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Direct reductive amination and selective 1,2-reduction of α,β-unsaturated aldehydes and ketones by $NaBH_4$ using $H_3PW_{12}O_{40}$ as catalyst

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Abstract—A simple and convenient procedure for direct reductive amination of aldehydes and ketones with sodium borohydride is described. The reaction has been carried out in methanol in the presence of a catalytic amount of $H_3PW_{12}O_{40}$ (0.5 mol %). α,β-Unsaturated aldehydes and ketones can be easily converted into the corresponding allyl alcohols by reaction with $H_3PW_{12}O_{40}$ (0.5 mol %)/$NaBH_4$.

1. Introduction

Direct reductive amination (of carbonyl compounds) or one-pot reductive alkylation (of amines) are attractive methods for the preparation of amine derivatives in organic synthesis.[1] Several reagents which effect reductive amination have been developed, including: catalytic hydrogenation,[2] Et_3SiH–CF_3CO_2H,[3] Zn–AcOH,[4] Bu_3SnH–DMF[5] $NaBH_3CN$,[6a] $NaBH(OAc)_3$,[6b] pyridine–BH_3,[6c] $ZnCl_2$–$NaBH_4$,[6d] silica gel–$Zn(BH_4)_2$,[6e] Ti(O-*i*-Pr)$_4$–$NaBH_4$,[6f] $NiCl_2$–$NaBH_4$,[6g] $NaBH_4$–$ZrCl_4$,[6h] $NaBH_4$–H_2SO_4,[6i] $NaBH_4$–wet clay-microwave[6j] and borohydride exchange resin.[6k] However, in terms of functional group tolerance, side reactions and reaction conditions, most of these reagents have one or more drawbacks. Reductive amination with $NaBH_4$ and Lewis acids requires an excess of the amine (up to five-fold) in order to drive the reaction to completion, since carbonyl compounds themselves are also reduced under the conditions used.[7] Pyridine–BH_3 is unstable to heat and must be handled with extreme care. Other hydrides such as zinc borohydride and nickel boride are not suitable for use in chemoselective reductions of imines having ketone, ester or amide groups.[8] Cyanoborohydride and tin hydride reagents are highly toxic and generate toxic by-products such as HCN, NaCN[9] or organotin compounds. $NaBH(OAc)_3$ is flammable, water-reactive and poorly soluble in most common organic solvents and has limitations with aromatic and unsaturated ketones. Furthermore, direct reductive amination is performed under anhydrous conditions in order to avoid decomposition of the reducing agents or catalysts, and to enhance generation of the intermediate imines or iminium ions.

In the past, $NaBH_4$ has been employed with various Brønsted acids,[6i] which facilitates Brønsted imine formation, for successful reductive amination. The use of Brønsted catalysts such as H_2SO_4 or *p*-toluenesulfonic acid are common, however, these are corrosive, toxic and difficult to separate from the reaction solution and thus there is interest to substitute these acids with more environmentally friendly solid acids. Heteropolyacids (HPAs) are strong acids and it has been demonstrated that HPAs are much more effective in acid catalysis than protonic mineral and organic acids. 12-Tungstophosphoric acid ($H_3PW_{12}O_{40}$) is considered to

Keywords: Direct reductive amination; $NaBH_4$; Heteropolyacid; $H_3PW_{12}O_{40}$; Imine; Iminium ion; α,β-Unsaturated aldehydes and ketones; Allyl alcohols; Chemoselectivity.
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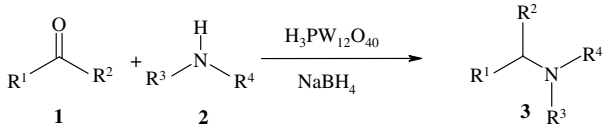
be the strongest heteropolyacid in the Keggin series.[10] Furthermore, $H_3PW_{12}O_{40}$ based catalysts, do not lead to side reactions which frequently occur with mineral acids and they are noncorrosive and environmentally benign. Due to the current challenges for developing environmentally benign synthetic processes and in continuation of our interest in the application of $H_3PW_{12}O_{40}$ for various organic transformation, we report a novel catalytic activity of $H_3PW_{12}O_{40}$ for the high yielding direct reductive amination of aldehydes and ketones with $NaBH_4$ in reagent grade methanol.

