Available online at www.sciencedirect.com
ScienceDirect
Tetrahedron Letters
Tetrahedron Letters 48 (2007) 17–20

Cleavage of alkoxycarbonyl protecting groups from carbamates by *t*-BuNH$_2$

Oscar R. Suárez-Castillo,* Luis Alberto Montiel-Ortega, Myriam Meléndez-Rodríguez and Maricruz Sánchez-Zavala

Centro de Investigaciones Químicas, Universidad Autónoma del Estado de Hidalgo, Apartado 1-622, Pachuca, Hidalgo 42001, Mexico

Received 3 October 2006; revised 1 November 2006; accepted 2 November 2006
Available online 21 November 2006

Abstract—An efficient, simple protocol for the selective cleavage of a variety of *N*-alkoxycarbonyl protecting groups by *t*-BuNH$_2$/MeOH is described. The scope of the procedure was explored for a series of indole, aniline and pyrrolidine carbamate derivatives containing other potentially reactive functional groups affording a clean cleavage of the carbamate group.

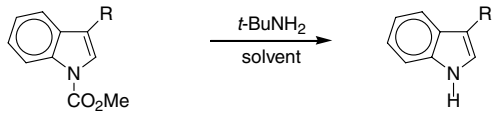
Protection and deprotection strategies of a functional group are extensively used in modern organic synthesis. Among the N-protecting groups the carbamate group is commonly used throughout organic synthesis for the protection of aliphatic and aromatic amines and amides.[1] Many simple carbamates have been used as protective groups. In particular, the *tert*-butoxy- and benzyloxy-carbonyl groups (Boc, Cbz) and, to a lesser extent, the methoxy- and ethoxy-carbonyl groups (CO_2Me, CO_2Et) are widely used for the synthesis of nitrogen-containing compounds.[1a,2] The synthetic utility of the Boc and Cbz groups is due to the easy and efficient protocols for their introduction and removal. It is known that *N*-carbamate protecting groups of amines and amides can be removed either under homogeneous or heterogeneous conditions;[1a,3] strongly acidic, basic or even neutral conditions. In addition, a recent free radical chemoselective cleavage of *N*-Cbz protected compounds induced by *n*-Bu_3SnH has been reported.[4] Mildly basic protocols using ammonia and simple amines like NH_2CH_2OH, Et_2NH, Et_3N, $(i\text{-}Pr)_2NH$, DBN, DBU, piperidine have been used in peptide synthesis to perform cleavage of the 9-florenylmethyloxycarbonyl (Fmoc) protecting group by β-elimination.[5] In addition, $PrNH_2$ has been used to deprotect 2-(trifluoromethyl)-6-chromonylmethyl (Tcroc) carbamate group[6] and the Cs_2CO_3–imidazole system for the removal of the Boc-group from amino compounds.[7] In this work, we report an experimentally simple procedure using *t*-BuNH$_2$/MeOH for the removal of methyl, ethyl, *i*-propyl, *t*-butyl and benzyl carbamate groups in indole and aniline derivatives. We observed that the reactivity of these alkoxycarbonyl groups with *t*-BuNH$_2$ is a function of the size of the alkyl group and a plausible mechanism for this deprotection is outlined.

Our experiments were first conducted with the ester indole *N*-carbamate derivative **1a**.[8] Thus, the treatment of **1a** with 10 equiv of *t*-BuNH$_2$ in MeOH at room temperature during 28 days resulted in the selective N-deprotection of **1a** to give **2a** in a quantitative yield (Table 1, entry 1). It is noteworthy to mention that under this reaction conditions the ester functionality was unaffected. Attempts to use equimolar quantities of *t*-BuNH$_2$ were unsuccessful and only traces of compound **2a** were isolated from the reaction mixture. Furthermore, a control experiment in MeOH without the amine gave no deprotection of **1a** at all. These results indicate that *t*-BuNH$_2$ is essential for deprotection and its concentration determines the rate of reaction. When **1a** was treated with 10 equiv of the amine in MeOH under reflux, the reaction was completed after 58 h (entry 2). Further optimization led us to find that the reaction was best carried out when 30 equiv of *t*-BuNH$_2$ were used. Accordingly, the clean conversion of **1a** into **2a** occurred efficiently in 4 h with 99% yield (entry 3). The use of other solvents such as DMF, toluene, THF, $CHCl_3$, CH_2Cl_2 and MeCN was explored (entries 4–9); but deprotection of **1a** to give **2a** failed in most of them with

