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A New Selective Cleavage of *N*,*N*-Dicarbamoyl-Protected Amines Using Lithium Bromide

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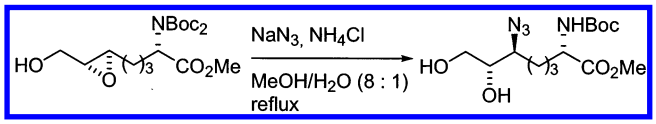
A mild and new procedure for the selective cleavage of an alkoxycarbonyl group (Boc, CBz) in *N*,*N*-dicarbamoyl-protected amino compounds is described. The method is based on the use of lithium bromide in acetonitrile and is compatible with a large range of other functionalities present in the substrates. Compared with other reported methodologies, the procedure is particularly useful for the Cbz-selective cleavage in *N*,*N*-Ts,Cbz-diprotected amines. A rationalization of the selectivity supported by ab initio calculations is also presented.

The *tert*-butoxycarbonyl (Boc) and the benzyloxycarbonyl (Cbz) groups are extensively used in synthesis for amino protection including with amino acids.[1] In the literature many methods can be found for the removal of such groups in N-protected amines,[1] but only a few can be found to selectively cleave an alkoxycarbonyl group in *N*,*N*-dicarbamoyl-protected amines.[2] We found that the selective reduction of *N*,*N*-di-Boc-α-amino diesters derived from natural α-amino acids (glutamic or aspartic acids) or the homologated compounds produced ω-semialdehydes in very good yields and with complete integrity at the stereocenter.[3] Although the introduction of the second *N*-Boc group is crucial for such selectivity, several changes in the reactivity of the vicinal ester were also produced. For instance, the alkaline hydrolysis of *N*,*N*-di-Boc-α-amino esters produced partial racemization,[3b] despite the occurrence of hydrolysis of *N*-Boc-α-amino esters without any epimerization.[4]

During our work directed to the synthesis of α-diamino acid derivatives, we found that treatment of the *N*,*N*-di-Boc-α-amino epoxy ester in Scheme 1 with NaN_3 produced the cleavage of a *N*-Boc group.[5] This promising result prompted us to apply these conditions to a series of *N*,*N*-di-Boc-α-amino-protected derivatives. However, in most cases the reaction proceeds sluggishly and with low conversions. As an alternative, we now report on a new and mild method to selectively deprotect an *N*-Boc group in *N*,*N*-di-Boc-protected amines and α-amino acids, in this case taking place without any detectable racemization. The use of lithium bromide in acetonitrile proved to be an excellent combination to achieve selectivity, mildness, and generality in the desired conversion.

SCHEME 1



To explore the scope and limitations of our method, we investigated a series of *N*,*N*-di-Boc-α-amino-protected compounds with different protecting groups and functionalities (Table 1). We found the procedure to be highly general, yielding the corresponding *N*-Boc amino derivatives. Particularly interesting is the possibility of applying the methodology to α-amino acids having an ω-aldehyde in their structure (entry 3).[3] When a hydroxy group is present in the substrates, the behavior depends on the position of such a group relative to the *N*,*N*-di-Boc amino derivatives. Thus, when that functionality was far from the reacting position, almost no influence was detected (entry 5). However, when the hydroxy group was close to the nitrogen, a negative influence arose (entry 10). The possible chelating competition was demonstrated by use of the corresponding silyl-protected compound, in which case the selective *N*-Boc cleavage was performed straightforwardly.

Considering that the method works with the *N*,*N*-di-Boc moiety, we wondered if the methodology can be extended to other situations in which the nitrogen is doubly protected with an additional protecting group besides the *N*-Boc protection (Table 2). We found that

(1) Greene, T. W.; Wuts, P. G. M. In *Protective Groups in Organic Synthesis*; Wiley: New York, 1999; pp 518−525, and references therein.

