

[A009]

Reductive deprotection of Boc-protected alcohols, amines and thiols via a DTBB-catalysed lithiation process

Cherif Behloul, David Guijarro and Miguel Yus*

*Departamento de Química Orgánica, Facultad de Ciencias and Instituto de Síntesis Orgánica (ISO), Universidad de Alicante, Apdo. 99, 03080 Alicante (Spain). Tel. +34-965903548. Fax +34-965903549.
E-mail: yus@ua.es. <http://www.ua.es/dept.quimorg>*

Abstract: The DTBB-catalysed lithiation of Boc-protected alcohols, amines and thiols in THF at 0°C led, after quenching with methanol, to the recovery of the free alcohols, amines and thiols in short reaction times and with very good yields. The procedure has been applied to primary, secondary and tertiary alcohols, secondary amines and a primary thiol. This method represents a reasonable alternative to the previously reported deprotection procedures.

Keywords: lithium; DTBB; *tert*-butoxycarbonyl; Boc; deprotection; alcohols; amines; thiols.

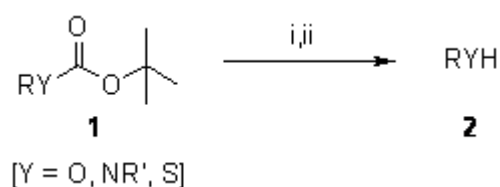
Introduction

The *tert*-butoxycarbonyl protecting group (Boc; introduced in 1957^[1]) has demonstrated to be one of the most efficient ones for compounds of the type RYH (Y = O, NR', S), especially for amines.^{[2] [3] [4]} Actually, the Boc group is the most frequently used as amino-protecting function in peptide chemistry. Its removal can be easily achieved under acidic conditions: hydrochloric acid (in dichloromethane, ether or ethyl acetate) or trifluoroacetic acid (neat or in dichloromethane). In especial cases, more sophisticated procedures can be used for its cleavage: trimethylsilyl^[5] or *tert*-butyldimethylsilyl triflate,^[6] boron trifluoride etherate,^[7] tetrabutylammonium fluoride,^[8] zinc dibromide,^[9] or cerium ammonium nitrate.^[10]

On the other hand, in the last few years we have been using an arene-catalysed lithiation to perform metallations under very mild reaction conditions.^{[11] [12] [13]} This methodology has been shown to be applicable to the cleavage of trityl ethers^[14] and amines,^[15] to the desilylation^[16] and the deallyloxy- or debenzoyloxycarbonylation^[17] of protected alcohols, amines and thiols, and to perform the deacylation of esters, thioesters and amides.^[18] In this communication we report our preliminary results on the reductive removal of the Boc group from protected alcohols, amines and thiols via a DTBB-catalysed lithiation process under very mild reaction conditions.

Results and discussion

The reaction of *O*-Boc protected alcohols **1a-c** with an excess of lithium powder (1:9 molar ratio) and a catalytic amount of 4,4'-di-*tert*-butylbiphenyl (DTBB; 1:0.1 molar ratio; 5 mol %) in THF at 0°C and for 1-3 h led, after quenching with methanol, to the corresponding alcohols **2a-c** (Scheme 1 and Table 1, entries 1-3). Yields of the deprotected products were very good, except when the R group was sterically hindered (Table 1, entry 3). The same procedure was also applied to the carbamates **1d,e** and the expected amines **2d,e** were obtained in good to excellent yields (Scheme 1 and Table 1, entries 4 and 5). The lithiation of the *S*-Boc thiol **1f** gave only a moderate yield of the thiol **2f**, probably due to oxidation of the latter to the corresponding disulfide by the air after the reaction had been quenched with methanol.



Scheme 1. Reagents and conditions: (i) Li, DTBB (5 mol %), THF, 0°C; (ii) MeOH, 0°C to rt.

Table 1. Reductive deprotection of compounds **1** via a DTBB-catalysed lithiation.

