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Zinc Promoted Simple and Convenient Synthesis of Carbamates : An Easy Access for Amino Group Protection.

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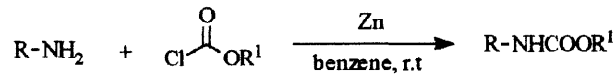
Abstract: Synthesis of alkyl, aryl, heterocyclic, carbohydrate and amino acid carbamates is described. The protection of the amino group in the presence of other functionality in amino acids demonstrates the importance of this method.

Carbamates are well known for their activity in the field of medicine[1] and agriculture[2]. They are also useful as protecting groups in organic synthesis, particularly, in peptide synthesis.[3a-c] Because of their high demand, continuous efforts have been made to make carbamates through simple and convenient methods.[3d] During the past decade, several methods have been reported for preparing carbamates from for example, aromatic nitro compounds,[4a] cyanates,[4b] isocyanates[4c] and amides.[4d]

One of the method is also accomplished with Lewis acid catalyst.[5] One method[6] utilizes an excess of amine and sodium hydride or triethylamine as base. Though these procedures are satisfactory, these are not suitable for peptide synthesis where the selective protection of an amino group is important. In this context, there is still scope to develop a general method under neutral conditions. In our recent work we have demonstrated zinc promoted facile esterification of acid chlorides with alcohols.[7] Herein we wish to report a simple, convenient and general method for the synthesis of carbamates using chloroformates and zinc (metal grade), as an inexpensive catalyst.

Scheme



R = alkyl, aryl, amino acid, R^1 = ethyl, isobutyl, benzyl

The reaction of a chloroformate with an amino group in the presence of zinc is remarkably fast and leads to high yields of products. Thus in a typical procedure, chloroformate (10 mmol) and activated zinc powder (10 mmol) are stirred in anhydrous benzene (25 ml) for 10 minutes. Then, anhydrous benzene solution of amine (10 mmol in 15 ml) is added slowly and stirred for stipulated time (see tables). After completion of the reaction, the mixture is filtered and the solid is washed with ether (100 ml). The combined filtrate is washed with 10% $NaHCO_3$ solution, then water and is dried

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Table-1 : Preparation of Carbamates from different amines

