A Simple Protocol for Direct Reductive Amination of Aldehydes and Ketones Using Potassium Formate and Catalytic Palladium Acetate

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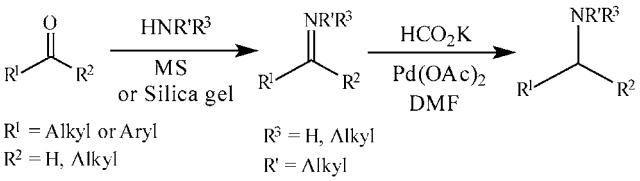
Received 29 October 2002

Abstract: A method for direct reductive amination of aldehydes and ketones, including α,β-unsaturated carbonyl compounds, has been developed, which requires potassium formate as reductant and palladium acetate as catalyst. Suitable amines include both primary and secondary aliphatic and aromatic amines.

Key words: reductive amination, potassium formate, palladium acetate, one-pot reaction

The direct reductive amination of carbonyl compounds[1] is a useful organic transformation for preparing primary, secondary and tertiary amines. The carbonyl compound initially reacts with ammonia or amine to form an imine, which then undergoes reduction in presence of hydrogen or hydride ion (Scheme 1). The term 'direct reductive amination' is used to describe a reaction in which a mixture of the carbonyl compound and the amine is treated with suitable reducing agent in a one-pot operation.[1b] Several reductive systems are known to effect the reduction of the C–N double bond of the imine. The Borch reduction,[2] one of the early methods, involves sodium cyanoborohydride, [$NaBH_3CN$], as the reductant. However, use of excess reagent (up to 5-fold) along with toxic cyanide as the by-product limits its wide applications. The alternative sodium triacetoxyborohydride, [$NaBH(OAc)_3$],[3] has not been successful for aromatic and unsaturated ketones. Other reagents include $ZnCl_2$–$Zn(BH_4)_2$;[4] $NiCl_2$–$NaBH_4$;[5] Ti(*i*-PrO)$_4$–polymethylhydrosiloxane;[6] Ti(*i*-PrO)$_4$–$NaBH_4$;[7] Bu_3SnH;[8] Bu_2SnClH and Bu_2SnIH;[9] decaborane;[10] silica gel–$Zn(BH_4)_2$;[11] Et_3SiH–trifluoroacetic acid;[12] pyridine–BH_3;[13] phenylsilane–dibutyltin dichloride.[14] All these methods require stoichiometric or excess quantities of the hydrides, which are generally highly reactive and expensive as well. Furthermore, use of tin hydrides in some protocols is not recommended for large-scale preparation as the residual insoluble tin compounds pose a great risk in its elimination. On the other hand, use of formic acid as the source of hydrogen, called the Wallach reaction, or ammonium salts of formic acid, called the Leuckart reaction, often yields the N-formyl derivative of the amine instead of the free amine.[15] Recently, we[16a] and other groups[16b] have shown that potassium formate promoted by palladium acetate can reduce efficiently the conjugated C-C double bond. It therefore appeared reasonable to investigate whether potassium formate, which is soluble in polar organic solvents and in water, with activation by palladium salt could significantly reduce the C-N double bond of the imine formed in the direct reductive amination reaction. We report herein our observation, which constitutes a one-pot reductive amination protocol for aldehydes and ketones, including conjugated ones, with the aid of potassium formate and catalytic palladium acetate.



Scheme 1

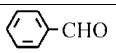
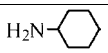
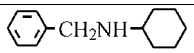
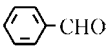
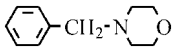
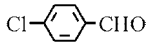
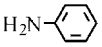
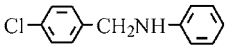
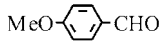
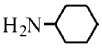
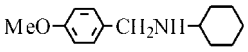
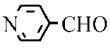
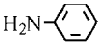
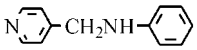
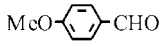
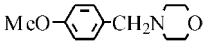
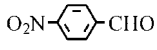
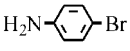
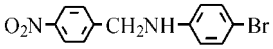
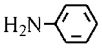
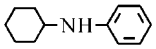
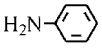
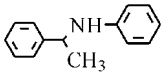
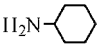
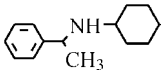
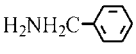
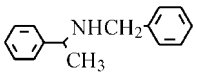
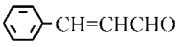
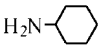
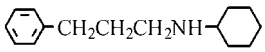
To examine the scope of this reaction, a variety of aldehydes and ketones were reductively aminated with aliphatic and aromatic amines (Table 1). Both primary and secondary amines, such as morpholine (entries 2 and 6) have been used. Reactions with substrates bearing potentially reducible functional groups including chloro (entry 3), bromo and nitro (entry 7) yielded anticipated products without detectable reductive side products. Although acetophenone is a difficult case for some reductive amination protocols, use of excess potassium formate (2–4 mmol) and a slight excess of palladium acetate (5 mol%) gave reductive amination of the ketones at a rate comparable to that of other substrates. The process is equally effective for heteroaromatic systems (entry 5). Reductive amination of cinnamaldehyde (entry 12) with cyclohexyl amine, however, proceeded with concomitant reduction of the C–C double bond. Unlike the Leukart reaction or the Wallach reaction, no N-formyl derivatives were formed in this protocol.

