# Highly Chemoselective Metal-Free Reduction of Tertiary Amides

*Research by G. Barbe and A.B. Charette,* J. Am. Chem. Soc. ***2008***, 130, *18*

*Condensation and commentary by* ***R.M. Kellogg****, Syncom BV*

## Condensation of the Research

**Purpose of the Study**

*To develop a mild, metal-free synthetic method for the reduction of tertiary amides to tertiary amines*

**Background**

At first glance, one would not think that the reduction of tertiary amides to tertiary amines should be a problem. There are many known methods for the reduction adequately summarized in the article under review. In addition to boron and aluminum hydrides, metal-catalyzed, silane reductions are especially popular despite that purification of the end product remains problematic. Hard-to-remove traces of metals in the product(s) and interference with other substituents in the reactant can be an additional complication. In practice, one finds that relatively small changes in structure within a target molecule can lead to serious complications during the reduction. A simple, mild, low-cost, and metal-free reduction method with straightforward purification would be a most welcome addition to the synthesis chemist's toolkit.

**What Researchers Accomplished**

The researchers have turned to some old chemistry to accomplish the above objective. The reducing agent is "Hantzsch ester" **3** (Scheme 1), which is easily prepared from the condensation of ethyl acetoacetate, ammonia, and formaldehyde.

This diester is an air-stable, mild reducing agent that delivers a hydride equivalent and during its oxidation is converted to stable pyridine **4** (Scheme 2). Many variations of the Hantzsch ester structure are known and its redox potential can be significantly increased by structural modification.[1] The authors have now shown that tertiary amides **1** can be

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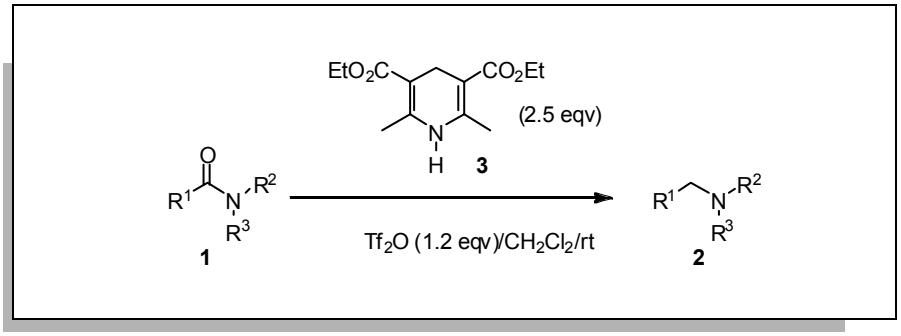


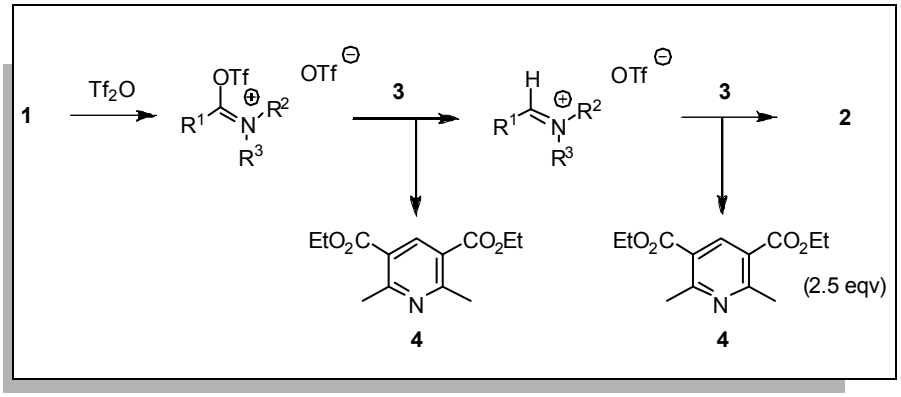

**Scheme 1**

converted to tertiary amines **2** using 1 eq of triflic anhydride as activator and 2 eq of **3** as the reducing agent. The mechanism is presumably that shown in Scheme 2.

