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Straightforward Synthesis of N-Protected Benzylic Amines by Carbamoalkylation of Aromatic Compounds

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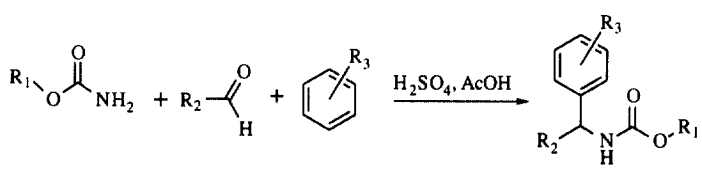
Abstract: A wide range of alkoxycarbonyl protected benzylic amines have been synthesized in a three component reaction involving a carbamate an aldehyde and an aromatic substrate. This reaction proceeds through electrophilic substitution of the aromatic compound by a N-carbamoyl iminium which is generated *in situ* by condensation of the carbamate with the aldehyde.

Aminoalkylation is a prevailing reaction for the synthesis of substituted benzylamines. This aromatic version of the Mannich reaction proceed by electrophilic substitution involving an iminium intermediate formed by condensation of an alkylamine with an aldehyde under acidic conditions [1]. Amidoalkylation is a synthetically useful modification in which the electrophilic species is a N-acyliminium, formed by reaction of amide with aldehyde [2]. In this case the free amines can be obtained by subsequent treatment of the N-acyl adduct under hard acidic or basic conditions. Both of these reactions have been extensively used in organic synthesis [3].

Herein we report our investigation on the one pot preparation of benzylamine derivatives through a three component reaction involving a carbamate an aldehyde and an aromatic substrate (Scheme 1).



Scheme 1

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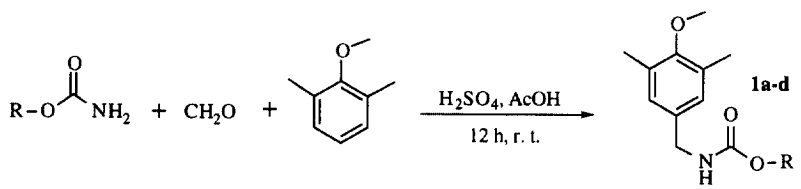
The use of carbamate instead of amide for the formation of the electrophilic transient was not described to date though it allows the one step preparation of valuable N-alkyloxycarbonyl protected amine which are of high interest as key intermediate for the synthesis of pharmaceuticals and natural products. Carbamoalkylation proceeds through a carbamoyl iminium species which to our knowledge could only be generated with moderate yield in the case of phenylglycine derivatives and starting from elaborated hydroxy-N-carbonyloxy glycine in a mixture of sulfuric and acetic acid [4].

First we evaluated the reaction of different alkoxycarbamates and paraformaldehyde using 2,5-dimethylanisole as the aromatic substrate to avoid the formation of regioisomers (Scheme 2).



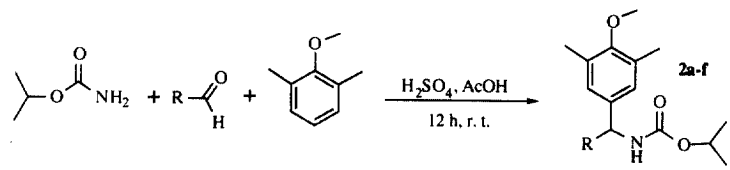
R = Et	80 %	**1a**
R = iPr	85 %	**1b**
R = CH_2CCl_3	84 %	**1c**
R = Bn	52 %	**1d**

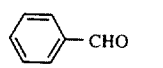
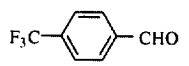
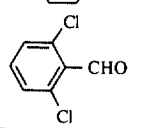
Scheme 2

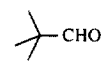
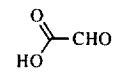
The reactions were conducted at room temperature in a mixture of sulfuric and acetic acids (1 / 4). Two equivalents of carbamate and one equivalent of paraformaldehyde were allowed to react for approximately two hours, until complete dissolution of the paraformaldehyde. One equivalent of 2,5-dimethylanisole was then added and the reaction monitored by TLC. The reaction time ranged from 1 to 12 hours. After completion, 5 mL of water was added and the crude mixture neutralized with a 10 % solution of sodium hydroxide. The product was then extracted with ethyl acetate and purified by silica gel chromatography. The reported yields are based on the conversion of 2,5-dimethylanisole and given for isolated pure compounds.