Keywords: Selective cleavage; Carbamate deprotection; *tert*-Butylamine; Indole derivatives.
* Corresponding author. Tel.: +52 771 71 72000x2206; fax: +52 771 71 72000x6502; e-mail: osuarez@uaeh.edu.mx

0040-4039/$ - see front matter © 2006 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2006.11.024

Table 1.



1a-f **2a-f**

Entry[a]	Compound	Equiv of *t*-$BuNH_2$	Time	Solvent	Product	Yield (%)
1	**1a**: R = CH_2CO_2Me	10	28 days	MeOH	**2a**	Quant
2	**1a**	10	58 h	MeOH	**2a**	Quant
3	**1a**	30	4 h	MeOH	**2a**	99
4	**1a**	30	24 h	DMF	**2a**	90
5	**1a**	30	24 h	Toluene	—	—
6	**1a**	30	24 h	THF	—	—
7	**1a**	30	24 h	$CHCl_3$	—	—
8	**1a**	30	24 h	CH_2Cl_2	—	—
9	**1a**	30	24 h	MeCN	—	—
10	**1b**: R = $CH(CO_2Me)_2$	30	2 h	MeOH	**2b**	Quant
11	**1c**: R = CO_2Me	30	0.5 h	MeOH	**2c**	Quant
12	**1d**: R = $COCO_2Me$	30	4 h	MeOH	**2d**	99
13	**1e**: R = CH_2CN	30	0.5 h	MeOH	**2e**	Quant
14	**1f**: R = $CH_2CONHMe$	30	1.5 h	MeOH	**2f**	Quant

[a] Reactions were carried out under reflux except for entry 1, which was carried out at rt.

the exception of DMF, which allowed the isolation of **2a** in 90% yield after 24 h of reaction (entry 4), showing that MeOH is critical for the deprotection reaction.

Having successfully established a protocol for the selective indole carbamate deprotection of **1a** we set out to examine this process on indole derivatives **1b–f** containing other base-sensitive groups like ester (entries 1, 10, 11 and 12), keto (entry 12) and cyano (entry 13). Among the different carbonyl groups present in compounds **1b–f** only the carbamate group reacted affording, respectively, products **2b–f** in high yields (entries 10–14) and no traces of the corresponding *tert*-butylamine derivatives were identified. The X-ray structure of compound **2b** (Fig. 1) evidences the deprotection at the N-atom in **1b**[9] and the presence of the methyl malonate groups at C3. It is worthwhile to note that as soon as TLC analysis shows the disappearance of the starting material, the *t*-$BuNH_2$/MeOH mixture can be removed from the reaction mixture just by evaporation under vacuum or by fractional distillation to recover *t*-$BuNH_2$. The procedure gave the desired N-deprotected products in excellent yields and purity. Neither column chromatography nor aqueous work-up was necessary to afford pure deprotected products **2a–f**.

The scope of this reaction was explored with indole derivatives **3a–d**[10] containing different alkylcarbamates (Table 2). Thus, when these compounds were treated with 30 equiv of *t*-$BuNH_2$ in MeOH under reflux, free indole **4** was obtained in excellent yields. The results in this table reveal that cleavage rate is a function of the size of the alkyl group. Methyl, ethyl and benzyl carbamates resulted to be notably more reactive than did Boc-carbamate. Even more, *N*-Boc derivative **3c** reacted only when the mixture was heated to reflux under pressure in a sealed tube for a longer reaction time (entry 4). Since it is known that the *N*-Boc protecting group is cleaved under thermal conditions giving rise to CO_2 and isobutylene,[11] to asses the role of the amine, compound **3c** was refluxed under pressure in a sealed tube in the absence of *t*-$BuNH_2$. After 14 h of reaction, a 3:1 mixture of **4**:**3c** was observed in the ^{1}H NMR of the reaction crude. This result indicates that in the case of **3c** thermal decomposition of the *N*-Boc group occurred, but it is slightly accelerated by *t*-$BuNH_2$ by a β-elimination process.[3h,7]