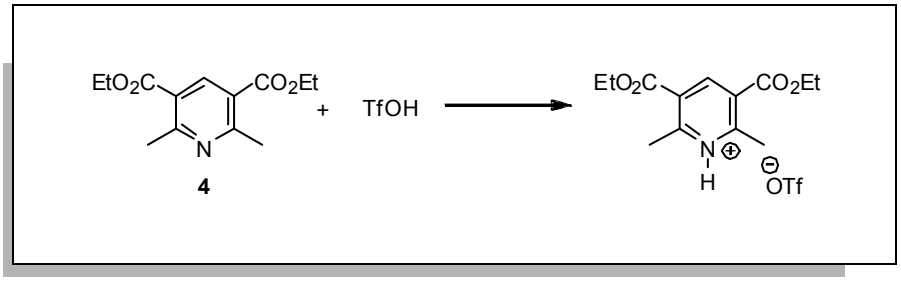
Significant decomposition of **3** caused by the triflic acid generated during the reaction is tempered by neutralization by the basic pyridine **4** formed during the reaction (Scheme 3). After completion of the reduction, the pyridine **4** formed as a side product is removed by washing with a strong base, under which conditions it apparently hydrolyzes to the dicarboxylic acid and is extracted in water (this point is not discussed in the publication).

As illustrated in Scheme 4, various types of tertiary amides are reduced cleanly. In some (but not all) cases, the use of flash chromatography is necessary for final purification. The reaction also works for aliphatic amides (conversion **9a** to **10a**), although it proceeds poorly or not at all if there is a great deal of steric hindrance (conversions **9b** to **10b** and **11** to **12**).

Sensitive groups are tolerated as exemplified by the conversions of oxirane **13** and acetylene **15** without serious decomposition. The conversion of **17** to **18** represents the final step in the synthesis of racemic donepezil, an acetylcholine esterase inhibitor (Scheme 5).[2]