It is well known that aldehydes generally form imines faster than ketones. In this protocol, separate conditions were employed for imine preparation prior to addition of reducing agent. Whereas the aldehydes (except cinnamaldehyde) were reacted with amines in presence of activated molecular sieves (4 Å), the imines from the ketones were prepared on a surface of silica gel following the procedure of Ranu et. al.[11] However the imines prepared by using either molecular sieves or silica gel were directly taken in dimethyl formamide and subjected to reduction by adding palladium acetate (2–5 mol%) and potassium formate

Synlett 2003, No. 4, Print: 12 03 2003.
Art Id.1437-2096,E;2003,0,04,0555,0557,ftx,en;D24402ST.pdf.

ISSN 0936-5214

Table 1 Direct Reductive Amination of Aldehydes and Ketones with HCO_2K and Catalytic $Pd(OAc)_2$

Entry	Substrate **1**	Amine **2**	Condition[a]/Temp./ Time (h)	Product**3**	Yield (%)[b]
1			A/40 °C/3		68
2			A/40 °C/4		62
3			A/50 °C/5		67
4			A/40 °C/3		75
5			A/40 °C/3		86
6			A/50 °C/5		67
7			A/50 °C/5		56
8			B/50 °C/5		70
9			B/60 °C/6		76
10			B/60 °C/6		83
11			B/60 °C/6		80
12			B/50 °C/5		69

[a] Conditions A: Aldehyde + Amine in DMF with MS (4 Å) and stirred at r.t. for 3–5 h; B: Ketone + Amine intimately mixed on activated silica and stirred at r.t. for 5–6 h.

[b] Yield are reported after chromatographic purification (2–3 runs). Satisfactory spectral data were obtained for all the amines (products).

(2–3 equiv) and heated at 40–60 °C for 3–6 hours.[17] The products were obtained after purification on column chromatography. In general, the reaction procedure is very simple and the reaction condition appears to be mild.

In summary, the method described here can be useful for preparing all classes of amines from suitable carbonyl compounds and the amines. Furthermore, the method can be of importance in view of cheap reducing agent, which decomposes to environmentally friendly chemicals. Since palladium catalysed hydride addition is probably the cause of the C–N double bond reduction, the possibility for asymmetric reductive amination in presence of a chiral ligand might be explored.

Acknowledgement

Financial support from the Department of Science & Technology, New Delhi (Grant No. SP/S1/G13/97) is gratefully acknowledged. We are thankful to Professor B. C. Ranu, Department of Oragnic Chemistry, Indian Association for the Cultivation of Science, Calcutta 700 032, India for his help in doing some of the experiments.

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(17) **General Procedure for Aldehydes.** For the aldehydes (listed in Table 1) except cinnamaldehyde:
A solution of *p*-anisaldehyde (680 mg, 5 mmol) and cyclohexylamine (500 mg, 5 mmol) in dry DMF (5 mL) was magnetically stirred at r.t. for 4 h, in presence of molecular sieves (4 Å). To the resulting reaction mixture were added HCOOK (840 mg, 10 mmol) and palladium acetate (22 mg, 0.1 mmol). The mixture was then heated at 40 °C for 3 h to complete the reaction (TLC) and after cooling it was diluted with ice-cold water (15 mL). The mixture was extracted with ether (3 × 20 mL). The combined extract was washed with brine, dried (Na_2SO_4), and evaporated to leave the crude product, which was purified by column chromatography over silica gel. Elution with ethyl acetate–hexanes (1:19; R_f 0.26) furnished *N*-cyclohexyl *p*-methoxybenzyl amine **4** (815 mg, 75%) as an oil: IR(neat): 1246, 1300, 1510, 1610, 2851, 2925 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 1.05–1.31 (m, 6 H), 1.61 (br, 1 H), 1.70–1.92 (m, 4 H), 2.43–2.50 (m, 1 H), 3.73 (s, 2 H), 3.78 (s, 3 H), 6.84 (d, 2 H, *J* = 8.3 Hz), 7.22 (d, 2 H, *J* = 8.3 Hz). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 24.9, 26.2, 33.4, 50.3, 55.2, 56.0, 113.7, 129.2, 132.9, 158.4.