(2) (a) Van Benthem, R. A. T. M.; Hiemstra, H.; Speckamp, W. N. *J. Org. Chem.* **1992**, *57*, 6083−6085. (b) Stafford, J. A.; Brackeen, M. F.; Karanewsky, D. S.; Valvano, N. L. *Tetrahedron Lett.* **1993**, *34*, 7873−7876. (c) Burkhart, F.; Hoffmann, M.; Kessler, H. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 1191−1193. After the experimental work presented herein was completed two new methods appeared in the literature: (d) Yadav, J. S.; Subba Reddy, B. V.; Reddy, K. S. *Synlett* **2002**, 468−470. (e) Yadav, J. S.; Reddy, B. V. S.; Srinivasa-Reddy, K.; Bhaskar-Reddy, K. *Tetrahedron Lett.* **2002**, *43*, 1549−1551.

(3) (a) Padrón, J. M.; Kokotos, G.; Martín, T.; Markidis, T.; Gibbons, W.; Martín, V. S. *Tetrahedron: Asymmetry* **1998**, *9*, 3381−3394. (b) Kokotos, G.; Padrón, J. M.; Martín, T.; Gibbons, W.; Martín, V. S. *J. Org. Chem.* **1998**, *63*, 3741−3744. (c) Sutherland, A.; Caplan, J. F.; Vederas, J. C. *J. Chem. Soc., Chem. Commun.* **1999**, 555−556. (d) Sutherland, A.; Vederas, J. C. *J. Chem. Soc., Chem. Commun.* **1999**, 1739−1740.

(4) Bodanszky, M.; Bodanszky, A. In *The Practice of Peptide Synthesis*; Springer-Verlag: Berlin, 1984, 177.

(5) Hernández, N.; Martín, V. S. *J. Org. Chem.* **2001**, *66*, 4934−4938.

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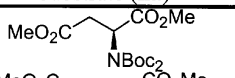
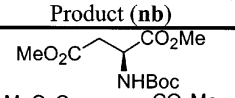
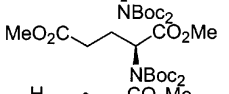
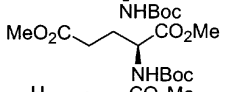
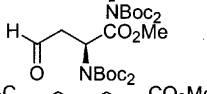
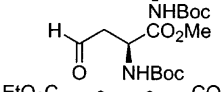
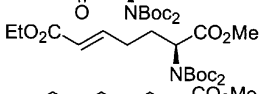
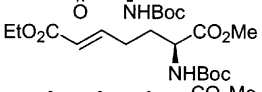
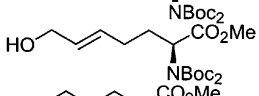
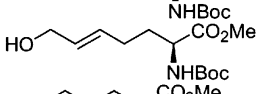
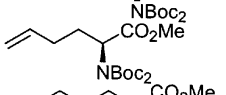
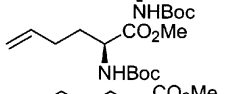
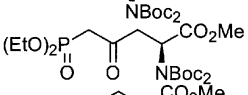
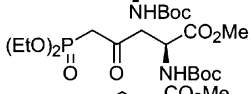
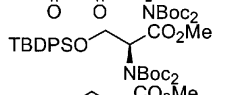
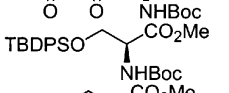
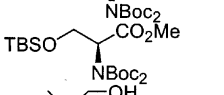
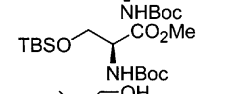
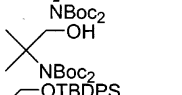
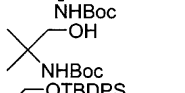
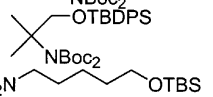
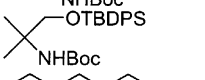
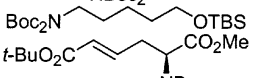
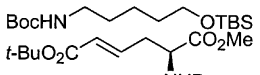
TABLE 1. Selective Cleavage of *N*,*N*-Di-Boc-Protected Amines and α-Amino Acids Using LiBr in CH_3CN

