Communication

Highly Chemoselective Metal-Free Reduction of Tertiary Amides

Guillaume Barbe, and Andr B. Charette
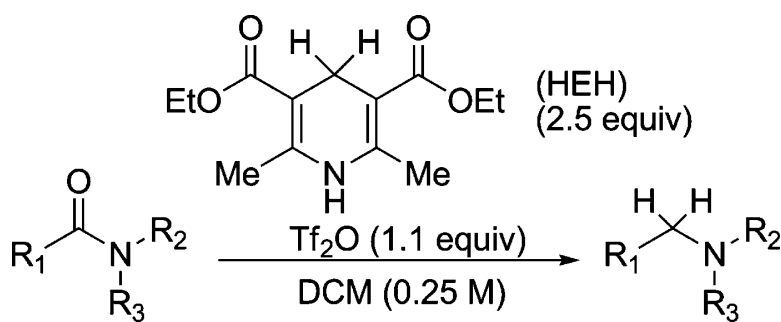
More About This Article

Additional resources and features associated with this article are available within the HTML version:

- Supporting Information
- Links to the 6 articles that cite this article, as of the time of this article download
- Access to high resolution figures
- Links to articles and content related to this article
- Copyright permission to reproduce figures and/or text from this article

View the Full Text HTML

ACS Publications
High quality. High impact.

# Highly Chemoselective Metal-Free Reduction of Tertiary Amides

Guillaume Barbe and André B. Charette*

*Département de chimie, Université de Montréal, P.O. Box 6128, Station Downtown,
Montréal, Quebec, Canada H3C 3J7*

Received September 27, 2007; E-mail: andre.charette@umontreal.ca

The reduction of amides to amines is a well-documented process for which a large number of reaction conditions have been reported in the literature. They include the use of highly reactive reagents such as aluminum and boron hydrides as the most frequently encountered hydrogen sources.[1] These methods are usually high yielding and have been efficiently applied to the synthesis of a wide array of biologically active alkaloids. However, the low functional-group tolerance and tedious purification procedures often associated with such reaction conditions still represent a major drawback.

Over the past decade, silanes have emerged as an alternative hydrogen source in the transition-metal-catalyzed reduction of amides. For example, Rh,[2a,b] Ru,[2c,d] Pt,[2e] Mo,[2f] and Ti[2g] complexes have been shown to exhibit catalytic activity in the hydrosilylation of carboxamides. Although improvements in terms of byproduct removal have been described, the high costs associated with catalysts and/or silane reagents along with the moderate chemoselectivity observed in most of these reduction reactions still impaired their generality. Herein, we describe a highly chemoselective metal-free reduction process for the reduction of tertiary amides.
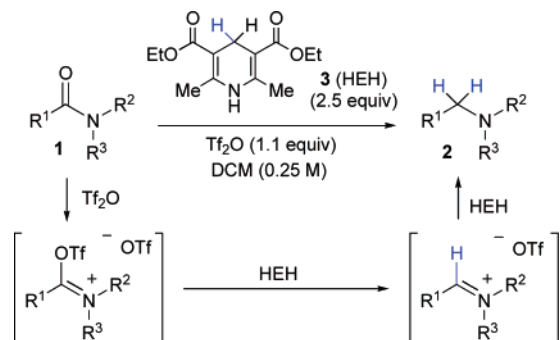
We previously reported that amides can be selectively transformed into a variety of carboxylic acid derivatives[3a] and chiral piperidines[3b] via an electrophilic activation with trifluoromethanesulfonic anhydride (Tf₂O) in the presence of pyridine and a suitable nucleophile. More recently, Movassaghi reported the synthesis of polysubstituted pyridines and pyrimidines from amides using Tf₂O and 2-chloropyridine as activating agents and alkynes/alkenes or nitriles as respective nucleophiles.[4] In an effort to find mild and chemoselective reaction conditions for the reduction of carboxamides, we hypothesized that treating an amide with Tf₂O would generate a highly electrophilic iminium derivative that could subsequently be reduced to the corresponding amine using a mild reducing agent.

Over the past century, 1,4-dihydropyridines have been widely studied as hydrogen transfer agents for the reduction of unsaturated organic compounds.[5] More specifically, the Hantzsch ester (HEH) has been shown to reduce a wide variety of ketiminium and aldiminium species even at low temperature. This has recently found

Table 1. Metal-Free Reduction of Tertiary Amides[a]

entry	amide	product	yield (%)
1		2a (X=H)	70
2		2a (X=H)	68[b]
3		2b (X=Cl)	73
4		2c (X=OMe)	72
5		2d (X=H)	48
6		2d (X=H)	46[b]
7		2e (X=OMe)	50
8		2f	53
9		2g (R=Allyl)	81[c]
10		2h (R=-(CH₂)₅-)	86[c]
11		2i (R=Et)	71[c]
12		2j (R=(CH₂)₂-Ph)	62
13		2k (R=t-Bu)	18
14		2l	<5

