An Efficient Method for Reductive Amination of Carbonyl Compounds under Nonacidic Conditions

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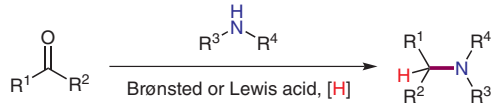
Abstract: A high yielding reductive amination procedure for ketones and aldehydes under neutral conditions is described. The key advantage for the method is the applicability to acid-sensitive substrates, and the procedure is applicable to a wide range of primary and secondary amines, on a multigram scale.

Key words: reductive amination, nonacidic conditions, carbonyl compounds, amines, imine formation, reduction

The construction of carbon–nitrogen bonds by reductive amination is one of the most widely used methods for preparation of industrially relevant amines.[1] The two-step process most often involves acid-catalysed imine formation (by condensation of an aldehyde or ketone with an amine) followed by reduction by an acid-stable metal hydride (Scheme 1).



Scheme 1 Reductive amination of carbonyl compounds with amines: a well-exploited process

The most-often used protocol for reductive amination uses complex metal hydrides reductants (such as sodium cyanoborohydride and sodium triacetoxyborohydride) in the presence of stoichiometric acid catalysts; the latter is usually essential both for formation of the intermediate imine and for the key reduction step. However, due to the competing equilibria in play, product yields are often suboptimal and in particular Brønsted catalysis is not suitable for acid-sensitive substrates. We report here the preliminary results of our study of a reliable and high yielding reductive amination procedure for carbonyl compounds with primary or secondary amines which avoids the use of acid catalysts. Thus a range of aldehydes and ketones undergo reduction amination by primary and secondary amines by sodium triacetoxyborohydride,[2] in the presence of magnesium sulfate. The reaction is efficient and since it is carried out under essentially neutral conditions, it is perfectly suited to amination of carbonyl compounds containing acid-sensitive functionality.

As part of a drug discovery program, we wished to carry out a reductive amination of tetrahydro-4*H*-pyran-4-one using (*R*)-*N*-[2-oxo-2(pyrrolidin-3-ylamino)ethyl]-3-(trifluoromethyl)benzamide (**1**) as the amine component (Scheme 2). Using standard conditions of acetic acid and sodium cyanoborohydride, with tetrahydrofuran as the solvent, the product amine **2** was obtained in 49% yield (after purification by silica gel chromatography).[3] We concluded that the low yield of the reaction was due to incompatibility of the substrates with the acidic conditions and therefore sought a protocol which proceeded at neutral or nonacidic pH. We therefore carried out the reaction under a range of neutral conditions and were delighted to observe that the pyranone reacted with sodium triacetoxyborohydride in the presence of magnesium sulfate and *N*,*N*-diisopropylethylamine to deliver our target tertiary amine in a much-improved yield of 86% (Scheme 3). Moreover, the amine was obtained essentially pure thereby obviating the need for chromatography.

We next examined the scope of our procedure using a range of amines and carbonyl compounds, which were reacted under the same conditions (Table 1).[4] Aldehydes reacted smoothly in the reaction (entries 1–4) and in good yields (69–97%). It is particularly noteworthy that acid-sensitive functionalities (such as Boc group, entries 3–5) were stable under this protocol and that hydroxy group was not subject to elimination reaction (entries 6–9), emphasising the nonacidic reaction environment. Cyclic five- and six-membered ketones (often sluggish substrates under acid-catalysed reactions) were also aminated in good yields in the reaction (entries 5–9), and ester functionality was not affected (entry 8). From the perspective of the amine coupling partner, the reaction proceeded efficiently for piperidines (entries 1–3), piperazines (entry 4) and pyrrolidines (entries 5–9). Amide functionality (entries 5–10) and *N*-benzyl protecting groups (entries 2 and 4) were tolerated under the reaction conditions. The only substrate class found to react poorly under the conditions were anilines (known[5] to be sluggish substrates for reductive amination) with which products were obtained only in low yields.

