ORGANIC LETTERS

2003
Vol. 5, No. 4
569−572

Chemoselective Radical Cleavage of Cbz-Protected Nitrogen Compounds

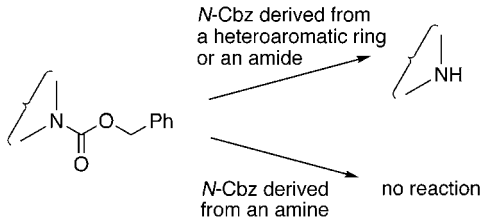
M.-Lluïsa Bennasar,* Tomàs Roca, and Ariadna Padullés

Laboratory of Organic Chemistry, Faculty of Pharmacy, University of Barcelona, Barcelona 08028, Spain

bennasar@farmacia.far.ub.es

Received December 19, 2002

ABSTRACT



Tributylstannyl radicals promote the deprotection of *N*-Cbz derivatives of amides and nitrogen-containing heteroaromatic rings. These radical conditions do not affect *N*-Cbz derivatives of basic amines.

Protection strategies using the Cbz (benzyloxycarbonyl) group have received considerable synthetic attention in the synthesis of nitrogen-containing compounds.[1] This carbamate moiety is easily introduced into the substrate following well established protocols, usually by reaction with Cbz-Cl or a related reagent. The possibility of removal under orthogonal[2] conditions, mainly dissolving metal reductions, catalytic hydrogenation, and acid treatment,[1,3] makes this protecting group particularly attractive. However, the majority of protection−deprotection schemes involve *N*-Cbz derivatives of amines rather than amides[4] or nitrogen heteroaromatic rings,[5] and as far as we know, the available deprotection methods do not discriminate among these different nitrogen functional groups.[6] In this Letter, we describe a novel set of conditions for the removal of the *N*-Cbz group, which are selective for originally nonbasic nitrogen atoms, both amide and those contained within a heteroaromatic ring (Figure 1).

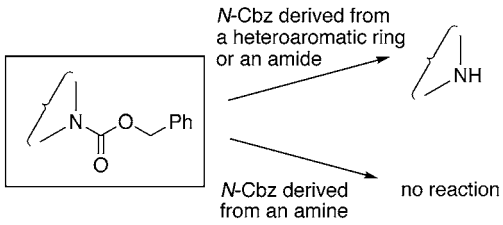


Figure 1.

During the course of our studies on the synthesis of 3-acylindole compounds through 3-indolylacyl radicals,[7] we became interested in the reaction of the Cbz-protected phenyl

(1) (a) Greene, T. W.; Wuts, P. G. M. *Protective Groups in Organic Synthesis*, 3rd ed.; Wiley: New York, 1999. (b) Jarowicki, K.; Kocienski, P. J. *J. Chem. Soc., Perkin Trans. 1* **1999**, 1589−1615. (c) Jarowicki, K.; Kocienski, P. J. *J. Chem. Soc., Perkin Trans. 1* **2000**, 2495−2527. (d) Jarowicki, K.; Kocienski, P. J. *J. Chem. Soc., Perkin Trans. 1* **2001**, 2109−2135.

(2) Kociensky, P. J. *Protecting Groups*; Thieme: Stuttgart, 1994; Chapter 1.

(3) For other procedures, see inter alia: (a) Sakaitani, M.; Ohfune, Y. *J. Org. Chem.* **1990**, *55*, 870−876. (b) Coleman, R. S.; Carpenter, A. J. *J. Org. Chem.* **1992**, *57*, 5813−5815.

(4) (a) Hungate. R. W.; Chen, J. L.; Starbuck, K. E.; Macaluso, S. A.; Rubino, R. S. *Tetrahedron Lett.* **1996**, *37*, 4113−4116. (b) Tsujimoto, T.; Murai, A. *Synlett* **2002**, 1283−1284.

(5) Weedon, A. C.; Zhang, B. *Synthesis* **1992**, 95−100.

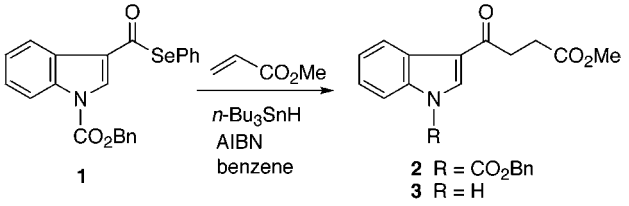
(6) For a recent example of a chemoselective removal of *N*-Cbz heteroaromatic rings, see: Lipshutz, B. H.; Pfeiffer, S. S.; Reed, A. B. *Org. Lett.* **2001**, *3*, 4145−4148.

