A Mild Deprotection of Trichloroethyl Carbamates Using Indium Metal

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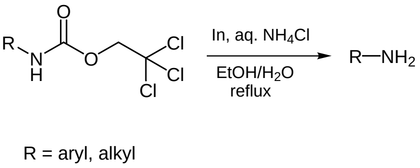
Abstract: The trichloroethoxycarbonyl moiety was efficiently removed from carbamates to furnish the corresponding amines using indium metal in good to excellent yields.

Key words: indium, deprotection, amines, 2,2,2-trichloroethyl carbamates, chemoselectivity

Protection strategies using the 2,2,2-trichloroethoxycarbonyl (Troc) group for the masking of hydroxy and amino groups, and the 2,2,2-trichloroethoxy group for carboxylic acids[1,2] have been exceedingly useful in total synthesis.[3–6] Furthermore, several methods exist for the cleavage of the Troc protecting group from carbamates. The Troc unit can be removed by reduction with Zn metal,[1,7] electrolysis,[8,9] Zn–Pb couple,[10] Cd dust,[11] Cd–Pb couple,[12] cobalt(I)-phthalocyanine anion,[13] and telluride reagents.[14] In recent years, indium-mediated reduction and deprotection reactions have received considerable attention as a convenient method for effecting various organic transformations.[15]

We have recently reported that deprotection of Troc- and trichloroacetyl-protected alcohols can be carried out chemoselectively with indium metal under mild conditions.[16] In an ongoing effort to develop indium-mediated chemistry, we have found that carbamates can also be cleaved chemoselectively under mild conditions, into the corresponding amines using indium metal. Herein, we wish to report the details of our studies on the release of amines from their trichloroethyl carbamates (Scheme).



Scheme

Applying the reaction conditions from our previous work,[16] deprotection of Troc-protected 4-aminobenzonitrile gave poor results even after 5 h of reflux, using 2 equiv of indium (Table 1, entry 1). When the amount of indium was increased to 5 equiv, the reaction proceeded to afford 84% of the desired 4-aminobenzonitrile (Table 1, entry 2). Unfortunately, unsatisfactory results were obtained with other substrates under the identical reaction conditions (Table 1, entries 3 and 4), prompting us to search for more suitable reaction conditions. The reaction was improved when the solvent was changed from MeOH–H_2O (5:1) to EtOH–H_2O (3:2), presumably due to the higher boiling point of EtOH (bp 78 °C) compared to MeOH (bp 65 °C). The most efficient deprotection of a Troc moiety was observed in the case of Troc-protected 4-aminobenzonitrile, requiring only 2 equiv of indium metal and 3 equiv of NH_4Cl (Table 1, entry 5).

Table 1 Optimization of Reaction Conditions[a]

Entry	R[1]	R[2]	Solvent	In (equiv)	NH_4Cl (equiv)	Yield[b] (%)
1 [c]	CN	H	MeOH–H_2O (5:1)	2	5	49
2	CN	H	MeOH–H_2O (5:1)	5	10	84
3	Ac	H	MeOH–H_2O (5:1)	5	10	22
4	H	Ac	MeOH–H_2O (5:1)	5	10	68
5	CN	H	EtOH–H_2O (3:2)	2	3	98

[a] All reactions were performed at reflux.
[b] Isolated yields.
[c] Starting material (33%) was also recovered.

Having improved the deprotection conditions, various aromatic and aliphatic carbamates were prepared by known methods[17] and subjected to the above deprotection conditions. Table 2 shows that the reaction proceeded smoothly to furnish the corresponding amines in good to excellent yields. Deprotection of halogenated aromatic carbamates was carried out without dehalogenation (Table 2, entries 3, 11, and 12). Under these reaction conditions, neither ketones nor nitriles underwent reduction in spite of the reductive property of indium metal (Table 2, entries 1, 7, and 8). The reaction also led to the desired amines without affecting methoxy groups (Table 2, entries 2, 4, 5, and 9).

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The release of 1-adamantylamine (Table 2, entry 6) and 2-aminobiphenyl (Table 2, entry 10) required extended reaction times for completion, presumably due to steric hindrance.