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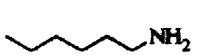
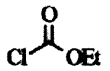
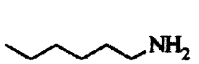
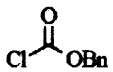
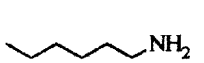
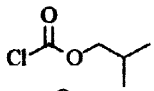
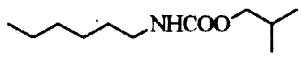
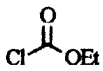
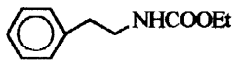
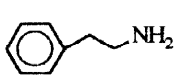
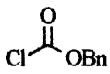
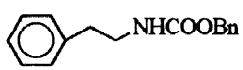
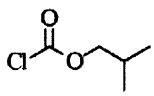
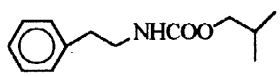
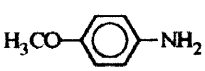
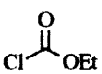
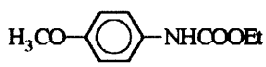
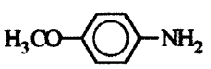
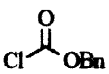
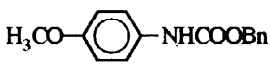
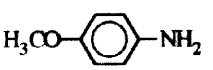
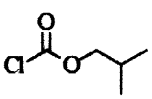
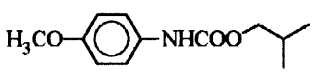
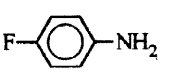
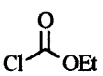
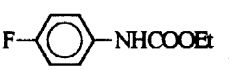
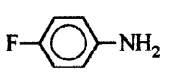
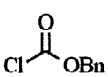
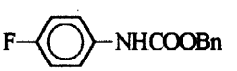
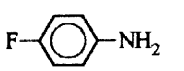
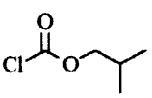
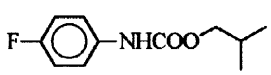
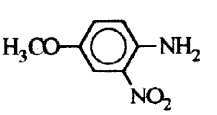
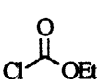
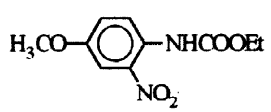
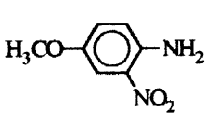
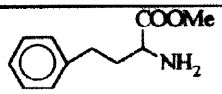
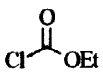
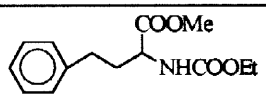
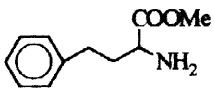
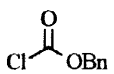
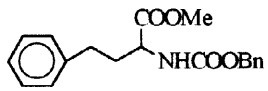
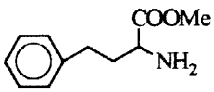
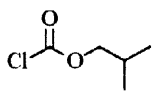
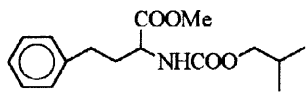
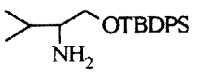
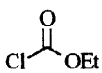
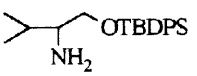
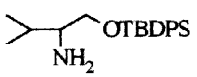
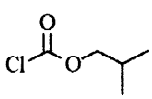
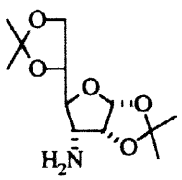
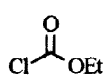
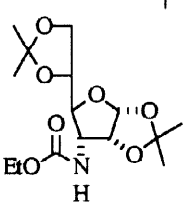
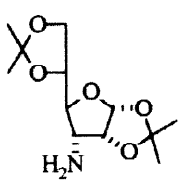
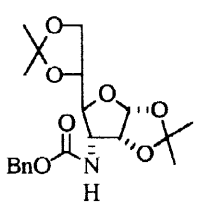
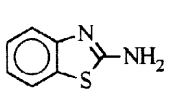
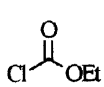
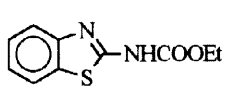
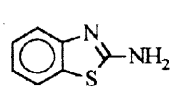
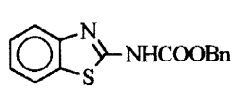
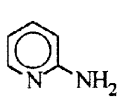
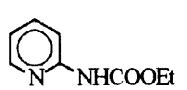
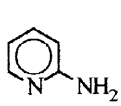
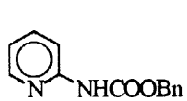
1.				10	96
2.				8	95
3.				9	96
4.				8	97
5.				10	98
6.				9	96
7.				9	96
8.				11	92
9.				10	94
10.				15	94
11.				13	96
12.				18	92
13.				360	92
14.				360	90
15.				360	96

All the products exhibited physical and spectral (NMR, IR & Mass) properties in accord with the assigned structures

Table-2 : Preparation of Carbamates from Amino acids, Carbohydrates and Heterocycles

entry	Amines	Chloro formate	Products	Time (min.)	Yield[a]
1.				15	96
2.				16	95
3.				18	98
4.				15	96
5.				15	94
6.				16	98
7.				15	90
8.				15	94
9.				10	91
10.				8	93
11.				10	92
12.				11	93

All the products exhibited physical and spectral (NMR, IR & Mass) properties in accord with the assigned structures

over Na_2SO_4. Evaporation of the solvent gives carbamates (90-98% yield) with high purity.

The reaction of amines and chloroformates is very rapid and is complete within minutes. We have observed that the presence of electron withdrawing groups suppresses the reaction. To support this observation, we have tested a substrate (table-1; entry 13-15) having both the groups (electron donating and withdrawing i.e., 4-methoxy-2-nitrobenzyl) and the reaction is indeed sluggish.

The importance of the procedure lies in the fact that it is applicable for the protection of the amino group in amino acids. Under the reaction conditions groups like silyl ethers and esters remain unaffected, so this protocol may be useful in peptide synthesis.

A separate experiment reacting chloroformate and amine without zinc does not yield the carbamate. We have also investigated the possibility that zinc could function catalytically or at least, in less than stoichiometric amounts. However, high yields of carbamates and high efficiency of the reaction are found only using 1 eq of zinc.

In conclusion, the present method is very simple, convenient and applicable for the prepartion of alkyl, aryl, heterocyclic, carbohydrate and amino acid carbamates. The advantage of the present method over existing methods is the use of zinc as a reusable catalyst. This is remarkable and makes the method economically valuable.

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