In conclusion we have demonstrated a high-yielding reductive amination procedure for carbonyl compounds

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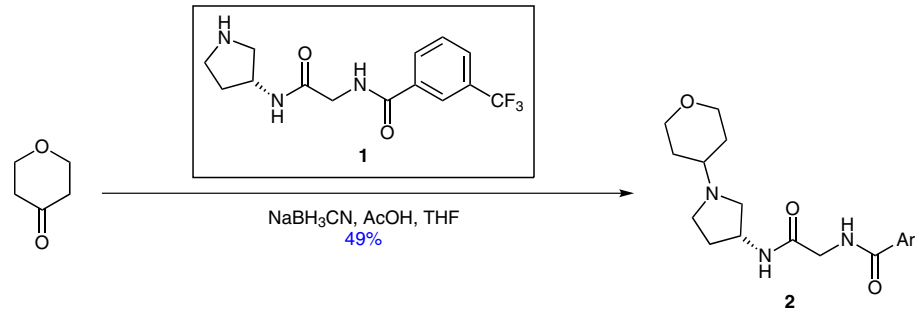
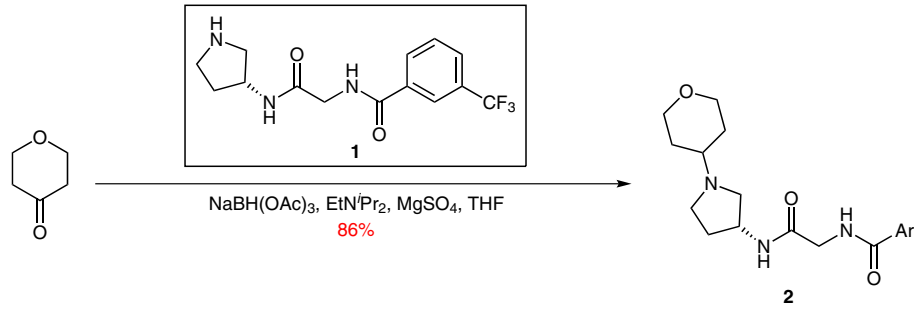


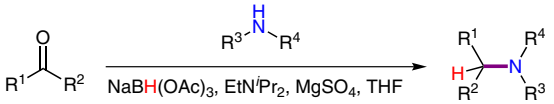
Scheme 2 Reductive amination of dipeptidyl amine **1**: acid catalysis is an inefficient process



Scheme 3 Reductive amination of dipeptidyl amine **1**: nonacidic conditions improve yield

which proceeds under nonacidic conditions and can be carried out on a multigram scale. The procedure delivers a range of pharmacologically relevant amines from primary and secondary aliphatic amines and is of broad applicability.

Table 1 Nonacidic Reductive Amination of Ketones and Aldehydes: A General Process



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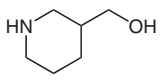
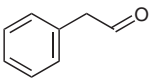
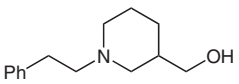
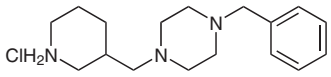
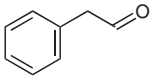
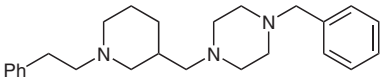
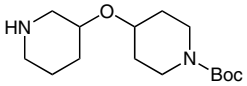
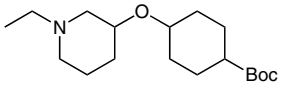
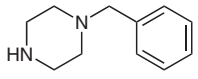
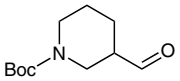
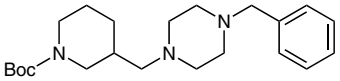
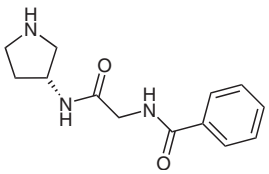
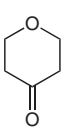
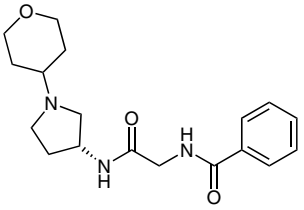
1				96
2				97
3				75
4				80
5				86