To determine the selectivity of the reaction conditions, we introduced triisopropylsilyl (TIPS), methoxyethoxymethyl (MEM), and *t*-butyldimethylsilyl (TBDMS) groups into Troc-protected compounds and performed the deprotection of the Troc group under the same reaction conditions. Both TIPS- and MEM-protected alcohols were resistant to these reaction conditions while only the Troc group was removed in excellent yields (Table 3, entries 1 and 2). When the Troc-protected aromatic amine moiety was placed *para* to a more acid sensitive *t*-butyldimethylsilyloxy moiety (Table 3, entry 4), deprotection of the Troc group nevertheless proceeded smoothly and in satisfactory yield. In contrast, when these two substituents were *ortho* to each other, the deprotecting reaction of the Troc group led initially to an unacceptably low yield. Upon increasing the amount of indium metal to 5 equiv (Table 3, entry 3), the deprotection was improved to 68% yield. The by-product in the deprotection of the Troc group from the *ortho*-TBDMS derivative is from loss of the silyl group, which does not occur with the *para*-TBDMS derivative (Table 3, entry 4). Thus, entry 3 may give lower yields as a result of the contribution of steric decompression to the enhancement of the TBDMS group's acid catalyzed hydrolysis rate. While acid sensitive protecting groups generally tolerate the indium condition, in certain instances, cleavage of the TBDMS (Table 3, entry 7) or ketal (Table 2, entry 13) groups can occur within short times in spite of the resistance of TBDMS group itself for relatively long times under indium condition (Table 3, entry 8). Overall, these results demonstrate chemoselectivity in the deprotection of Troc-protected amines with indium metal, further expanding the array of multifunctional protecting strategies for amines in the presence of alcohols.

Table 2 Deprotection of Troc Groups Using Indium[a]

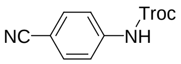
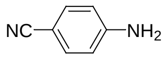
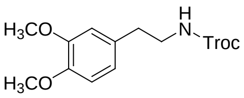
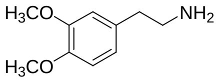
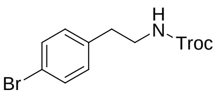
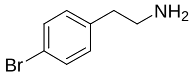
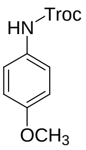
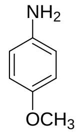
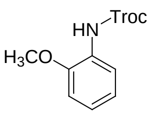
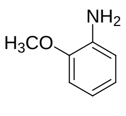
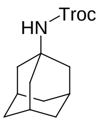
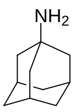
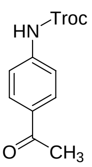
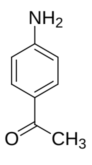
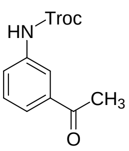
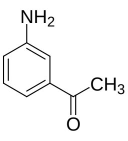
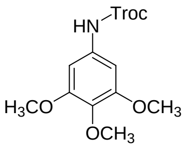
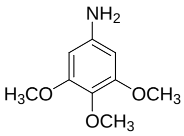
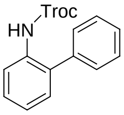
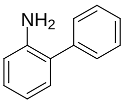
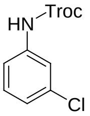
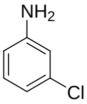
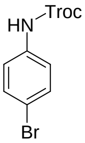
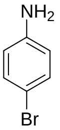
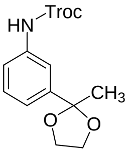
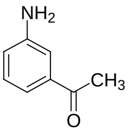
Entry	Starting Material	Product	Time (h)	Yield[b] (%)
1			3	98
2			3	76
3			3	88
4			4	83
5			4	76
6			6	91
7			3	93
8			3	84

Table 2 Deprotection of Troc Groups Using Indium[a] (continued)

Entry	Starting Material	Product	Time (h)	Yield[b] (%)
9			3.5	66
10			6	80
11			2.5	86
12			2.5	86
13			2.5	91

[a] All reactions were performed at reflux.

[b] Isolated yields.

We compared our method to other *N*-Troc deprotecting conditions for chemoselectivity. The common method for Troc deprotection is the use of zinc metal in acetic acid, which is not typically used in the presence of acid-sensitive protecting groups.[1,7] Using excess zinc in acetic acid deprotected both Troc and TBDMS groups of the *para*-TBDMS derivative leading to mixtures of products (Table 3, entry 5). On the other hand, the silyl group of the TBDMS protected aryl ethanol (Table 3, entry 6) was more stable than the former silylphenoxide (Table 3, entry 5). Another mild cleavage method of Troc-carbamates to amines using zinc and NH_4OAc–THF deprotected both protecting groups as well as required relatively longer reaction times and large excess zinc to complete the reaction (Table 3, entry 9).[7] The other disadvantage of zinc methods is the development of a slurry during the reaction. Overall, zinc condition not only gave lower yields because of cleavage of the silyl group but also required longer reaction times (Table 3, entries 5, 6, and 9).

In summary, we have developed an improved and mild method for the deprotection of Troc groups from various protected amines. We also demonstrated that this deprotection method could be utilized in the presence of various acid labile protecting groups. Compared to conventional conditions employing zinc metal and acetic acid, indium methodology is generally more chemoselective and higher yielding. Further applications of these methods are in progress.

General experimental procedure: The Troc protected amine (1 mmol) was combined with indium powder[18] (2 mmol), NH_4Cl (3 mmol), and EtOH–H_2O, 3:2 (5 mL). The mixture was refluxed and monitored for completion by TLC. Indium was filtered off, and the solvent was removed by rotary evaporation under vacuum. The residue was combined with aqueous NaOH solution (1 M, 10 mL) and extracted with ethyl acetate (3 × 15 mL). The combined organic layers were washed with brine and dried over anhydrous Na_2SO_4. The mixture was filtered and concentrated by rotary evaporation. The resulting residue was purified by silica gel flash column chromatography to afford the desired amines. All products were consistent with their required physical and spectral data.