(7) (a) Bennasar, M.-L.; Roca, T.; Griera, R.; Bassa, M.; Bosch, J. *J. Org. Chem.* **2002**, *67*, 6268−6271. See also: (b) Bennasar, M.-L.; Roca, T.; Griera, R.; Bosch, J. *Org. Lett.* **2001**, 3, 1697−1700.

10.1021/ol027495c CCC: $25.00
Published on Web 01/30/2003

selenoester **1** with alkene acceptors (e.g., methyl acrylate, Scheme 1). As we had previously observed with other indoles

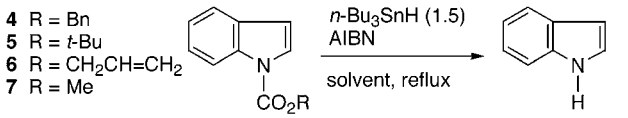
Scheme 1



substituted at the nitrogen by an electron-withdrawing group, the use of standard reductive conditions (*n*-Bu_3SnH−AIBN, benzene, 80 °C) resulted in the isolation of the expected adduct **2** in only moderate yields (40−50%). However, a closer examination of reaction mixtures revealed an interesting result: trace amounts of the deprotected adduct **3** had been formed, particularly in one assay in which the reaction temperature was accidentally increased. This fortuitous observation prompted us to investigate the possibility of developing a novel deprotection strategy for the *N*-Cbz group based on radical technology.

We set out to examine several experimental conditions to achieve the desired transformation using *N*-Cbz indole **4** as a model substrate, which was allowed to react with 1.5 equiv of *n*-Bu_3SnH and catalytic amounts of AIBN at the reflux temperature of different solvents (Table 1). Following the

Table 1. Reaction of Indole Carbamates **4**−**7** with *n*-Bu_3SnH−AIBN[a]



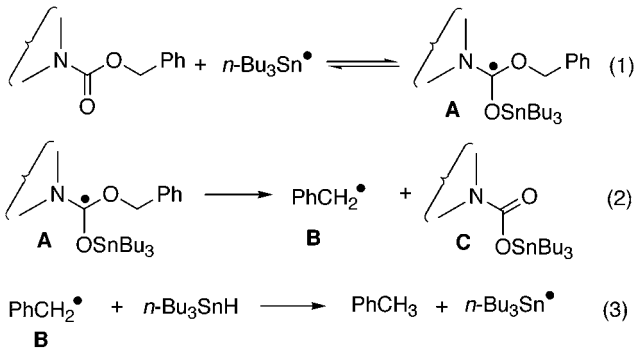
entry	indole	solvent	reaction time	conversion (%)
1	**4**	benzene	2 h	<5%
2	**4**	toluene	2 h	35
3	**4**	ethylbenzene	1.5 h	100
4	**5**	ethylbenzene	2 h	0
5	**5**	*p*-cymene	1 h	100
6	**6**	ethylbenzene	2 h	0
7	**6**	*p*-cymene	3.5 h	75
8	**7**	ethylbenzene	2 h	0
9	**7**	*p*-cymene	2 h	0

[a] Indoles **4**−**7** (0.6 mmol), *n*-Bu_3SnH (0.9 mmol), and AIBN (0.06 mmol) in the solvent (6 mL) were heated (reflux). Additional AIBN (0.06 mmol) was added every 30 min.

first unsuccessful attempts using benzene (entry 1), we were pleased to find that the reaction proceeded to completion over a period of 1.5 h in ethylbenzene (136 °C, entry 3). The deprotection in toluene was considerably slower, requiring 2 h to reach 35% conversion (entry 2). The reaction temperature seemed to be a critical factor, but the use of polar solvents (diglyme or DMF) with boiling points similar to ethylbenzene was unsuccessful. As a confirmation of the radical nature of the process, no reaction occurred without AIBN.[8]

A possible rationale for the above results is as follows (Scheme 2). Reversible addition of a tributylstannyl radical

