R = $CO_2C_2H_5$



XI. R = CH_3
XII. R = $CO_2CH_2CCl_3$
XIII. R = H

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