Entry (n)	Substrate (**na**)	Time (h)	Product (**nb**)	Yield (%)
1		10		97
2		12		98
3[3]		10		94
4[5]		10		90
5[5]		7		95
6		10		85
7		12		89
8[6]		12		97
9[6]		12		95
10		48		50
11		12		97
12		10		94
13		10		92

when another carbamoyl-based protecting group, such as Cbz, is used, the cleavage of the N,C-bond is randomly performed, yielding almost equivalent amounts of both *N*-monoprotected amino derivatives (entry 1). However, when the additional protecting group is a carboxylic acyl derivative (e.g. acetate) the cleavage of the *N*-Boc group was not performed (entry 2). In both cases, however, the use of magnesium perchlorate produced the selective cleavage of the *N*-Boc group.[2b] The procedure worked very well when the other ester functionality is a sulfonate, in which case the *N*-carbamoyl cleavage was performed in excellent yields (entries 3 and 4).[7] Interestingly, under the magnesium method, the *N*-Cbz,Ts-amino acid remained unaffected (entry 3). Finally, the procedure is respectful of *N*-Boc-protected secondary and *N*-Cbz-protected primary amines (entries 5 and 6). Although our comparative experimental work has been performed between magnesium and lithium salts, the newly described procedures using cerium(III)−NaI,[2d] Zn−MeOH,[2e] and In−MeOH[2e] seems to give results closer to those using magnesium salts than the result obtains by our method.

The mechanism proposed by Stafford et al.[2b] for the cleavage of *N*-Boc amines catalyzed by $Mg(ClO_4)_2$ based on the formation of a six-membered chelate seems roughly applicable to our method. However, in our previous study, we were able to show that the lithium and magnesium salts behave differently. It should be remembered that LiBr allows the cleavage of both benzyl and *tert*-butyl carbamoyl derivatives, but the magnesium system only cleaves the latter type. Moreover, we found that lithium perchlorate is not active as a catalyst, and when using *N*-Cbz derivatives, we have been able to detect benzyl bromide as a reaction product. To explain these experimental observations, we believe that the anion is very important,[8] but differences are also probably related to structural changes produced in the chelation with the metal.

To find a possible explanation of such differences and the possible role of externals anions, we performed some calculations over the structures of *tert*-butyl *N*-methyl-*N*-acetylcarbamate associated with the Li^+ and Mg^{2+} cations. We chose this molecule considering both structural simplicity and as an extreme in the comparative action of both metals, since only the magnesium cleavage operated.[9] The B3LYP/6-31G*[10] calculations suggested that the structure **A** (Scheme 2), in which both carbonyls

(6) (a) Garner, P. *Tetrahedron Lett.* **1984**, *25*, 5855−5858. (b) Garner, P.; Ramakanth, S. *J. Org. Chem.* **1986**, *51*, 2609−2612. (c) Kozikowski, A. P.; Nieduzak, R. T.; Konoike, T.; Springer, J. P. *J. Am. Chem. Soc.* **1987**, *109*, 5167−5175. (d) Garner, P.; Park, J. M. *J. Org. Chem.* **1987**, *52*, 2361−2364. (e) Garner, P.; Park, J. M., Malecki, E. J. *J. Org. Chem.* **1988**, *53*, 4395−4398. (f) McKillop, A.; Taylor, R. J. K.; Watson, R. J.; Lewis, N. *Synthesis* **1994**, *8*, 31−33.

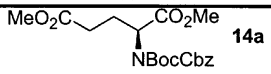
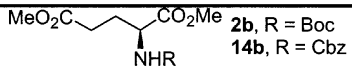
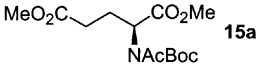
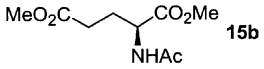
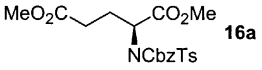
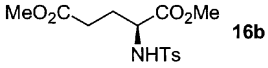
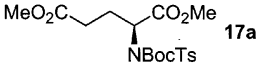
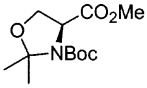
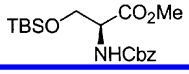
(7) For the use and removal of *N*-arylsulfonyl protecting groups, see: (a) Roemmele, R. C.; Rappoport, H. *J. Org. Chem.* **1988**, *53*, 2367−2371. (b) Ferraris, D.; Young, B.; Cox, C.; Dudding, T.; Drury, W. J.; Ryzhkov, L.; Taggi, A. E.; Lectka, T. *J. Am. Chem. Soc.* **2002**, *124*, 67−77.

