ORGANIC LETTERS

2000
Vol. 2, No. 8
1049−1051

Selective Hydrogenolysis of Novel Benzyl Carbamate Protecting Groups

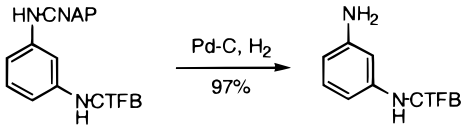
Edward A. Papageorgiou, Matthew J. Gaunt, Jin-quan Yu, and Jonathan B. Spencer*

University Chemical Laboratory, Lensfield Road, Cambridge, United Kingdom, CB2 1EW

jbs20@cam.ac.uk

Received January 27, 2000

ABSTRACT



Highly efficient and selective hydrogenolysis of the 2-naphthylmethyl carbamate group (CNAP) in the presence of the 4-trifluoromethylbenzyl carbamate group (CTFB) has been observed for a wide range of substrates.

Benzyl-type protecting groups constitute one of the major strategies for the protection of oxygen and nitrogen functional groups in organic synthesis.[1] Recently we have determined that the removal of the benzyl group by hydrogenolysis is strongly influenced by the electronic properties of the aromatic ring and its affinity to the metal surface.[2] This has led to the introduction of the 2-naphthylmethyl (NAP) group as a new benzyl-type protecting group for hydroxyl and carboxyl functions that can be removed by hydrogenolysis in the presence of a benzyl group.[2,3]

Here we report the extension of this methodology to the protection of the amine functional group and the development of novel benzyl carbamate derivatives that can be sequentially removed by hydrogenolysis (Figure 1).

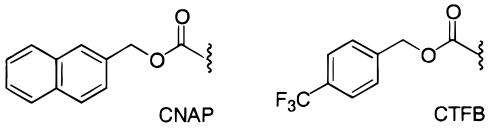
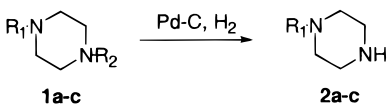


Figure 1. The structures of the novel benzyl carbamate groups CNAP and CTFB.

Benzyl carbamate (Cbz) protection of amines was introduced as a versatile alternative to the ethoxy carbamate group in peptide synthesis.[4] It has found widespread application owing to its ease of removal by hydrogenolysis. Attempts to modify the activity of the Cbz group to achieve orthogonal deprotection under hydrogenolysis conditions have not been successful.[5] Assuming the mechanism of hydrogenolysis of the Cbz group is similar to that of the benzyl group, we anticipated that this goal might be achieved using the combination of Cbz and 2-naphthylmethyl carbamate (CNAP) groups.[6,7]

To assess the relative reactivities of these two groups, intramolecular competition experiments using a piperazine linker were carried out (Table 1). Attempts to remove CNAP in the presence of Cbz from **1a** gave low selectivity. This

Table 1. Competitive Hydrogenolysis of Benzyl Carbamates Separated by a Symmetrical Linker



1a-c **2a-c**

	R_1	R_2	Pd−C, mg/mmol	reaction time	yield, %
1a	Cbz	CNAP	15.0	24 h	29
1b	CTFB	Cbz	10.3	45 min	66
1c	CTFB	CNAP	30.1	45 min	94

10.1021/ol005589l CCC: $19.00
Published on Web 03/18/2000

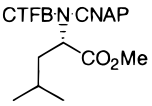
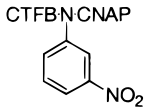
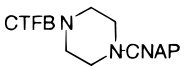
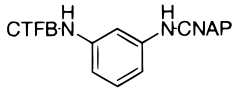
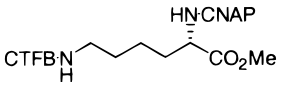
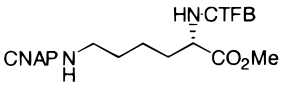
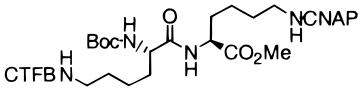
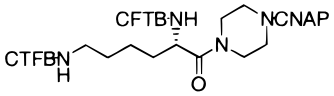
result was in sharp contrast to observations with other NAP−Bn systems,[2,3] which is probably due to the higher inherent reactivity of benzyl carbamates. In a previous study it was determined that the introduction of a trifluoromethyl substituent onto the aromatic ring of the benzyl group reduced its reactivity toward hydrogenolysis.[2] This prompted us to investigate the effect the trifluoromethyl substituent would have on the Cbz group. The result from the competition of Cbz against 4-trifluoromethylbenzyl carbamate (CTFB) **1b**, shows that the carbamate can be substantially deactivated by the electron−withdrawing group. This suggested that the combination of CTFB and CNAP might give the desired orthogonal deprotection. This was demonstrated by the excellent selectivity observed in the hydrogenolysis of piperazine **1c**.

To demonstrate the synthetic utility of the CNAP−CTFB amino protection strategy, the selective removal of CNAP in the presence of CTFB was performed on substrates **5a**−**h**, to afford the mono-deprotected amines[8] in excellent yields (Table 2).[9,10]

Of particular interest in the above table is entry **5g,** as it highlights the potential application of CNAP−CTFB amino protection to the synthesis of peptides. The mild removal conditions are ideally suited for the deprotection of the amines in these sensitive molecules.