On the other hand, the effect of an electron-withdrawing or an electron-donating group was evaluated with aniline derivatives **5a–f**, which were also treated with *t*-$BuNH_2$/MeOH (Table 3). Compounds **5a–e** with the electron-withdrawing group NO_2 reacted to a different extent to give **6a**, whereas aniline **5f** with the electron-donating group OMe remained unchanged. In addition, as can be seen in Table 3, the steric effect in **5a–e** influ-

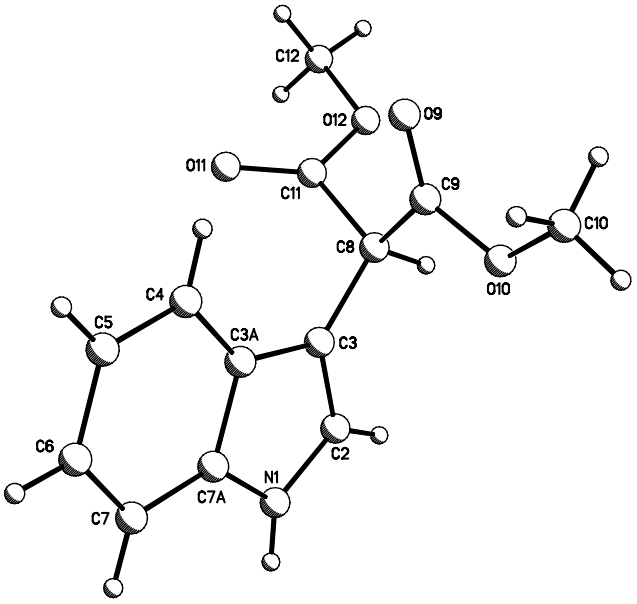
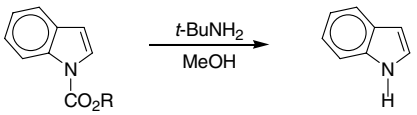


Figure 1. X-ray structure of **2b**.

Table 2.



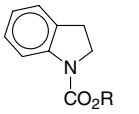
3a-d **4**

Entry[a]	Substrate	Time (h)	Yield (%)
1	**3a**: R = Me	5	98
2	**3b**: R = Et	10	98
3	**3c**: R = *t*-Bu	30	Traces
4		14[b]	97
5	**3d**: R = Bn	30	98

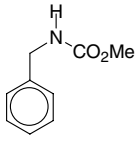
[a] Reactions were carried out under reflux.
[b] Under pressure in a sealed tube.

enced the reaction rate in the order Me > Et ≈ *i*-Pr > Bn > *t*-Bu. These results, together with those obtained by the treatment of **3a**–**d** (Table 2), clearly indicate that the carbamate undergoes cleavage with *t*-$BuNH_2$/MeOH by a direct nucleophilic attack at the carbonyl of the carbamate group. Further exchange of N-compound by *t*-$BuNH_2$ leads to deprotection.

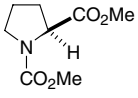
Contrary to the case of previous indole and aniline *N*-carbamate derivatives, carbamate groups in compounds



7a: R = Me
7b: R = Et
7c: R = *i*-Pr
7d: R = *t*-Bu
7e: R = Bn

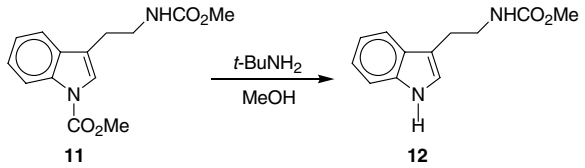


8



9

10



11 **12**

Scheme 1.