(8) External iodide is also necessary to achieve complete conversion when the cerium(III) method is used. See ref 2d.

(9) Ramírez, M. A.; Hernández, J. N.; Martín, V. S. Manuscript in preparation.

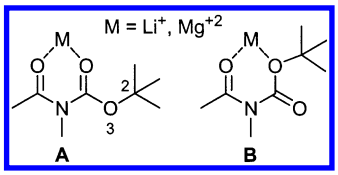
(10) B3LYP: (a) Lee, C.; Yang, W.; Parr, R. G. *Phys. Rev. B* **1988**, *37*, 785−789. (b) Becke, A. D. *J. Chem. Phys.* **1993**, *98*, 5648−5652. 6-31G*: (c) Hehre, W. J.; Radom, L.; Schleyer, P. V. R.; Pople, J. A. In *Ab Initio Molecular Orbital Theory*; Wiley-Interscience: New York, 1986.

TABLE 2. Comparative Study of the Cleavage of *N*-Carbamoyl-Protected α-Amino Acids with an Additional Protection at the Nitrogen Using Lithium and Magnesium Salts

Entry	Substrate	Conditions[a]	Product	Yield (%)
1	 **14a**	A (10 h)	 **2b**, R = Boc **14b**, R = Cbz	97 (1 : 1)
		B (3 h)	**14b**, R = Cbz	85
2	 **15a**	A (48 h)	--	Fully recovered
		B (10 h)	 **15b**	81
3	 **16a**	A (12 h)	 **16b**	95
		B (10 h)	--	Fully recovered
4	 **17a**	A (12 h)	**16b**	95
		B (12 h)	"	90
5[6]		A (48 h)	--	Fully recovered
		B (5 h)	--	"
6[6]		A (12 h)	--	"

[a] Conditions: (A) LiBr, CH_3CN, 65 °C; (B) $Mg(ClO_4)_2$, CH_3CN, room temperature.

SCHEME 2



are chelated with the cation, is clearly more stable (10.4 and 13.6 kcal/mol, for lithium and magnesium, respectively) than **B**.[11]

The most prominent facts of our analysis involve the *tert*-butyl oxygen (C2−O3) bond. A detailed analysis of the electronic density[12] using the Laplacian of the charge density, $\nabla^2\rho$,[13] shows a neat difference when considering the nature of that bond in the structures of the Li^+ and Mg^{2+} complex (Figure 1). The lithium shows a weak covalent bond (panel a), but this interaction becomes roughly ionic in the case of the magnesium complex (panel b). This result is coincident with the experimental observations that indicate a greater decarboxylative facility for magnesium salt-assisted breaking, provided that the break of the C2−O3 bond is assumed to be the rate-controlling process (Scheme 3).

Conclusions

A new and mild procedure to selectively cleave a carbamoyl group in *N*,*N*-dicarbamoyl-protected amines is reported. The procedure is very mild and simple to use, being compatible with a wide range of additional protecting groups in the substrate. The method is particularly useful for the Cbz-selective cleavage in *N*,*N*-Ts,Cbz-diprotected amines. In addition, we have performed ab initio calculations over a simplified system showing that the Mg(II) chelation produces an almost neat cleavage between the *tert*-butyl group and the oxygen of the oxycarbonyl group of the carbamoyl group to be decarboxylated. The lithium, however, produces just a weak-