The observation that the aromatic nitro group in **5b** is not reduced during the removal of the CNAP group, further

Table 2. Selective Hydrogenolytic Removal of CNAP in the Presence of CTFB

	Substrate	Pd-C mg/mmol	Reaction Time	Yield %
5a		19.0	30 min	93
5b		8.0	3 h	92[11]
5c		30.1	45 min	94
5d		20.7	30 min	97
5e		30.2	35 min	91
5f		29.1	40 min	82[12]
5g		20.0	12 h	94
5h		66.0	17 h	86[12]

(1) Greene, T. W.; Wutts, P. G. M. Protection for the Amino Group. In *Protective Groups in Organic Synthesis*, 3rd ed.;, John Wiley & Sons Inc: New York, 1999. Kunz, H.; Waldmann, H. In Protecting Groups. *Comprehensive Organic Synthesis: Selectivity, Strategy and Efficiency in Modern Organic Chemistry*; Trost, B. M., Fleming, I., Eds.; Pergamon Press: Elmsford, NY, 1991; Vol. 6, pp 631−642. Kocienski, P. J. In *Protecting Groups*; Georg Thieme: Stuttgart, 1994 and references therein.

(2) Gaunt, M. J.; Yu, J.; Spencer, J. B. *J. Org. Chem.* **1998**, *63*, 4172−4173.

(3) Gaunt, M. J.; Boschetti, C. E.; Yu, J.; Spencer, J. B. *Tetrahedron. Lett.* **1999**, *40*, 1803−1806.

(4) Bergmann, M.; Zervas, L. *Ber. Dtsch. Chem. Ges.* **1932**, *65*, 1192−1201.

(5) For discussions, see: Berse, C.; Boucher, R.; Piché, L. *J. Org. Chem.* **1957**, *22*, 805−808. Carpino, L. A.; Tunga, A. *J. Org. Chem.* **1986**, *51*, 1930−1932.

(6) The CNAP and CTFB groups were introduced with excellent yields onto the amines using the corresponding chloroformates, CNAP−Cl and CTFB−Cl. **Carbamate Preparations. CNAP:** To a vigorously stirred $CHCl_3$−water mixture (1:1, 20 mL/mmol of amine) were added the amine, $NaHCO_3$ (2.0 equiv), and CNAP−Cl (1.05 equiv). The reaction was stirred at room temperature until complete as judged by TLC (3−10 h). The aqueous layer was extracted with DCM and washed with brine. Condensation under reduced pressure afforded crude product that was purified by flash column chromatography (silica gel, gradient elution with EtOAc−hexane or MeOH−DCM). **CTFB:** To a solution of amine in acetone−water (9:1, 10 mL/mmol of amine) were added $NaHCO_3$ (2.0 equiv) and CTFB−Cl (1.2 equiv) in acetone. The reaction was stirred at room temperature until complete by TLC (30 min to 4 h). Volatile material was removed under reduced pressure. The solid residue was partitioned between water and DCM. The aqueous layer was extracted with DCM and washed with brine. Condensation under reduced pressure afforded crude product that was purified by flash column chromatography (silica gel, gradient elution with EtOAc−hexane or MeOH−DCM). The chloroformates were prepared in excellent yields by treatment of the alcohols with phosgene solution. **Chloroformate Preparations. CNAP−Cl:** 2-Naphthylmethanol was added in one portion to $COCl_2$ (1.3 equiv of a 20% solution of $COCl_2$ in PhMe) in dry THF (1.5 mL/mmol). The reaction was stirred at room temperature for 2 h. Volatile material was removed under reduced pressure. The solid residue was dissolved in boiling hexane and filtered. Pure *2-naphthylmethyl chloroformate* was obtained as a white solid (>95%) by condensation of the filtrate. **CTFB−Cl:** Similar procedure was followed with 2.0 equiv of $COCl_2$ and stirring for 20 h. Condensation of volatile material afforded *4-trifluoromethylbenzyl chloroformate* as a clear colorless oil that was purified by filtration through Florisil with 10% Et_2O/hexane as the eluent. Both chloroformates could be stored for long periods (12 months) without decomposition in a refrigerator.

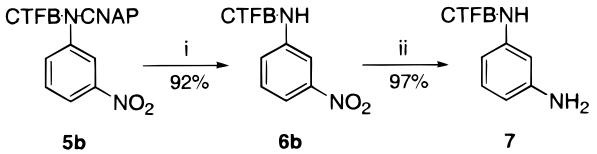
(7) In the assembly of the substrates for the hydrogenolysis experiments, both carbamates, CNAP and CTFB, were found to be resistant to acidolysis in refluxing MeOH−HCl solution for 5 h or 15% TFA in DCM at room temperature for 3 h, conditions that were used for the cleavage of ^{t}Boc groups. They were also found to be resistant to hydrolysis by aqueous base (NaOH or LiOH), conditions used for the saponification of methyl esters.

(8) For the purposes of subsequent discussion the mono-deprotected amines carry the designations **6a**−**h**.