7a–**e**, **8** and **9**, attached to the nitrogen atoms of primary or secondary amines either aromatic or aliphatic were left unaffected under the above protocol. Interestingly, compound **10** was easily deprotected in 3 h in a quantitative yield. The observed selectivity when a mixture of **3a** and **8** gave deprotection of only **3a**, and the reaction of **11** gave quantitatively product **12**[12] (Scheme 1), points to the importance of charge delocalization in the leaving N-compound.

In summary, we have demonstrated the use of a simple and efficient method for the removal of carbamate protecting groups including methyl, ethyl, *i*-propyl, *t*-butyl and benzyl from indoles and some anilines bearing an electron-withdrawing group.[13] Different base-sensitive groups like esters, aldehydes and nitriles remained unchanged under this protocol. Except for **6a**, these reactions proceed without need for an aqueous work-up or column chromatography for the removal of reagents. The simplicity of this reaction, low cost of the reagents and mild nature of *t*-$BuNH_2$ in comparison with other methods, enhance the attractiveness of the protocol described here.

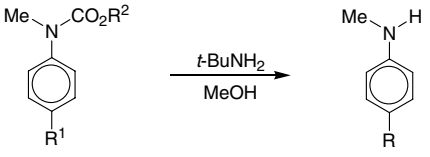
Acknowledgement

This research was supported in part by CONACYT (Mexico) Grant 2002-C01-40641/A-1 and UAEH-PAI 2006-28B.

References and notes

1. (a) Green, T. W.; Wuts, P. G. M. In *Protective Groups in Organic Synthesis*, 3rd ed.; Wiley: New York, 1999; (b)

Table 3.



5a-f **6a,b**

Entry[a]	Compound	Time (h)	Product	Yield (%)
1	**5a**: $R^1 = NO_2$, R^2 = Me	14	**6a**: R = NO_2	Quant
2	**5b**: $R^1 = NO_2$, R^2 = Et	56	**6a**	86
3	**5c**: $R^1 = NO_2$, R^2 = *i*-Pr	56	**6a**	75
4	**5d**: $R^1 = NO_2$, R^2 = Bn	24	**6a**	86
5	**5e**: $R^1 = NO_2$, R^2 = *t*-Bu	24[b]	**6a**	7[c]
6	**5f**: R^1 = OMe, R^2 = Me	60	**6b**: R = OMe	—

[a] Reactions were carried out under reflux.
[b] Under pressure in a sealed tube.
[c] Starting material was recovered.