[a] All reactions were performed on 1 mmol of amide. *[b]* Reaction was performed on 1 g scale. *[c]* No column chromatography required.

clever applications in organocatalytic enantioselective hydrogen transfer reactions.[6]

After surveying the reaction conditions, we were pleased to find that submitting *N,N*-dibenzylbenzamide to triflic anhydride[7] and HEH[8,9] in DCM[10] at room temperature led to the formation of tribenzylamine in 70% isolated yield after 1 h (Table 1, entries 1 and 2).[9] We then investigated the electronic and steric effects of the reaction. By substituting the benzamide with electron-withdrawing (entry 3) and -donating (entry 4) groups at the *para* position of the benzoyl moiety, similar yields could be obtained. Moreover, *N*-aryl- (entries 5−8) and *N*-allylbenzamides (entry 9) were also found to be reduced under these conditions, albeit in slightly lower yields. Interestingly, these classes of substrates are known to produce considerable amounts of the corresponding primary alcohols and secondary amines when reduced with LiAlH₄.[11] However, under our reaction conditions, the sequestration of the oxygen atom by the electrophilic triflyl moiety completely prevented the formation of such byproducts.

It is noteworthy that the reaction can also be performed on 1 g scale without affecting the yield (entries 2 and 6). As shown in entries 10 and 11, amides bearing aliphatic substituents on either the nitrogen or the carbonyl unit were also found to be suitable substrates for the reaction. However, increasing the steric demand on either side of the amide moiety drastically impairs the reduction step (entries 13 and 14).

We evaluated the chemoselectivity of the reduction process by grafting different functionalities on *N*-benzoylpiperidine (Table 2). By positioning these functionalities at the 4-position of the

Table 2. Reduction of Functionalized Amides^a

entry	amide	product	yield (%)^b
1	Ph—C(O)—N(piperidine-4-one)	**2m**	86
2	Ph—C(O)—N(piperidine-CO$_2$Et)	**2n**	81
3	Ph—C(O)—N(piperidine-OAc)	**2o**	82
4	Ph—C(O)—N(piperidine=CHCO$_2$Et)	**2p**	78
5	Ph—C(O)—N(piperidine-O-CH$_2$CN)	**2q**	91
6	Ph—C(O)—N(piperidine-O-epoxide)	**2r**	65
7	Ph—C(O)—N(piperidine-O-alkyne)	**2s**	75

^{a} All reactions were performed on 1 mmol of amide. ^{b} No column chromatography required.

Scheme 1. Chemoselective Synthesis of Donepezil
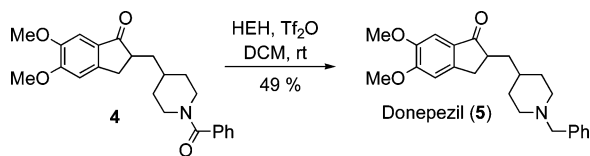
piperidine moiety, we minimized both the steric and electronic influence of the functional group on the reaction. We were delighted to find that, under our reaction conditions, a ketone (entry 1), esters (entries 2−4), an α,β-unsaturated ester (entry 4), a nitrile (entry 5), an epoxide (entry 6), an alkyne (entry 7), and ethers (entries 5−7) were all tolerated, providing the corresponding amines in moderate to excellent yields. It should be noted that, in all of these cases, none of the reduced functionalities could be observed, thereby demonstrating the high chemoselectivity of the reduction process.

A demonstration of the synthetic potential is shown in Scheme 1. Donepezil (**5**), an acetylcholine esterase inhibitor used for the management of Alzheimer's disease, was marketed in the U.S. as Aricept (donepezil hydrochloride) in 1996.[12] It was originally synthesized from **4** via a debenzoylation/benzylation sequence.[13] This two-step process can now be reduced to a single step of amide reduction, providing donepezil (**5**) in 49% yield without the necessity of a flash chromatography. It is also noteworthy that the presence of the amide functionality results in crystalline material for all of the donepezil synthetic intermediates.

In conclusion, a highly chemoselective metal-free reduction of tertiary amides has been developed. As was demonstrated in the chemoselective synthesis of donepezil, we believe this could find great interest in the synthesis of highly functionalized molecules and especially in the synthesis of natural products. Efforts are actually directed toward the extension of this methodology to secondary amides, and the results will be reported in due course.

Supporting Information Available: Experimental details and spectroscopic data (PDF). This material is available free of charge via the internet at http://pubs.acs.org.