Scheme 2



to the carbonyl oxygen would produce the intermediate carbon-centered radical **A**, which would undergo, if the temperature was appropriate, fragmentation into a stabilized radical (benzyl, **B**) and a tin carbamate (**C**). Reduction of the former by the hydride would give a new stannyl radical to propagate the chain. Complete deprotection is probably accomplished by hydrolysis of carbamate **C** during the workup. This reaction pathway closely resembles the one first proposed by Khoo and Lee[9] for the deoxygenation of benzyl and allyl alcohols via the corresponding benzoates. More recently, Zard[10] reported a similar stannane addition−fragmentation process for the generation of several nitrogen-centered radicals from oxime esters and hydroxamic acid derivatives.[11]

In full accordance with the proposed mechanism, indole carbamates **5** or **6**, able to produce a stabilized (*tert*-butyl or allyl) radical after the fragmentation step (eq 2), could also be deprotected under the *n*-Bu_3SnH−AIBN conditions, although a higher temperature was required (Table 1). Complete removal of the Boc moiety of **5** occurred when the reaction was performed at the reflux temperature of *p*-cymene (178 °C, entry 5).[12] A similar result was obtained from *N*-Alloc indole **6**, although in this case the reaction was slower, probably due to the interference of the allyl

(8) *n*-Bu_3SnH efficiently participates as a hydride donor in the palladium-catalyzed deprotection of allyl carbamates: Dangles, O.; Guibé, F.; Balavoine, G.; Lavielle, S.; Marquet, A. *J. Org. Chem.* **1987**, *52*, 4984−4993.

(9) (a) Khoo, L. E.; Lee, H. H. *Tetrahedron Lett.* **1968**, 4351−4354. See also: (b) Dolan, S. C.; MacMillan, J. *J. Chem. Soc., Chem. Commun.* **1985**, 1588−1589.

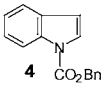
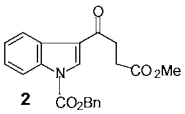
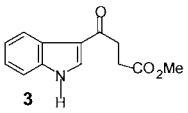
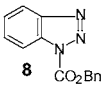
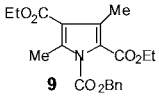
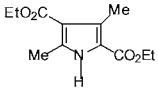
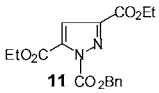
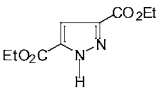
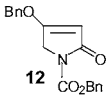
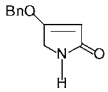
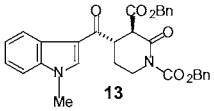
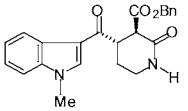
(10) Boivin, J.; Callier-Dublanchet, A.-C.; Quiclet-Sire, B.; Schiano, A.-M.; Zard, S. Z. *Tetrahedron* **1995**, *51*, 6517−6528.

(11) Addition of a stannyl radical to a *thiocarbonyl* group followed by fragmentation constitutes the first step of the powerful Barton−McCombie deoxygenation reaction. For a review, see: Motherwell, W. B.; Crich, D. *Free Radical Chain Reactions in Organic Synthesis*; Academic Press: London, 1992; Chapter 3.

double bond (entry 7). As expected, no deprotection was observed from methyl carbamate **7** (entries 8 and 9).

Having established a functional protocol for the deprotection of the indole *N*-Cbz group, we next studied the scope of the process (Table 2). Thus, the *n*-Bu_3SnH−AIBN−ethylbenzene conditions were applied to 3-acylindole **2** and a variety of *N*-Cbz derivatives of commercially available *aromatic heterocycles*, including benzotriazole, pyrrole, imidazole, and pyrazole, most of them carrying additional carbonyl functions. To our delight, the reaction proceeded efficiently to give the deprotected products in high isolated yields. As can be observed, deprotection of 3-acylindole **2** (entry 2) as well as of heterocycles **8**−**11** (entries 3−6) took place in shorter reaction times (0.5−1 h) than that of simple indole **4** (entry 1). These differences were tentatively attributed to the presence of pendant electron-withdrawing groups or other annular nitrogen atoms that would diminish the electronic density of the nitrogen carbamate group, thus increasing the reactivity of the carbonyl unit toward stannyl radicals (Scheme 2, eq 1).