Vatèle, J. M. *Tetrahedron* **2004**, *60*, 4251–4260; (c) Theodoridis, G. *Tetrahedron* **2000**, *56*, 2339–2358.
2. (a) Morales-Ríos, M. S.; Suárez-Castillo, O. R.; Joseph-Nathan, P. *Trends Heterocycl. Chem.* **1999**, *6*, 111–124, and references cited therein; (b) Shishido, K.; Shitara, E.; Komatsu, H.; Hiroya, K.; Fukumoto, K.; Kametani, T. *J. Org. Chem.* **1986**, *51*, 3007–3011; (c) Morales-Ríos, M. S.; Suárez-Castillo, O. R.; Joseph-Nathan, P. *Tetrahedron* **2002**, *58*, 1479–1484, and references cited therein.
3. (a) Apelqvist, T.; Wensbo, D. *Tetrahedron Lett.* **1996**, *37*, 1471–1472; (b) Siro, J. G.; Martín, J.; García-Navío, J. L.; Remuiñan, M. J.; Vaquero, J. J. *Synlett* **1998**, 147–148; (c) Bose, D. S.; Lakshminarayana, V. *Synthesis* **1999**, 66–68; (d) Shaikh, N. S.; Gajare, A. S.; Deshpande, V. H.; Bedekar, A. V. *Tetrahedron Lett.* **2000**, *41*, 385–387; (e) Trivedi, H. S.; Anson, M.; Steel, P. G.; Worley, J. *Synlett* **2001**, 1932–1934; (f) Yadav, J. S.; Subba Reddy, B. V.; Srinivasa Reddy, K. *Synlett* **2002**, 468–470; (g) Tom, N. J.; Simon, W. M.; Frost, H. N.; Ewing, M. *Tetrahedron Lett.* **2004**, *45*, 905–906; (h) Routier, S.; Saugé, L.; Ayerbe, N.; Coudert, G.; Mérour, J.-Y. *Tetrahedron Lett.* **2002**, *43*, 589–591; (i) Tsujimoto, T.; Murai, A. *Synlett* **2002**, 1283–1284; (j) Tsukamoto, H.; Suzuki, T.; Kondo, Y. *Synlett* **2003**, 1105–1108; (k) Bose, D. S.; Kumar, K. K.; Narsimha Reddy, A. V. *Synth. Commun.* **2003**, *33*, 445–450; (l) Ravindranath, N.; Ramesh, C.; Reddy, M. R.; Das, B. *Adv. Synth. Catal.* **2003**, *345*, 1207–1208; (m) Zhu, X.; Schmidt, R. R. *Synthesis* **2003**, 1262–1266.
4. Bennasar, M.-L.; Roca, T.; Padullés, A. *Org. Lett.* **2003**, *5*, 569–572.
5. (a) Carpino, L. A. *Acc. Chem. Res.* **1987**, *20*, 401–407; (b) Ramage, R.; Blake, A. J.; Florence, M. R.; Gray, T.; Raphy, G.; Roach, P. L. *Tetrahedron* **1991**, *47*, 8001–8024.
6. Kemp, D. S.; Hanson, G. *J. Org. Chem.* **1981**, *46*, 4971–4975.
7. Mohapatra, D. K.; Durugkar, K. A. *ARKIVOC* **2005**, *xiv*, 20–28.
8. Suárez-Castillo, O. R.; Sánchez-Zavala, M.; Meléndez-Rodríguez, M.; Castelán-Duarte, L. E.; Morales-Ríos, M. S.; Joseph-Nathan, P. *Tetrahedron* **2006**, *62*, 3040–3051.
9. Gillespie, R. J.; Porter, A. E. A. *J. C. S. Chem. Commun.* **1979**, 50–51.
10. (a) Jacquemard, U.; Bénéteau, V.; Lefoix, M.; Routier, S.; Mérour, J.-Y.; Coudert, G. *Tetrahedron* **2004**, *60*, 10039–10047; (b) Macor, J. E.; Cuff, A.; Cornelius, L. *Tetrahedron Lett.* **1999**, *40*, 2733–2736.
11. Dias, E. L.; Hettenbach, K. W.; Ende, D. J. *Org. Process Res. Dev.* **2005**, *9*, 39–44.
12. (a) Somei, M.; Fukui, Y.; Hasegawa, M.; Oshikiri, N.; Hayashi, T. *Heterocyles* **2000**, *53*, 1725–1736; (b) Ishikawa, H.; Takayama, H.; Aimi, N. *Tetrahedron Lett.* **2002**, *43*, 5637–5639.
13. In a typical experiment, *N*-carbamate derivative (0.52 mmol) was dissolved in MeOH (5 mL) and 30 equiv of *t*-$BuNH_2$ were added. The mixture was stirred under reflux for the appropriate time (Tables 1–3). After complete conversion, as indicated by TLC, the reaction mixture was cooled to room temperature and the volatile reagents were evaporated to afford pure N-deprotected products. Only in the case of compound **6a** purification by flash chromatography[14] using silica gel 60 (230–400 mesh) and hexane/EtOAc, 8:2 v/v was required.
The identity and the purity of the reaction products were established by their spectral (^{1}H NMR, IR and MS) data and by a direct comparison with authentic samples. Crystallographic data (excluding structure factors) for **2b** have been deposited with the Cambridge Crystallographic Data Centre as a Supplementary Publication Number CCDC 626181. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [fax: +44(0) 1223 336033 or e-mail: deposit@ccdc.cam.ac.uk].
14. Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923–2925.