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BORON TRIFLUORIDE PROMOTED CLEAVAGE OF BENZYL CARBAMATES

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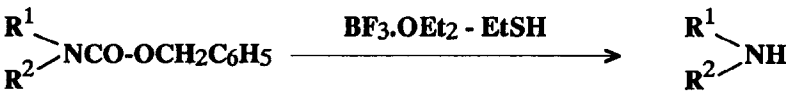
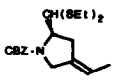
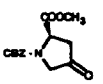
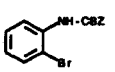
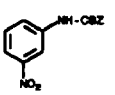
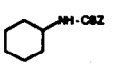
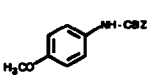
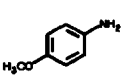
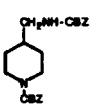
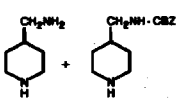
Abstract: A new efficient method for the cleavage of benzyl carbamates (CBZ protective groups) is described that involves a hard acid ($BF_3.OEt_2$) - soft nucleophile (EtSH) system. Unlike other available methods, this combination avoids the reduction of olefins, acetylenes, imines, halides and nitro groups, or the possibility of carboxylic ester hydrolysis.

Carbamates are extensively used as protective groups during the synthesis of peptides and other natural products[1]. In particular, benzyl carbamates are useful for peptide synthesis as they are readily cleaved and can minimize the racemization of amino acids[2]. In the course of our studies on sequence-selective DNA-binding pyrrolo[2,1-c][1,4]benzodiazepines[3], we required a mild method for the removal of a CBZ protective group from tomaymycin precursors of type **1** and **4**. Although several methods are available for CBZ cleavage, catalytic and transfer[4] hydrogenation were unsuitable because of possible reduction of the exocyclic double bond of **1**. Similarly, TMS-I or TMS-Cl/NaI systems[5] are capable of cleaving carboxylic ester groups present in the same molecule (eg. **4**). Strong acids such as HBr can hydrolyse esters or acetals, and are also known to cause C2-racemization in proline derivatives (eg. **1** or **4**). In order to overcome these problems, the method described here was developed.



Among the known Lewis acid catalysts, $BF_3.OEt_2$ is the most widely used for the cleavage of functional groups such as ethers, acetals and esters. Based on the suggested mechanism[6] for the cleavage of benzyl ethers by boron trifluoride etherate - ethanethiol complex, it seemed likely that this system might also cleave benzyl carbamates to afford $PhCH_2SEt$ and the corresponding carbamic acids (R_2N-COOH), which would lose CO_2 to give the amines. We found that, as expected, deprotection of benzyl carbamates proceeded smoothly at room temperature upon treatment with these reagents, which

Table 1. Cleavage of Benzyl Carbamates with $BF_3.OEt_2$ - EtSH

Entry	Substrate[8]	Product[9]	Time (h)	Solvent	Yield
1			10	CH_2Cl_2	90%
2			8	Et_2O	92%
3			12	Et_2O	96%
4			10	CH_2Cl_2	88%
5			14	$CHCl_3$	93%
6			36	Neat[a]	85%
7			28	Neat	80%
8			48	Neat	84%
9			32	Neat	81%
10		 a b	16	CH_2Cl_2	76%, 86%

[a] $BF_3.OEt_2$ - EtSH complex used without solvent.

prompted us to investigate the scope and limitations of the procedure. The results shown in Table 1 indicate that the reaction is successful for a variety of CBZ-protected primary and secondary amines.

When CH_2Cl_2/Et_2O was used as co-solvent, efficient cleavage of secondary carbamates resulted, whereas in the case of primary carbamates, reaction was relatively slow. The use of neat reagents was found to enhance the rate of cleavage of primary carbamates. The selection of reactions outlined in Table 1 shows that, for secondary carbamates of pyrrolidine, piperidine and morpholine ring systems, cleavage is complete within 10 - 14 hours when solvents are used. However, reaction of both the aromatic and alicyclic primary carbamates summarized in Table 1 is notably slower (28 - 48 hours), even though undiluted reagents are used. In addition, it appears that electron withdrawing (eg. m-nitro; **7**) or electron donating (eg p-OMe; **9**) groups do not significantly affect the rate of reaction.

A typical procedure using solvent involves dropwise addition of a solution of the carbamate (1mmol) in CH_2Cl_2 (1ml) to a stirred solution of EtSH (1.8g, 29mmol) and $BF_3.OEt_2$ (1.45g, 10mmol) at room temperature. Stirring is continued until the reaction is complete by TLC. The solvent is evaporated *in vacuo*, the residue quenched with water (5ml) and then extracted with ethyl acetate or chloroform (3 x 25ml). The combined organic phase is washed with saturated brine (25ml), dried ($MgSO_4$) and the solvent removed *in vacuo* to afford the crude product. The examples given in Table 1 were purified by flash chromatography on silica gel. For deprotection using neat reagents, a similar procedure is followed, except that BF_3OEt_2 and EtSH are added directly to the carbamate prior to stirring.

To study the selectivity of the reaction towards primary *vs* secondary carbamates, the dicarbamate **10** was synthesized. With diluted reagents, complete cleavage of the secondary carbamate group occurred. However, significantly less cleavage of the primary carbamate was observed and a mixture of 10a and 10b was isolated in a ratio of approximately 1:9. This observation suggests that the reaction may also be useful in situations where selectivity between primary and secondary amines is required.

In summary, a versatile, high yielding method of cleaving CBZ protective groups is described, that may be generally applicable in organic synthesis where functional groups present in the same molecule are sensitive to other known methods of cleavage available in the literature.

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8. Substrates were prepared by treatment of the corresponding amines (all available from Aldrich Chemical Co. Ltd, except 1 and 4[7]) with CBZ-Cl in either aq. NaOH or $NaHCO_3$.
9. Products were characterized by standard spectroscopic methods and no attempt was made to optimize yields.

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