Table 2. Cleavage of *N*-Cbz Carbamates Using *n*-Bu_3SnH-AIBN[a]

entry	substrate	time	product[b]	yield (%)[c]
1	 **4**	1.5 h		90
2	 **2**	1 h	 **3**	95
3	 **8**	0.5 h		92
4	 **9**	0.5 h		80
5	 **10**	1 h		85
6	 **11**	1 h		86
7	 **12**	1h		80
8	 **13**	1h		90

[a] General procedure: A solution of the substrate (0.6 mmol), *n*-Bu_3SnH (0.9 mmol), and AIBN (0.06 mmol) in ethylbenzene (6 mL) was heated (reflux). Additional AIBN (0.06 mmol) was added every 0.5 h. Upon the disappearance of the starting material, the reaction mixture was concentrated. The residue was partitioned between hexanes and acetonitrile, and the polar layer was washed with hexanes to remove tin compounds. The solvent was removed, and the crude product was chromatographed on SiO_2. [b] All new compounds were fully characterized by NMR analysis and gave satisfactory HRMS and/or combustion data. [c] Isolated yields.

At this point we wondered whether the feasibility of the radical deprotection of the *N*-Cbz group could depend on the basic character of the nitrogen atom, giving opportunities for a discrimination among different nitrogen-containing functional groups. With this in mind, several *N*-Cbz derivatives of originally nonbasic *amides* and basic *amines* were subjected to the above experimental conditions. Our reasoning proved to be correct, since *N*-acyl carbamates **12** (entry 7) and **13**[7a] (entry 8) cleanly afforded the corresponding secondary amides, without affecting the enol ether or the benzyl ester function, respectively. In contrast, carbamates **14**−**16** (Figure 2) did not lead to any detectable amounts of the corresponding deprotected amines even under forcing conditions (*p*-cymene, reflux).

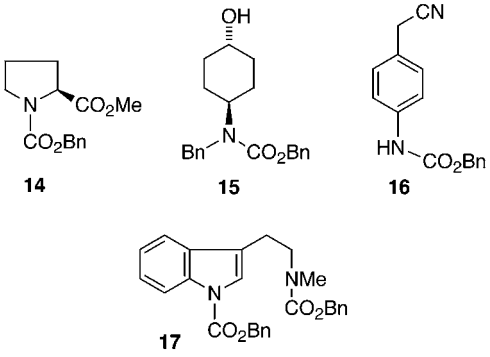


Figure 2.

Therefore, deprotection only occurs in those substrates in which the nitrogen lone pair is less available as a result of its participation in aromaticity or resonance, i.e., in originally nonbasic nitrogen compounds. Consequently, the carbamate carbonyl group is sufficiently reactive toward stannyl radicals to productively participate in the radical chain depicted in Scheme 2. On the contrary, the lower reactivity of the carbamate carbonyl group derived from basic amines would cause the equilibrium of eq 1 to shift much more to the left, the overall process being inefficient.

However, tryptamine **17** (Figure 2), containing both types of *N*-Cbz groups, remained untouched under *n*-Bu_3SnH−AIBN−ethylbenzene conditions even after prolonged exposure to the reagents. Similarly, when *nonreactive* carbamate **14** was mixed (1:1) with *reactive* carbamates **4** or **12**, neither substrate showed any loss of the Cbz group. The radical chain leading to deprotection seems to be somehow inhibited by the presence of a Cbz group derived from a basic amine.

(12) We appreciate the suggestion of one of the reviewers, pointing out the possibility of a thermal deprotection (by a retro-ene reaction) competing with the radical process. However, simple heating of **5** in *p*-cymene for 1 h only led to a partial (15%) removal of the Boc group.

We do not have any convincing explanation for this unexpected observation, which deserves further attention.

In conclusion, an unprecedented radical-mediated deprotection of *N*-Cbz derivatives of amides and nitrogen-containing heterocycles, which is well tolerated by other functional groups, has been developed. Further work is currently underway to more fully establish the scope and limitations of this novel reaction.

Acknowledgment. Financial support from the "Ministerio de Ciencia y Tecnología" (Spain, project BQU2000-0785) is gratefully acknowledged. We also thank the DURSI (Generalitat de Catalunya) for Grant 2001SGR00084.

Supporting Information Available: Representative experimental procedures and characterization data of new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

OL027495C