Tetrahedron Letters, Vol. 33, No. 19, pp. 2677-2680, 1992
Printed in Great Britain

0040-4039/92 $5.00 + .00
Pergamon Press Ltd

A Convenient Synthesis of N-Boc Protected Primary Amines via the Reaction of Organoboranes with Li or K t-Butyl-N-Tosyloxycarbamate.

Jean-Pierre Genêt, Josef Hajicek[1], Laurent Bischoff and Christine Greck

Laboratoire de Synthèse Organique Associé au CNRS- Ecole Nationale Supérieure de Chimie de Paris
11, rue Pierre et Marie Curie- 75231 Paris Cedex 05

Keywords: Amination, Organoboranes, t-Butyl-N-tosyloxycarbamate.

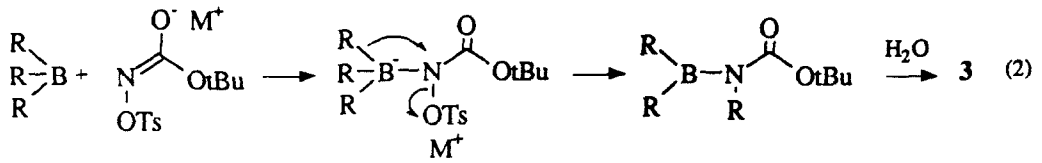
Abstract: Primary and secondary alkylboranes reacted rapidly at low temperature with Li or K t-butyl-N-tosyloxycarbamate (LiBTOC or KBTOC) to give the corresponding N-Boc protected primary amines in modest to good yields (16- 81%).

We recently reported that Li t-butyl-N-tosyloxycarbamate (LiBTOC) reacted with various organometallics as an electrophilic aminating reagent to afford N-Boc protected primary amines.[2]
Organoboranes have proven to be useful synthetic intermediates for the formation of carbon-carbon bond.[3] They could be utilized to produce primary free amines by treating them with chloramine,[4] hydroxamine-O-sulfonic acid[4,5] or hydrazoic acid.[6] Reaction of organoboranes with organic azides,[7] N-chloroalkylamines[8] or the O-2,4-dinitrophenyl derivative of chlorohydroxyamine[9] gave secondary amines. To our knowledge, there is only one example of similar reaction leading to N-protected amines: sulfonamides are obtained by reaction of trialkylboranes with chloramine-T,[10] but this protecting group is quite difficult to remove.[11]
We wish to report the synthesis of N-Boc protected primary amines from organoboranes using metallated t-butyl-N-tosyloxycarbamate 2 as aminating reagent (eq 1). t-Butyloxycarbonyl is an usual protecting group for amines and the deprotection occurs under mild acidic conditions.

$$\underset{\mathbf{1}}{\text{TsONHBoc}} \xrightarrow{\text{Base}} \underset{\begin{array}{l}\mathbf{2a}\ \text{M=Li}\\ \mathbf{2b}\ \text{M=K}\end{array}}{\text{TsON(M)Boc}} \xrightarrow{R_3B} \underset{\mathbf{3}}{\text{RNHBoc}} \qquad (1)$$

The reagent itself, t-butyl-N-tosyloxycarbamate **1**, did not react with trialkylborane (e.g. tributylborane). In contrast the reaction with borane proceeded smoothly in the presence of Li or K salts of **1** (LiBTOC **2a** or KBTOC **2b**).

The reaction presumably proceeds via the aniotropic rearrangement of an organoborate complex (eq 2).



(2)

In preliminary experiments, we observed that trialkyl primary boranes rapidly reacted with LiBTOC **2a** in 1:1 molar ratio at low temperature (entry 1) to give N-Boc protected n-butylamine in good yield: 81%. Use of 1:3 trialkylborane / LiBTOC molar ratio afforded it in 20% yield (entry 2). Only one of the three alkyl groups is transferred with the lithio salt of t-butyl-N-tosyloxycarbamate. Then we investigated the reactivity of organoboranes containing secondary alkyl groups: the reaction proceeded rapidly with LiBTOC to give moderate yield of the N-Boc protected amine: 30% (entry 4). However, the reagent KBTOC **2b** generated by treatment of t-butyl-N-tosyloxycarbamate **1** with KHMDS in THF, produced an acceptable yield of N-Boc-s-butylamine: 65% (entry 5). Under the same conditions, the reaction of KBTOC **2b** with tri-n-octylborane or tricyclohexylborane was rapid, leading to the formation of the N-Boc protected corresponding amines (entries 6-7). Interestingly, tri n-butylborane reacted more rapidly with KBTOC (1/3 molar ratio) to afford N-Boc n-butylamine in 40% yield (entry 3): slightly more than one of the three butyl groups are transferred. Different attempts under various conditions (temperature, solvent) failed to improve the utilization of the three alkyl groups on boron.