Entry	Substrate				Product	
	No.	Y	R	Time (h)	No.	Yield (%) ^a
1	1a	O	Me(CH ₂) ₉	1.5	2a	>99
2	1b	O	Me(CH ₂) ₅ CH(Me)	3.0	2b	70
3	1c	O	Pr ⁱ (CH ₂) ₃ C(Me)(Et)	1.0	2c	45
4	1d	Me(CH ₂) ₇ N	Me(CH ₂) ₇	1.5	2d	>99
5	1e	MeN	Ph	2.0	2e	62
6	1f	S	Me(CH ₂) ₉	5.0	2f	47

^a Yield determined by quantitative GLC, using commercially available compound **2** and *n*-dodecane (internal standard) in the determination of response factors.

Starting materials **1** were prepared from commercially available alcohols **2a-c**, amines **2d,e** and the thiol **2f** by reaction with di-*tert*-butyl dicarbonate and a catalytic amount of 4-(dimethylamino)pyridine (DMAP; 1:0.4 molar ratio) in toluene at room temperature.

Conclusion

In conclusion, from the results described here, we think that the reductive deprotection of Boc-protected alcohols, amines and thiols by a DTBB-catalysed lithiation procedure represents a reasonable alternative to other deprotection techniques.

Experimental part

For general experimental information, see reference 15. All reagents used for the synthesis of Boc-protected substrates **1** and DTBB were commercially available (Acros, Aldrich) and were used without further purification.

Lithium powder was prepared according to the procedure described in reference [19]. Commercially available toluene (Merck) and anhydrous THF (99.9%, water content £ 0.006%, Acros) were used as solvents in the reactions. All glassware was dried in an oven at 100°C and cooled to room temperature under Ar before use.

Preparation of the starting Boc-protected materials 1. General procedure.

4-(Dimethylamino)pyridine (96 mg, 0.4 mmol) was added in one portion to a stirred solution of the corresponding alcohol, amine or thiol **1** (10.0 mmol) and di-*tert*-butyl dicarbonate (2.18 g, 10.0 mmol) in toluene (15 mL) at room temperature. After stirring for 30 min at the same temperature, the crude reaction mixture was adsorbed on basic aluminium oxide, transferred to a short column of basic aluminium oxide and eluted with hexane. Evaporation of the solvent (15 Torr) afforded the expected Boc-protected compounds **1** in pure form.

DTBB-catalysed lithiation of compounds 1. Preparation of products 2. General procedure.

A solution of the protected substrate **1** (1.0 mmol) in THF (2 mL) was dropwise added to a green suspension of lithium powder (63 mg, 9.0 mmol) and 4,4'-di-*tert*-butylbiphenyl (DTBB, 27 mg, 0.1 mmol) in THF (5 mL), under Ar, at 0 °C. After stirring at the same temperature for the time indicated in Table 1, methanol (5 mL) was carefully added, the cooling bath was removed and the reaction was stirred till it reached room temperature. The yields of the deprotected products were determined by quantitative GC. Commercially available alcohols, amines or thiols **2** and *n*-dodecane (internal standard) were used in the determination of response factors.

Acknowledgements

This work was generously supported by the Dirección General de Enseñanza Superior (DGES) of the current Spanish Ministerio de Educación y Ciencia (MEC; grant no. CTQ2004-01261) and the Generalitat Valenciana (grant no. GRUPOS03/135). C. B. thanks the University of Alicante for a predoctoral fellowship. We also thank MEDALCHEMY S.L. for a gift of chemicals.