(9) **General Hydrogenolysis Procedure.** Pd−C (10%) was dispersed in EtOAc−EtOH (40 mL/mmol) under argon. The mixture was degassed and saturated with hydrogen. After 30−60 min of vigorous stirring, the substrate was added in a single portion (solids) or as a solution in reaction solvent (oils). The reaction was stirred at room temperature under a hydrogen atmosphere (balloon) until complete by TLC. The catalyst was removed by filtration through Celite with EtOAc or MeOH as the eluent. Condensation of the filtrate afforded the crude product. **Purification of amines 2a−c and 6a−e:** flash column chromatography (silica gel, gradient elution with MeOH−DCM). **Purification of Amines 6f−h.** The crude was dissolved in MeOH−water (3:1 to 1:1 mixture) and extracted with hexane (5 × 20 mL). The resultant 2-naphthylmethane-free solution was condensed to afford the amine, pure by ^{1}H NMR.

highlights the ease with which the CNAP group may be removed under particularly mild conditions. If either the remaining CTFB or nitro group can be preferentially reduced it would liberate three amines in sequence from one molecule. Indeed, it was found that the nitro group was selectively reduced in the presence of the CTFB group (Scheme 1).

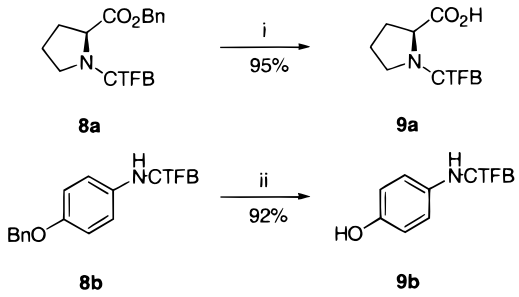
Scheme 1. Hydrogenation of an Aromatic Nitro Group in the Presence of CTFB[a]



[a] Reagents and conditions: (i) anhydrous EtOAc, 10% Pd−C (8 mg/mmol), 3 h; (ii) EtOH−EtOAc (1:1), 10% Pd−C (30 mg/mmol), 2.2 h.

Apart from opening up the possibility of an alternative orthogonal protection strategy for amines,[13] selective nitro reduction to **7** is noteworthy because it cannot be replicated with Cbz in place of CTFB.[14] The apparent stability of the CTFB group prompted us to consider the selective reduction/hydrogenolysis of other susceptible functionality in its presence. In view of our previous studies on benzyl-type protecting groups for oxygen,[2,3] we were particularly interested in investigating the removal of benzyl ethers and esters in CTFB-containing molecules. Preliminary results from this study (Scheme 2) demonstrate that use of the CTFB group should be widely applicable in synthesis.

Scheme 2. Hydrogenolysis of a Benzyl Ester and a Benzyl Ether in the Presence of CTFB[a]



[a] Reagents and conditions: (i) EtOH−EtOAc (1:1), 10% Pd−C (25 mg/mmol), 1.3 h; (ii) EtOH−EtOAc (1:1), 10% Pd−C (20 mg/mmol), 3.0 h.

In summary, orthogonal deprotection for amines has been achieved. This is based on the highly efficient and selective deprotection of the CNAP over the CTFB carbamate under standard hydrogenolysis conditions.

Acknowledgment. The authors acknowledge The Royal Society for the award of a Royal Society University Research Fellowship (J.B.S), The A.G. Leventis Foundation and St John's College, Cambridge (E.A.P.), and The Wellcome Trust (M.J.G.).

OL005589L

(10) **Hydrogenolysis of the CTFB Group.** Removal of the CTFB group is generally facile, requiring only small increases in the amount of catalyst compared to the CNAP−CTFB competition experiments. For example, complete (95%) *N* deprotection of *N*-CTFB leucine methyl ester, **6a**, was effected in 85 min with 60 mg/mmol Pd−C (10%). In cases where deprotection is sluggish with Pd−C (10%) use of the more active Pearlman's catalyst, $Pd(OH)_2$ (20%) is recommended. For example, complete (97%) *N* deprotection of *N*-CTFB 3-aminobenzonitrile could be effected in 130 min with 20 mg/mmol $Pd(OH)_2$ (20%) without detectable reduction of the nitrile, but not with Pd−C (10%).

(11) For selective hydrogenolysis of CNAP over hydrogenation of the aromatic nitro group, the reaction had to be performed in dry EtOAc.

(12) ^{1}H NMR of the crudes showed a single product in each case. The lower than expected isolated yields resulted from the purification procedure that had to be employed with these compounds. Their very polar nature excluded flash column chromatography.

(13) The generality of this approach is being investigated.

(14) Attempts to selectively reduce the aromatic nitro group in *N*-Cbz 3-nitrophenylamine with Pd−C (10%) afforded a mixture of all possible products (23% of desired product). Similar results have been reported with Pd−C/diamine complexes, with which hydrogenolysis of benzyl-type groups is generally inhibited in the presence of other reducible functionality (Sajiki, H.; Hattori, K.; Hirota, K. *J. Org. Chem.* **1998**, *63*, 7990−7992).