The organoboranes derived from 9-borabicyclo-(3.3.1)-nonane (9-BBN) have been extensively used to achieve improved utilization of the alkyl group on boron.[12] Consequently we carried out the reaction of these alkyl derivatives of 9-BBN with LiBTOC **2a** or KBTOC **2b** (entries 8-9-10). However, the B-cyclooctyl group migrated producing N-Boc-5-aminocyclooctanol: the carbon-boron bond was oxidized under these conditions.[13]

N-Boc aniline was obtained from the reaction of LiBTOC with the corresponding borinic ester[14] in poor yield: 16% (entry 11). Using KBTOC again, the N-Boc aniline was isolated with a substantial increase of the chemical yield: 52% (entry 12).

In summary, the use of primary or secondary organoboranes with metallated t-butyl-N-tosyloxycarbamates provides an interesting route to N-Boc primary amines with moderate to good yields. The reaction is rapid. However, only one of the three alkyl groups on boron is utilized and we are exploring this reaction to improve its usefulness in synthesis.

Table: Reactions of Organoboranes with LiBTOC **2a** or KBTOC **2b**.

Entry	Borane[a]	TsN(M)Boc M	Conditions Temp (°C)	Time (h)	Product	Yield (%)[b]
1	n-Bu_3B	Li	-78, -10	1	n-BuNHBoc	81
2	n-Bu_3B	Li	-78, -35	1.25	n-BuNHBoc	20
3	n-Bu_3B	K	-78, -35	1.25	n-BuNHBoc	40
4	s-Bu_3B	Li	-78, -10	3	s-BuNHBoc	30
5	s-Bu_3B	K	-78, -50	1.75	s-BuNHBoc	65
6	cy-hexyl$_3$B	K	-78, -50	1.75	cy-hexylNHBoc	34
7	n-octyl$_3$B	K	-78, -50	1.75	n-octylNHBoc	36
8	B-(n-octyl)-9-BBN	Li	-78	1	HO⁓NHBoc	64
9	B-(n-octyl)-9-BBN	K	-78	0.5	HO⁓NHBoc	64
10	B-(norbornyl)-9-BBN	Li	-78	1.75	HO⁓NHBoc	58
11	PhB(Me)O$(CH_2)_3$OAc	Li	-78	7	PhNHBoc	16
12	PhB(Me)O$(CH_2)_3$OAc	K	-78	7	PhNHBoc	52

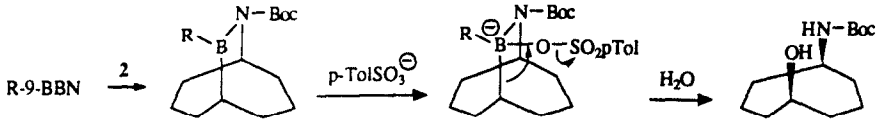
a) All reactions were run with an equimolar ratio of borane and aminating reagent, except entries 2 and 3: a 1/3 molar ratio of borane and aminating reagent was used.
b) Isolated yields are based on generation of 1 mol. of N-Boc protected amine from 1 mol. of aminating reagent.

General procedure: To a stirred solution of aminating reagent 1 (0.862g ; 3.0 mmol) in THF (8 ml) at -78°C, was added dropwise a 2.5M solution of n-BuLi in hexane (1.24 ml ; 3.1 mmol). After 20 min at this temperature, a 1M solution of n-Bu3B in THF (3 ml ; 3.0 mmol) was added . The mixture was stirred 10 minutes at -78°C, allowed to warm up to -10°C during 1 hour and quenched by addition of an aqueous solution of ammonium chloride. The organic layer was separated and the aqueous layer was extracted with ether. The organic layers were combined, dried on magnesium sulphate, filtered and evaporated in vacuo. After flash chromatography, 0.421g (81%) of carbamate 3 were obtained.