References

- [1] . (a) Carpino, L. A. *J. Am. Chem. Soc.* **1957**, *79*, 98. (b) For a review, see: Carpino, L. A. *Acc. Chem. Res.* **1973**, *6*, 191.
- [2] . Kunz, H.; Waldmann, H. In *Comprehensive Organic Synthesis*; Trost, B. M.; Fleming, I.; Winterfeldt, E., Eds.; Pergamon Press: Oxford, 1991; Vol. 6; Chapter 3.1.
- [3] . Greene, T. W.; Wuts, P. G. M. *Protective Groups in Organic Synthesis*, 3rd ed.; John Wiley & Sons: New York, 1999.; pp. 281, 484-485, 518-524.
- [4] . Kocienski, P. J. *Protecting Groups*; Thieme: Stuttgart, 2004.; pp. 341-343, 378, 505-511.
- [5] . Fujii, N.; Otaka, A.; Ikemura, O.; Akaji, K.; Funakoshi, S.; Hayashi, Y.; Kuroda, Y.; Yajima, H. *J. Chem. Soc., Chem. Commun.* **1987**, 274.
- [6] . Sakaitani, M.; Ohfuné, Y. *J. Org. Chem.* **1990**, *55*, 870.
- [7] . Evans, E. F.; Lewis, N. J.; Kapfer, I.; Macdonald, G.; Taylor, R. J. K. *Synth. Commun.* **1997**, *27*, 1819.
- [8] . (a) Routier, S.; Saugé, L.; Ayerbe, N.; Coudert, G.; Mérour, J.-Y. *Tetrahedron Lett.* **2002**, *43*, 589. (b) Jacquemard, U.; Bénéteau, V.; Lefoix, M.; Routier, S.; Mérour, J.-Y.; Coudert, G. *Tetrahedron* **2004**, *60*, 10039.
- [9] . Nigam, S. C.; Mann, A.; Taddei, M.; Wermuth, C.-G. *Synth. Commun.* **1989**, *19*, 3139.
- [10] . Hwu, J. R.; Jain, M. L.; Tsay, S.-C.; Hakimelahi, G. H. *Tetrahedron Lett.* **1996**, *37*, 2035.
- [11] . For reviews, see: (a) Yus, M. *Chem. Soc. Rev.* **1996**, *25*, 155. (b) Ramón, D. J.; Yus, M. *Eur. J. Org. Chem.* **2000**, 225. (c) Yus, M. *Synlett* **2001**, 1197. (d) Yus, M.; Ramón, D. J. *Latv. J. Chem.* **2002**, *79*. (e) Ramón, D. J.; Yus, M. *Rev. Cubana Quim.* **2002**, *14*, 76. (f) Yus, M. Arene-catalyzed lithiation. In *The Chemistry of Organolithium Compounds*; Rappoport, Z.; Mareck, I., Eds.; J. Wiley & Sons: Chichester, 2004; Chapter 11.
- [12] . For mechanistic studies, see: (a) Yus, M.; Herrera, R. P.; Guijarro, A. *Tetrahedron Lett.* **2001**, *42*, 3455. (b) Yus, M.; Herrera, R. P.; Guijarro, A. *Chem. Eur. J.* **2002**, *8*, 2574. (c) Herrera, R. P.; Guijarro, A.; Yus, M. *Tetrahedron Lett.* **2003**, *44*, 1309.

- [13] . For a polymer version of this reaction, see: (a) Gómez, C.; Ruiz, S.; Yus, M. *Tetrahedron Lett.* **1998**, *39*, 1397. (b) Gómez, C.; Ruiz, S.; Yus, M. *Tetrahedron* **1999**, *55*, 7017. (c) Yus, M.; Gómez, C.; Candela, P. *Tetrahedron* **2002**, *58*, 6207. (d) Candela, P.; Gómez, C.; Yus, M. *Russ. J. Org. Chem.* **2004**, *40*, 795.
- [14] . Yus, M.; Behloul, C.; Guijarro, D. *Synthesis* **2003**, 2179.
- [15] . Behloul, C.; Guijarro, D.; Yus, M. *Synthesis* **2004**, 1274.
- [16] . Behloul, C.; Guijarro, D.; Yus, M. *Tetrahedron* **2005**, *61*, 6908.
- [17] . Behloul, C.; Guijarro, D.; Yus, M. *Tetrahedron* **2005**, *61*, 9319.
- [18] . Behloul, C.; Guijarro, D.; Yus, M. *Synthesis* **2005**, in press.
- [19] . Yus, M.; Martínez, P.; Guijarro, D. *Tetrahedron* **2001**, *57*, 10119.