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# A CONVENIENT METHOD FOR THE SYNTHESES OF BENZYL N-MONOALKYLCARBAMATES AND N-BENZYLOXYCARBONYLAMINO ACIDS

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A convenient method for the preparations of benzyl N-monoalkylcarbamates and N-benzyloxycarbonylamino acids have been established. Benzyl N-monoalkylcarbamates were obtained in good yields by the reactions of potassium salt of benzyl N-(p-chlorophenylthio)carbamate with alkyl halides and the subsequent treatment of the alkylated carbamates with p-chlorobenzenethiol.

In the previous paper, a convenient method for the preparation of primary amines by the use of bisarylsulfenimide has been reported.[1] According to this method, primary amines were obtained in good yields under mild reaction conditions by treating N-substituted bisarylsulfenimides, prepared from lithium salt and alkyl halides, with hydrochloric acid or mercaptan. The most characteristic feature of this method is that amino compounds with nitrile, ester or amide groups in the same molecule could be prepared in good yields different from the most general method known as the Gabriel synthesis.

It is well known that benzyloxycarbonyl group, which is one of the most useful N-protecting groups of amino compounds, widely used in organic synthesis especially in peptide synthesis, can be easily removed by either acid hydrolysis or hydrogenation. Therefore, it is expected that benzyl N-alkylcarbamates would be used as useful intermediates in organic synthesis if the carbamates can be easily prepared from benzyl carbamate and alkyl halides. However, it is reported that N-monoalkylurethane is obtained in low yield from the reaction of sodium salt of urethane with alkyl halide accompanied with the formation of dialkylated carbamate[2] and when α-haloester is used as an alkyl halide, α-haloacylurethane resulted instead of the expected N-alkylation reaction.[3] These results would be attributed to both the strong basicity and the low nucleophilicity of sodium salt of urethane.

In the present study, a convenient method for the preparation of benzyl N-monoalkylcarbamates from benzyl N-(p-chlorophenylthio)carbamate and alkyl halides was investigated with the following considerations; a) a replacement of one hydrogen atom of benzyl carbamate by p-chlorophenylthio group would decrease the basicity of the nitrogen to afford an N-monoalkylated carbamates by the nucleophilic substitution with alkyl halides, b) the sulfur-nitrogen bond of the N-monoalkylated carbamates would be easily cleaved by mercaptan to afford the corresponding benzyl N-alkylcarbamates together with disulfide as shown in the case of the preparation of the primary amines using bisarylsulfenimide. Indeed, benzyl N-monoalkylcarbamates were obtained in good yields by treating benzyl N-alkyl-N-(p-chlorophenylthio)-carbamates, prepared by the reaction of potassium salt of benzyl N-(p-chlorophenylthio)carbamate and alkyl halides, with p-chlorobenzenethiol. For example, benzyl N-

p-nitrobenzyl-N-(p-chlorophenylthio)carbamate [I] was obtained in 87% yield by the reaction of benzyl N-(p-chlorophenylthio)carbamate with potassium t-butoxide in DMF -20°C for 10 min, and the subsequent reaction with p-nitrobenzyl bromide for 10 hr. Benzyl N-p-nitrobenzylcarbamate was obtained in quantitative yield by treating the alkylated product [I] thus obtained with equimolar amount of p-chlorobenzenethiol in DMF for 15 min. Similarly, various benzyl N-alkylcarbamates were prepared from alkyl halides and potassium salt of benzyl N-(p-chlorophenylthio)carbamate (See Table 1).

$$C_6H_5CH_2OCON(K)SC_6H_4Cl(p) + RX \longrightarrow C_6H_5CH_2OCON(R)SC_6H_4Cl(p)$$
$$C_6H_5CH_2OCON(R)SC_6H_4Cl(p) + p\text{-}ClC_6H_4SH \longrightarrow C_6H_5CH_2OCONHR + p\text{-}ClC_6H_4SSC_6H_4Cl(p)$$

Table 1. Yields of Benzyl N-alkylcarbamates by the Reaction of Potassium Benzyl N-(p-Chlorophenylthio)carbamate with Alkyl Halides

| RX | $C_6H_5CH_2OCONHR$ Yield % |
|---|---|
| $n\text{-}C_4H_9Br$ | 90 |
| $n\text{-}C_8H_{17}Br$ | 86 |
| $C_6H_5CH_2Br$ | 79 |
| $p\text{-}NO_2C_6H_4CH\ Br$ | 87 |
| $HOCH_2CH_2CH_2Br$ | 64 |

Further, it was established that N-benzyloxycarbonylamino acids are successfully prepared in good yields by the condensation reaction of potassium salt of benzyl N-(p-chlorophenylthio)carbamate with α-halo esters, and the subsequent reaction with p-chlorobenzenethiol and alkaline hydrolysis of the ester group. These results are listed in Table 2.

Table 2. Yields of N-Cbzoamino Acids[a)]

| α-Haloester | N-Cbzoamino Acid | Yield (%) |
|---|---|---|
| $BrCH_2CO_2C_2H_5$ | Cbzoglycine | 78 |
| $CH_3CH(Br)CO_2C_2H_5$ | Cbzo-DL-alanine | 79 |
| $(CH_3)_2CHCH_2CH(Br)CO_2C_2H_5$ | Cbzo-DL-leucine | 78 |
| $CH_3(CH_2)_3CH(Br)CO_2C_2H_5$ | Cbzo-DL-α-aminocaproic acid | 67 |
| $Br(CH_2)_3CH(Br)CO_2C_2H_5$ | α,δ-Dicbzo-DL-ornithine | 47 |
| $C_6H_5CH_2OCH_2CH(Br)CO_2C_2H_5$ | N-Cbzo-O-Benzyl-DL-serine | 73 |

a) Cbzo: $C_6H_5CH_2OCO$-

In conclusion, it is noted that benzyl N-monoalkylcarbamates and N-benzyloxycarbonylamino acids could be prepared in good yields starting from benzyl N-(p-chlorophenylthio)carbamate and alkyl halides. Further application to organic synthesis is now being investigated.

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