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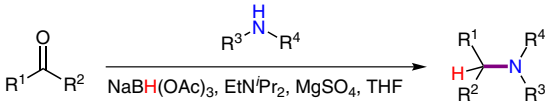
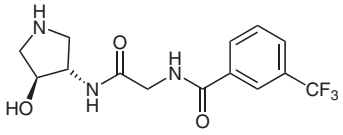
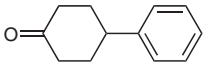
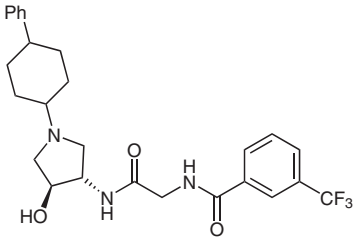
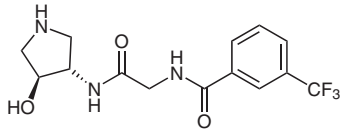
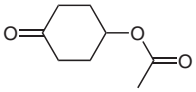
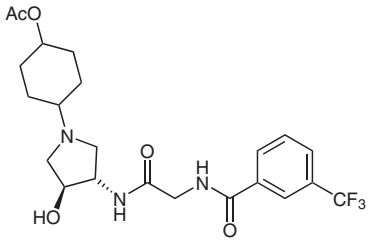
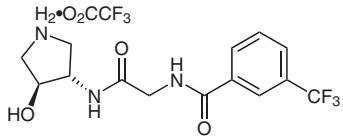
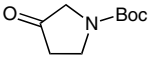
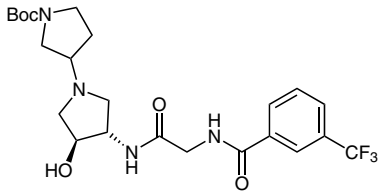
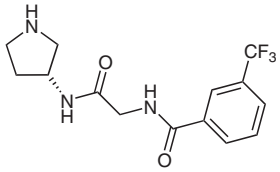
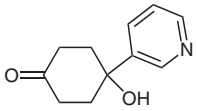
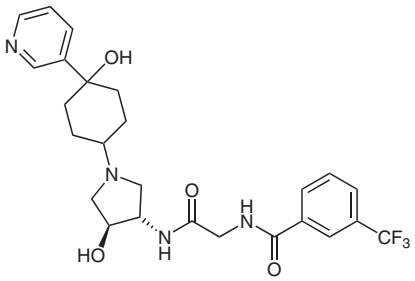
Table 1 Nonacidic Reductive Amination of Ketones and Aldehydes: A General Process (continued)



Entry	Amine	Carbonyl compound	Product	Yield (%)
6				72
7				78
8				95
9				65

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(1) For reviews, see: (a) Margaretha, P. In *Science of Synthesis, Knowledge Updates*; Vol. 2010/4, Section 40.1.1.1.2; Procter, D. J.; Molander, G. A., Eds.; Thieme: Stuttgart, **2011**, 405–442. (b) Tripathi, R. P.; Verma, S. S.; Pandey, J.; Tiwari, V. K. *Curr. Org. Chem.* **2008**, *12*, 1093. (c) Baxter, E. W.; Reitz, A. B. *Org. React. (N. Y.)* **2002**, *59*, 1. (d) Hutchins, R. O.; Hutchins, M. K. In *Comprehensive Organic Synthesis*, Vol. 8; Trost, B. M.; Fleming, I., Eds.; Pergamon Press: Oxford, **1991**, 25–78. (e) Lane, C. F. *Synthesis* **1975**, 135. (f) Emerson, W. S. *Org. React. (N. Y.)* **1948**, *4*, 174.

(2) (a) Abdel-Magid, A. F.; Carson, K. G.; Harris, B. D.; Maryanoff, C. A.; Shah, R. D. *J. Org. Chem.* **1996**, *61*, 3849. (b) Abdel-Magid, A. F.; Mehrman, S. J. *Org. Process Res. Dev.* **2006**, *10*, 971.

(3) Key data for **2**: ^{1}H NMR (400 MHz, DMSO): δ = 8.61 (s, 1 H), 8.11–8.26 (m, 2 H), 7.88 (d, *J* = 7.6 Hz, 1 H), 7.60–7.79 (m, 2 H), 4.12–4.36 (m, 1 H), 3.77–4.03 (m, 4 H), 3.32 (t, *J* = 11.2 Hz, 2 H), 2.74 (dt, *J* = 8.0, 25.5 Hz, 2 H), 2.41–2.49 (m, 2 H), 2.30 (t, *J* = 10.2 Hz, 1 H), 2.00–2.18 (m, 1 H), 1.74 (d, *J* = 12.1 Hz, 2 H), 1.62 (dd, *J* = 12.8, 6.5 Hz, 1 H), 1.31–1.55 (m, 2 H). MS (ES+): *m*/*z* = 400.30 [M + H]$^+$.

(4) **General Procedure**: $MgSO_4$ (0.75 mmol) was added to a solution of the primary or secondary amine (1.28 mmol), the carbonyl compound (1.28 mmol) and *N*,*N*-di-isopropylethylamine (3.83 mmol) in THF (30 mL). The resulting suspension was stirred at r.t. for 5 min. $NaBH(OAc)_3$ (2.55 mmol) was added and stirring was continued overnight. The solvent was removed in vacuo, and the residue was dissolved in CH_2Cl_2 (150 mL). The solution was washed with sat. aq $NaHCO_3$ (50 mL), dried (Na_2SO_4) and concentrated in vacuo to yield the desired product.

(5) See, for instance: Righi, M.; Bedini, A.; Piersanti, G.; Romagnoli, F.; Spadoni, G. *J. Org. Chem.* **2011**, *76*, 704.

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