Acknowledgments : We thank the Centre National de la Recherche Scientifique (C.N.R.S.) for financial support to J. H. during his stay and for a grant to L.B.

REFERENCES AND NOTES :

1. Present address: Pharmaceutical and Biochemical Research Institute, 17 Kourimska, CS-13060 Prague Czechoslovakia.
2. Genêt, J.P.; Maillart, S.; Greck, C.; Piveteau, E. *Tetrahedron Lett.* **1991**, *32*, 2359.
3. Barton, D.R.H., Ollis, W.D. *Comprehensive Organic Chemistry*; Pergamon Press: Oxford. 1979; Vol. 3; pp. 687 ; Pelter, A.; Smith, K.; Brown, H.C. *Borane Reagents*; Academic Press: London. 1988 ; Suzuki, A.; Dhillon, R.S. *Topics Current Chem.* **1986**, *130*, 23.
4. Brown, H.C.; Heydkamp, W.R.; Breuer, E.; Murphy, W.S. *J. Am. Chem. Soc.* **1964**, *86*, 3565 ; Kabalka, G.W.; Sastry, K.A.R.; Mc Collum, G.W.; Yoshioka, H. *J; Org. Chem.* **1981**, *46*, 4296 ; Kabalka, G.W.; Sastry, K.A.R.; Mc Collum, G.W.; Lane, C.A. *J. Chem. Soc. Chem. Commun.* **1982**, 62.
5. Rathke, M.W.; Inoue, N.; Varma, K.R.; Brown, H.C. *J. Am. Chem. Soc.* **1966**, *88*, 2870 ; Verbit, L.; Heffron, P.J. *J. Org. Chem.* **1967**, *32*, 3199 ; Tamura, Y.; Minamikawa, J.; Fujii, S.; Ikeda, M. *Synthesis* **1974**, 196 ; Bullen, N.P.; Cluhem, K;S.; Thorpe, F.G. *J. Organomet. Chem.* **1980**, *195*, 147.
6. Kabalka, G.W.; Henderson, D.A.; Varma, R.S. *Organometallics* **1987**, *6*, 1369.
7. Suzuki, A.; Sono, S.; Itoh, M.; Brown, H.C.; Midland, M.M. *J. Am. Chem. Soc.* **1971**, *93*, 4329; Brown, H.C.; Midland, M.M.; Levy, A.B. *J. Am. Chem. Soc.* **1972**, *94*, 2114 ; Brown, H.C.; Midland, M.M.; Levy, A.B. *J. Am. Chem. Soc.* **1973**, *95*, 2394; Carboni, B.; Vaultier, M.; Carrié, R. *Tetrahedron Lett.* **1988**, *29*, 1279.
8. Kabalka, G.W.; Wang, Z. *Organometallics* **1989**, *8*, 1093.
9. Mueller, R.H. *Tetrahedron Lett.* **1976**, 2925.
10. Jigajinni, V.B.; Pelter, A.; Smith, K. *Tetrahedron Lett.* **1978**, 181.
11. Greene, T.W.; Wuts, P.G.M. *Protective Groups in Organic Synthesis*; Wiley Interscience: New York. 1991; 2nd Ed.; pp.379.
12. Brown, H.C.; Rogic, M.M.; Nambu, H.; Rathke, M.W. *J. Am. Chem. Soc.* **1969**, *91*, 2147.
13. Brown and coworkers published similar migration in the reaction of organic azides with alkyl derivatives of 9-BBN, but an oxidative step was necessary to produce the aminoalcohol. See: Brown, H.C.; Midland, M.M.; Levy, A.B.; Suzuki, A.; Sono, S.; Itoh, M. *Tetrahedron* **1987**, *43*, 4079.
    In our case, this in situ oxidation of carbon-boron bond may be due to the presence of p-toluene sulfonate which is able to produce the ate complexe followed by classical aniotropic rearrangement and hydrolysis into N-Boc 5-aminocyclooctanol.



14. Brown, H.C.; Kim, K.W.; Cole, T.E. Singaram, B. *J. Am. Chem. Soc.* **1986**, *108*, 6761.

(Received in France 17 February 1992)