(11) The 6-31G* Gaussian basis set and the hybrid functional B3LYP, to include electronic correlation, was used with the Gaussian 98W program: Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Zakrzewski, V. G.; Montgomery, J. A., Jr.; Stratmann, R. E.; Burant, J. C.; Dapprich, S.; Millam, J. M.; Daniels, A. D.; Kudin, K. N.; Strain, M. C.; Farkas, O.; Tomasi, J.; Barone, V.; Cossi, M.; Cammi, R.; Mennucci, B.; Pomelli, C.; Adamo, C.; Clifford, S.; Ochterski, J.; Petersson, G. A.; Ayala, P. Y.; Cui, Q.; Morokuma, K.; Malick, D. K.; Rabuck, A. D.; Raghavachari, K.; Foresman, J. B.; Cioslowski, J.; Ortiz, J. V.; Stefanov, B. B.; Liu, G.; Liashenko, A.; Piskorz, P.; Komaromi, I.; Gomperts, R.; Martin, R. L.; Fox, D. J.; Keith, T.; Al-Laham, M. A.; Peng, C. Y.; Nanayakkara, A.; Gonzalez, C.; Challacombe, M.; Gill, P. M. W.; Johnson, B. G.; Chen, W.; Wong, M. W.; Andres, J. L.; Head-Gordon, M.; Replogle, E. S.; Pople, J. A. *Gaussian 98, revision A.6;* Gaussian, Inc.: Pittsburgh, PA, 1998.

(12) The method used was that developed by Bader et al. in their theory "Atom in Molecules (AIM)": (a) Bader, R. F. W. In *Atoms in Molecules: A Quantum Theory; The International Series of Monographs of Chemistry*; Halpen, J., Green, M. L. H., Eds.; Clarendon Press: Oxford, 1990; pp 1−438. (b) Bader, R. F. W. *Chem Rev.* **1991**, *91*, 893−928. (c) Popelier, P. In *Atoms in Molecules: An Introduction*; Prentice Hall: Harlow, 2000; pp 1−164. (d) Gilespie, R. J.; Popelier, P. L. A. In *Chemical Bonding and Molecular Geometry: From Lewis to Electron Densities*; Oxford University Press: Oxford, 2001; pp 134−268. The program used was AIM2000, Version 1.0, designed by Biegler-König, F. and programed by Biegler-König, F.; Bayles, D.; Schönbohm J., with chemical advice by Bader, R. F. W.

(13) The Laplacian of the electron density shows where the electron density is locally concentrated or depleted as assumed.

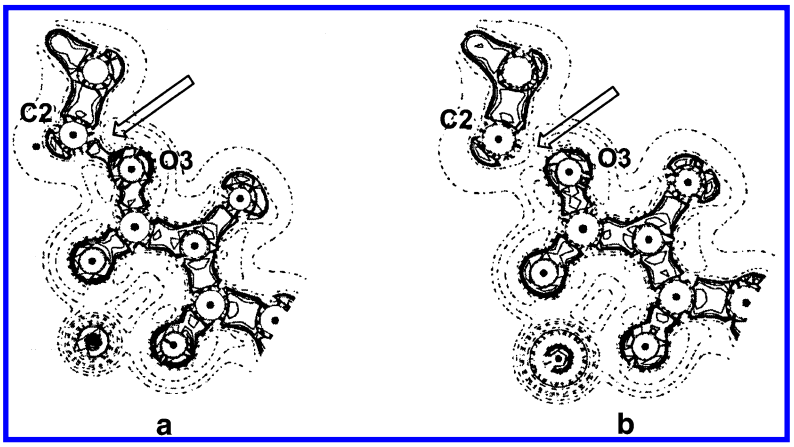
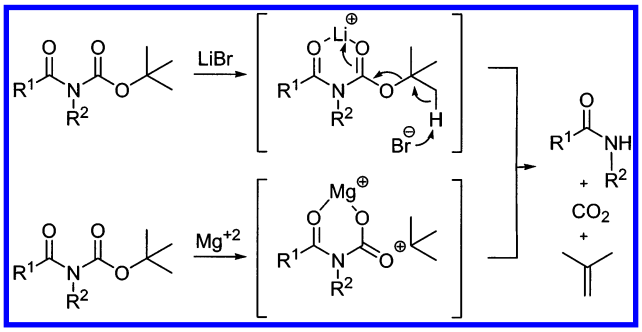