References

(1) Seyden-Penne, J. *Reductions by the Alumino and Borohydrides in Organic Synthesis*, 2nd ed.; Wiley: New York, 1997.
(2) (a) Ohta, T.; Kamiya, M.; Nobutomo, M.; Kusui, K.; Furukawa, I. *Bull. Chem. Soc. Jpn* **2005**, *78*, 1856−1861. (b) Kuwano, R.; Takahashi, M.; Ito, Y. *Tetrahedron Lett.* **1998**, *39*, 1017−1020. (c) Motoyama, Y.; Mitsui, K.; Ishida, T.; Nagashima, H. *J. Am. Chem. Soc.* **2005**, *127*, 13150−13151. (d) Igarashi, M.; Fuchikami, T. *Tetrahedron Lett.* **2001**, *42*, 1945−1947. (e) Hanada, S.; Motoyama, Y.; Nagashima, H. *Tetrahedron Lett.* **2006**, *47*, 6173−6177. (f) Fernandes, A. C.; Romao, C. C. *J. Mol. Catal. A* **2007**, *272*, 60−63. (g) Selvakumar, K.; Rangareddy, K.; Harrod, J. F. *Can. J. Chem.* **2004**, *82*, 1244−1248.
(3) (a) Charette, A. B.; Grenon, M. *Can. J. Chem.* **2001**, *79*, 1694−1703 and references therein. (b) Charette, A. B.; Grenon, M.; Lemire, A.; Pourashraf, M.; Martel, J. *J. Am. Chem. Soc.* **2001**, *123*, 11829−11830.
(4) (a) Movassaghi, M.; Hill, M. D.; Ahmad, O. K. *J. Am. Chem. Soc.* **2007**, *129*, 10096−10097. (b) Movassaghi, M.; Hill, M. D. *J. Am. Chem. Soc.* **2006**, *128*, 14254. (c) Movassaghi, M.; Hill, M. D. *J. Am. Chem. Soc.* **2006**, *128*, 4592.
(5) (a) Lavilla, R. *J. Chem. Soc., Perkin Trans. 1* **2002**, 1141−1156. (b) Stout, D. M. *Chem. Rev.* **1982**, *82*, 223−243. (c) Eisner, U.; Kuthan, J. *Chem. Rev.* **1972**, *72*, 1−42.
(6) (a) Yang, J. W.; Hechavarria Fonseca, M. T.; Vignola, N.; List, B. *Angew. Chem., Int. Ed.* **2005**, *44*, 108−110. (b) Ouellet, S. G.; Tuttle, J. B.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2005**, *127*, 32−33. (c) Mayer, S.; List, B. *Angew. Chem., Int. Ed.* **2006**, *45*, 4193−4195. (d) Tuttle, J. B.; Ouellet, S. G.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2006**, *128*, 12662−12663. (e) Martin, N. J. A.; List, B. *J. Am. Chem. Soc.* **2006**, *128*, 13368−13369. (f) Rueping, M.; Sugiono, E.; Azap, C.; Theissmann, T.; Bolte, M. *Org. Lett.* **2005**, *7*, 3781−3783. (g) Hoffmann, S.; Seayad, A. M.; List, B. *Angew. Chem., Int. Ed.* **2005**, *44*, 7424−7427. (h) Storer, R. I.; Carrera, D. E.; Ni, Y.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2006**, *128*, 84−86. (i) Hoffmann, S.; Nicoletti, N.; List, B. *J. Am. Chem. Soc.* **2006**, *128*, 13074−13075. (j) Rueping, M.; Antonchick, A. P.; Theissmann, T. *Angew. Chem., Int. Ed.* **2006**, *45*, 3683−3686. (k) Rueping, M.; Antonchick, A. P.; Theissmann, T. *Angew. Chem., Int. Ed.* **2006**, *45*, 6751−6755.
(7) Unlike other reagents that were screened (e.g., POCl$_3$, (COCl)$_2$, Et$_3$$^+OBF_4$$^-$), Tf$_2$O reacts rapidly (<5 min) and is not substrate-dependent.
(8) A small excess is necessary due to some HEH decomposition in the reaction conditions: (a) van Bergen, T. J.; Mulder, T.; Kellogg, R. M. *J. Am. Chem. Soc.* **1976**, *98*, 1960−1962. (b) van Bergen, T. J.; Kellogg, R. M. *J. Am. Chem. Soc.* **1976**, *98*, 1962−1964.
(9) See Supporting Information for more details.
(10) Other solvents such as MTBE, Et$_2$O, THF, or toluene led to low conversion due to low solubility of the iminium triflate and HEH.
(11) Akamatsu, H.; Kusumoto, S.; Fukase, K. *Tetrahedron Lett.* **2002**, *43*, 8867−8869 and references therein.
(12) (a) Roberson, E. D.; Mucke, L. *Science* **2006**, 781−784. (b) Melnikova, I. *Nat. Rev. Drug Discovery* **2007**, *6*, 341−342.
(13) Sugimoto, H.; Iimura, Y.; Yamanishi, Y.; Yamatsu, K. *J. Med. Chem.* **1995**, *38*, 4821−4829.

JA077463Q