References

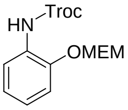
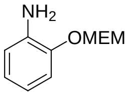
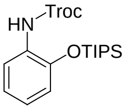
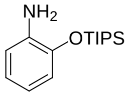
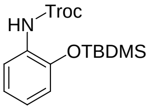
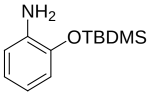
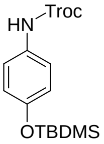
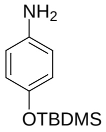
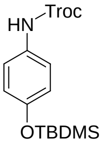
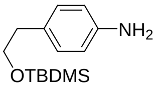
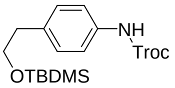
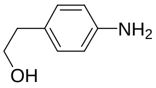
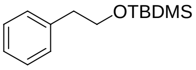
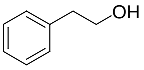
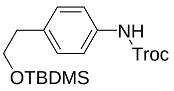
(1) Woodward, R. B.; Heusler, K.; Gosteli, J.; Naegeli, P.; Oppolzer, W.; Ramage, R.; Ranganathan, S.; Vorbrüggen, H. *J. Am. Chem. Soc.* **1966**, *88*, 852.

(2) Windholz, T. B.; Johnston, D. B. R. *Tetrahedron Lett.* **1967**, *27*, 2555.

(3) Dvorak, C. A.; Schmitz, W. D.; Poon, D. J.; Pryde, D. C.; Lawson, J. P.; Amos, R. A.; Meyers, A. I. *Angew. Chem. Int. Ed.* **2000**, *39*, 1664.

(4) Xie, C.; Runnegar, M. T. C.; Snider, B. B. *J. Am. Chem. Soc.* **2000**, *122*, 5017.

Table 3 Chemoselective Deprotection of Troc Group

Entry	Starting Material	Product	Condition	Time (h)	Yield (%)
1			2 equiv In aq. NH_4Cl	2	91
2			2 equiv In aq. NH_4Cl	1.5	92
3			5 equiv In aq. NH_4Cl	3	68
4			2 equiv In aq. NH_4Cl	1.5	93
5		mixture[a]	6 equiv Zn in AcOH	24	–
6[b]			6 equiv Zn in AcOH	24	61
7			2 equiv In aq. NH_4Cl	1.5	78
8			2 equiv In aq. NH_4Cl	12	60
9		mixture[c]	10 equiv Zn NH_4OAc–THF	48	–

[a] 4-TBDMS-oxyaniline, *N*-Troc-4-hydroxyaniline, and 4-hydroxyaniline.

[b] The minor product was 4-aminophenylethanol.

[c] Starting material, *O*-TBDMS-4-aminophenylethanol, and 4-aminophenylethanol.

(5) Takayama, H.; Ichikawa, T.; Kuwajima, T.; Kitajima, M.; Seki, H.; Aimi, N.; Nonato, M. G. *J. Am. Chem. Soc.* **2000**, *122*, 8635.

(6) Peschko, C.; Steglich, W. *Tetrahedron Lett.* **2000**, *41*, 9477.

(7) Just, G.; Grozinger, K. *Synthesis* **1976**, 457.

(8) Hijfte, L. V.; Little, R. D. *J. Org. Chem.* **1985**, *50*, 3940.

(9) Semmelhack, M. F.; Heinsohn, G. E. *J. Am. Chem. Soc.* **1972**, *94*, 5139.

(10) Overman, L. E.; Freerks, R. L. *J. Org. Chem.* **1981**, *46*, 2833.

(11) Hancock, G.; Galpin, I. J.; Morgan, B. A. *Tetrahedron Lett.* **1982**, *23*, 249.

(12) Dong, Q.; Anderson, C. E.; Ciufolini, M. A. *Tetrahedron Lett.* **1995**, *36*, 5681.

(13) Eckert, H.; Ugi, I. *Angew. Chem. Int. Ed. Engl.* **1976**, *15*, 681.

(14) Lakshmikantham, M. V.; Jackson, Y. A.; Jones, R. J.; O'Malley, G. J.; Ravichandran, K.; Cava, M. P. *Tetrahedron Lett.* **1986**, *27*, 4687.

(15) Pitts, M. R.; Harrison, J. R.; Moody, C. J. *J. Chem. Soc., Perkin Trans. 1* **2001**, 955; and references cited therein.

(16) Valluri, M.; Mineno, T.; Hindupur, R. M.; Avery, M. A. *Tetrahedron Lett.* **2001**, *42*, 7153.

(17) Windholz, T. B.; Johnston, D. B. R. *Tetrahedron Lett.* **1967**, 2555.

(18) Aldrich Chemical Company. Indium powder, 99.99%. Catalog # 27,795-9.