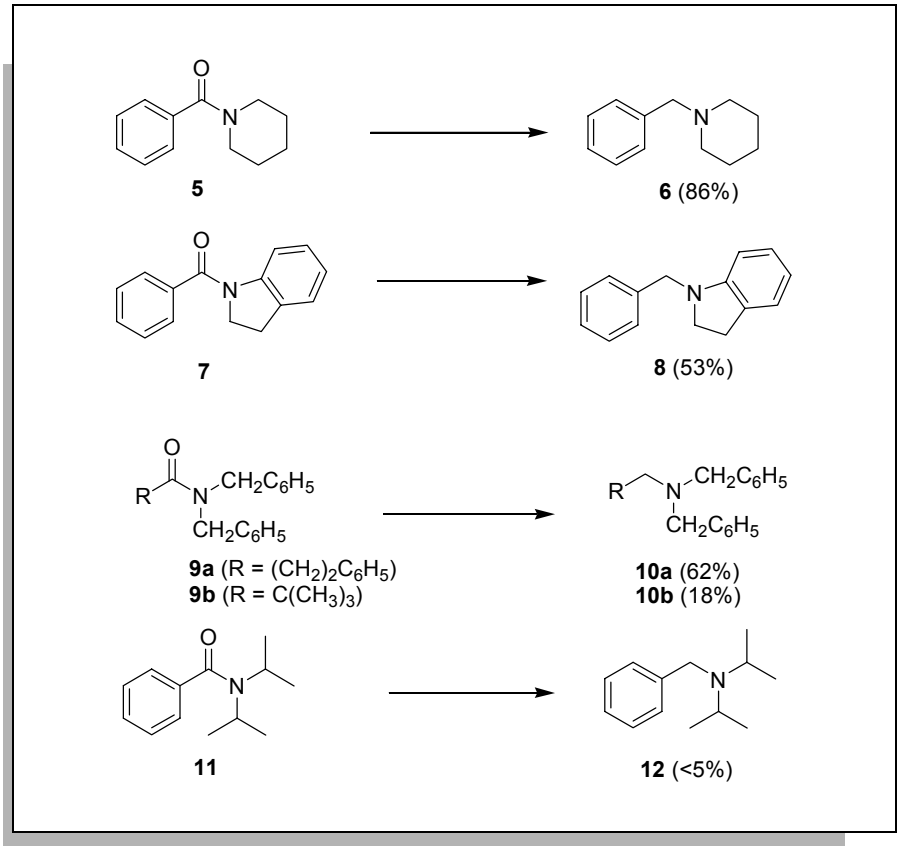

**Scheme 2**



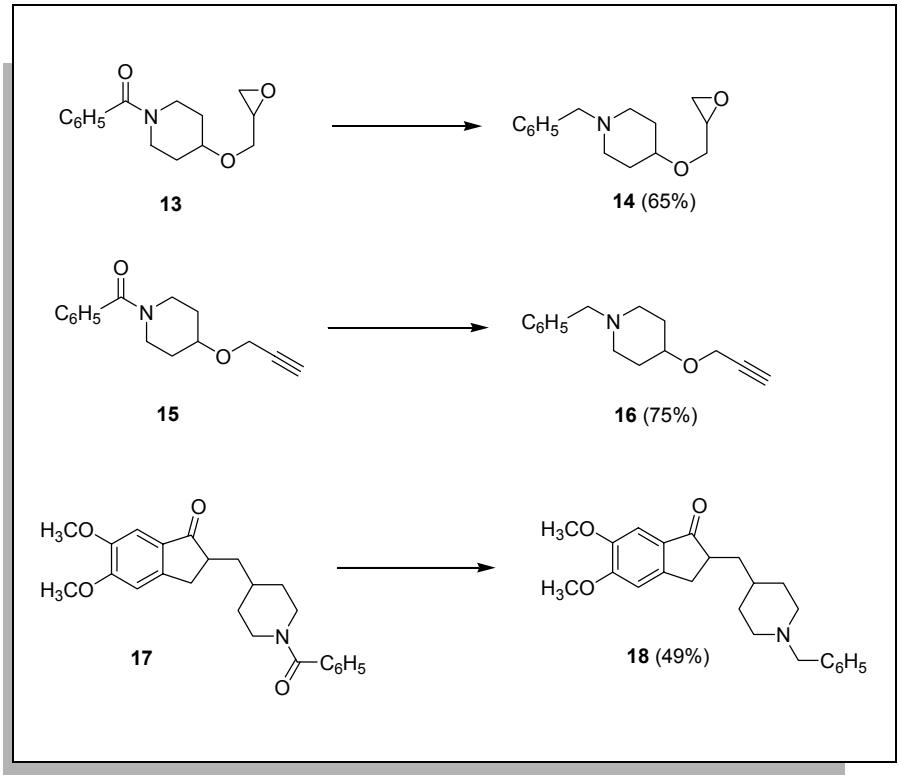

**Scheme 3**

## Commentary on the Research

This reduction procedure is quite clean, the Hantzsch ester **3** is readily prepared, reported yields are in general synthetically useful, purification of the end product is achieved readily, and the authors have carried out several reactions on a 1-g scale without reduction in yield. The concentrations used, 0.25 M, are fairly high so that excessive amounts of solvent (which is unfortunately dichloromethane) are not involved. Steric hindrance clearly lowers reactivity. Unfortunately, only one example of the successful reduction of an




**Scheme 4**




**Scheme 5**

aliphatic tertiary amide is given and so further work is needed for such examples. The amide nitrogen can be substituted with aryl and/or alkyl groups. However, whether other substituents (e.g., Boc, sulfonyl, or silyl groups) can be tolerated is not reported.

The simplicity of this procedure makes it attractive. It remains to be seen, however, how broad the scope will be.

## References


1. Piepers, O., Kellogg, R.M. *J. Chem. Soc. Chem. Commun*. **1982**, 402.
2. (a) Sugimoto, H., Iimura, Y., Yamanishi, Y., Yamatsu, K. *J. Med. Chem.* **1995**, *38*, 4821; (b) Roberson, E.D., Mucke, L. *Science* **2006**, *314*, 781.