Ethyl-, isopropyl- and 2,2,2-trichloroethyl-oxycarbonyl protected benzylic amines **1a,b,c** were obtained in good yields, 80, 85 and 84 % respectively. Under identical conditions benzyloxycarbamate only leads to the condensation product **1d** with 30 % yield. This is explained by the degradation of the carbamate that occurs in the acidic reaction media. Benzyl acetate is formed as side product even if the reaction is conducted using only 10 % of sulfuric acid. To compensate this degradation the amount of benzylcarbamate was increased to four equivalents and the paraformaldehyde to two equivalents. Under these conditions the adduct was obtained in 52 % yield. It is noteworthy that all N-alkoxycarbonyl benzylamines products were found to be stable in the reaction media.

In a second set of reactions we varied the aldehyde keeping isopropylcarbamate and 2,5-dimethylanisole as substrates (Scheme 3).



RCHO	Product	Yield
	2a	50 %
	2b	80 %
	2c	75 %

RCHO	Product	Yield
nC_7H_{15} – CHO	2d	----
	2e	15 %
	2f	75 %

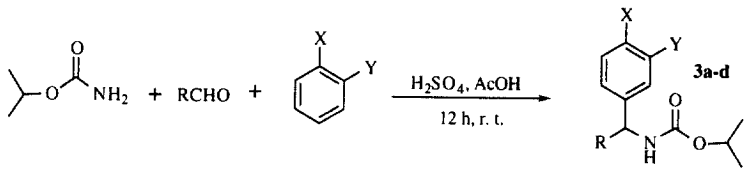
Scheme 3

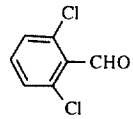
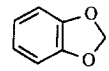
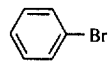
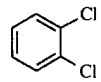
Benzaldehyde gave the condensation product **2a** only in moderate yield (50 %). A side product arising from the acid catalyzed bis condensation of 2,5-dimethylanisole on the benzaldehyde was obtained in 50 % yield. 4-Trifluoromethyl- and 2,5-dichloro-benzaldehyde lead to **2b** and **2c** in 80 and 75 % yield respectively. For these two substrates no acid catalyzed side reaction could be observed.

When octanal **2d** was used as substrate the reaction mixture turned immediately dark brown and no condensation product could ever be detected. Pivalaldehyde leads to the desired product **2e**, but in only 15 % yield. In contrast, glyoxylic acid gave the condensation products **2f** in good yield. These results point out that only activated aldehydes gave the N-alkoxycarbonyl benzylamine with satisfactory yield.

In a last study we varied the aromatic part using isopropylcarbamate and aldehydes which has proved to be good substrate for the reaction (Scheme 4).

The condensation reaction seems to be very sensitive to the substitution of the aromatic substrates. Benzodioxole and *tert*-butylbenzene gave the products **3a** and **3b** in good yield 75 % and 70 % respectively. Whereas bromobenzene and 1,2-dichlorobenzene gave no product even when the reaction was heated or conducted in 50 % sulfuric acid. These results showed that only electron rich aromatics undergoes electrophilic substitution.



RCHO	Aromatic	Product	Yield
		3a	75 %
CO_2H-CHO	X = tBu, Y = H	3b	70 %
CH_2O		3c	-----
CH_2O		3d	-----

Scheme 4

In summary carbamoalkylation appears to be a versatile reaction for the synthesis of a wide range of N-alkoxycarbonyl protected benzylic amines. Our study reveals that electron deficient aromatics are not sufficiently reactive to undergo electrophilic substitution with N-alkoxycarbonyl iminium cation even though the reaction occurs with the corresponding N-acyl iminium.

Typical procedure :

Carbamate (0.14 mmol, 2 eq) and aldehyde (0.7 mmol, 1 eq) are successively added in a mixture of acetic acid (1.6 mL) and sulfuric acid (0.4 ml) at room temperature. Stirring was continued 2 hours or until complete dissolution of the reagents. Aromatic (0.7 mmol, 1 eq) is then added and the mixture allowed to react during 16 hours. Water (5 mL) is added and the mixture neutralized with a 10 % aqueous solution of sodium hydroxide. The product is extracted with 5 x 20 mL of ethyl acetate. The combined organic layers are dried over sodium sulfate and the crude is concentrated under vacuum, purified by silica gel chromatography to afford the pure product.

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