FIGURE 1. Contour plots of the Laplacian of the electron density, $\nabla^2\rho$, for chelated structures: (a) Li^+ and (b) Mg^{2+}. $\nabla^2\rho < 0$ (continuous lines) represents covalent interactions; $\nabla^2\rho > 0$ (dotted lines) shows noncovalent interactions.

SCHEME 3



ness of such a bond, providing a reasonable indication of the necessary presence of external anions to produce the selective cleavage.

Experimental Section

Materials and Methods. NMR spectra were measured at 400 or 300 MHz (^{1}H) and 75 MHz (^{13}C), and chemical shifts are reported relative to internal Me_4Si ($\delta = 0$). Optical rotations were determined for solutions in chloroform or carbon tetrachloride. Melting points are reported in degrees Celsius and are uncorrected. Column chromatography was performed on Merck silica gel, 60 Å and 400−500 mesh. Compounds were visualized by use of UV light and/or 2.5% phosphomolybdic acid in ethanol and/or ninhydrin both in ethanol stain with heating. All solvents were purified by standard techniques.[14] Reactions requiring anhydrous conditions were performed under argon. Anhydrous magnesium sulfate was used for drying solutions.

(14) Armarego, W. L. F.; Perrin, D. D. In *Purification of Laboratory Chemicals*, 4th ed; Butterworth-Heinemann: Oxford, 1996.

General Procedure for the Selective Cleavage of Dicarbamoyl-Protected Amines Using Lithium Bromide. Preparation of Dimethyl (2*S*)-2-[(*tert*-Butoxy)carbonylamino]butane-1,4-dioate (1b). To a stirred solution of dimethyl (2*S*)-2-[bis(*tert*-butoxycarbonyl)amino]-butane-1,4-dioate **1a**[3] (223.6 mg, 0.62 mmol) in acetonitrile (7 mL) placed into a round-bottomed flask (25 mL) equipped with a stopper was added commercially available lithium bromide (163 g, 1.9 mmol). The mixture was warmed with stirring to 65 °C for 10 h, at which time the reaction was completed. The reaction mixture was concentrated and purified by silica gel chromatography to yield **1b** (157 mg, 97% yield) as a white solid: mp 66−65 °C; $[\alpha]^{25}_D = +28.02$ (*c* 5, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 1.36 (s, 9H), 2.77 (dd, J = 4.75 Hz, 16.9 Hz, 1H), 2.92 (dd, J = 4.1 Hz, 16.95 Hz, 1H), 3.61 (s, 3H), 3.67 (s, 3H), 4.48 (br, 1H), 5.47 (br, 1H); ^{13}C NMR ($CDCl_3$) δ 28.2 (q), 36.5 (t), 49.9 (d), 51.8 (q), 52.5 (q), 79.9 (s), 155.3 (s), 171.4 (s), 171.2 (s); IR ($CHCl_3$) (cm^{-1}) 3374, 2979, 1742, 1438, 1166, 1046; HRMS calcd for $C_{11}H_{19}NO_6$ $(M - 1)^+$ 261.1212, found 261.1225; MS *m*/z 284 $(M + Na)^+$, 262 $(M + 1)^+$, 206 $(M - t\text{-Bu})^+$, 162 $(M - Boc)^+$. Anal. Calcd for $C_{11}H_{19}NO_6$: C, 50.57; H, 7.33; N 5.36. Found: C, 50.54; H, 7.36; N, 5.36.

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Supporting Information Available: ^{1}H and ^{13}C NMR spectra and preparation for the new compounds and Cartesian coordinates and total energy for the full-optimized B3LYP/6-31G(d) structures (GAUSSIAN 98). This information is available free of charge via the Internet at http://pubs.acs.org.

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