We initially studied the direct reductive amination of benzaldehyde with aniline in methanol in the presence of $H_3PW_{12}O_{40}$ (0.5 mol %), which afforded the corresponding imine which was then reduced with $NaBH_4$ to give *N*-benzylaniline in 93% isolated yield. Various aldehydes were subjected to direct reductive amination using this procedure. Acyclic and conjugated carbonyl compounds underwent successful reductive amination with aniline or diethylamine to produce the corresponding secondary or tertiary amines in good to excellent yields. Without $H_3PW_{12}O_{40}$, reductive amination in the presence of $NaBH_4$, did not proceed smoothly, the reaction instead generally gave reductive products of the carbonyl compounds. Under our standard conditions, direct reductive amination of *p*-cyano- or *o*-nitrobenzaldehydes with aniline proceeded smoothly giving good yields of the desired alkylated anilines (Scheme 1, entries d and e).

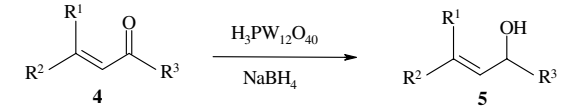
With these results in hand, we next studied the regioselective one-pot reductive amination of *trans*-cinnamaldehyde with aniline or diethylamine. The expected substituted cinnamyl amines were obtained in high isolated yields. The use of our procedure also enabled the reductive amination of ketones.[11]

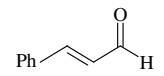
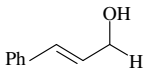
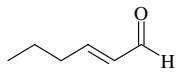
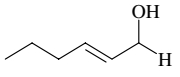
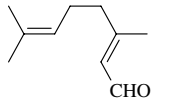
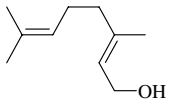
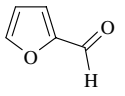
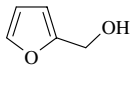
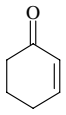
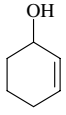
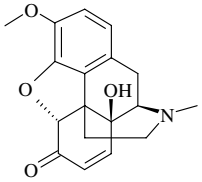
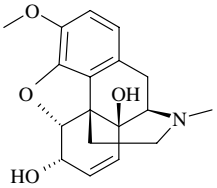


	R^1	R^2	R^3	R^4	yield (%) **3**
a	*tert*-Butyl	H	Phenyl	H	100
b	Phenyl	H	Phenyl	H	93
c	4-Cl-C_6H_4	H	Phenyl	H	89
d	4-NC-C_6H_4	H	Phenyl	H	91
e	2-NO_2-C_6H_4	H	Phenyl	H	95
f	4-Pyridyl	H	Phenyl	H	100
g	2-Furyl	H	Phenyl	H	86
h	*trans*-Cinnamyl	H	Phenyl	H	100
i	Citryl	H	Phenyl	H	98
j	Benzyl	Me	Phenyl	H	96
k	Phenyl	Me	Phenyl	H	90
l	*iso*-Propyl	H	Ethyl	Ethyl	84
m	2-Furyl	H	Ethyl	Ethyl	81
n	4-Pyridyl	H	Ethyl	Ethyl	87
o	4-Me-C_6H_4	H	Ethyl	Ethyl	89
p	4-Cl-C_6H_4	H	Ethyl	Ethyl	89
q	*trans*-Cinnamyl	H	Ethyl	Ethyl	90

Scheme 1. Direct reductive amination of aldehydes and ketones.

Allylic alcohols are important intermediates in the production of pharmaceuticals, agrochemicals and fragrance compounds. They can be produced by allylic oxidation of olefins,[12] 1,2-alkylation or reduction of conjugated aldehydes or ketones. Chemoselective reduction of conjugated aldehydes or ketones to the corresponding allylic alcohols is a useful functional group transformation in organic synthesis. However, selective hydrogenation of the C=O group is much more difficult in the presence of a C=C bond, as hydrogenation of C=C is thermodynamically more favoured. On the other hand, when conjugated ketones are reduced with sodium borohydride, a mixture of the corresponding allylic and saturated alcohol is formed. There are several reports in the literature on the development of various reducing agents for selective 1,2-reduction of conjugated aldehydes and ketones, however, only a few have proven to be practical and general in scope.[13] Stoichiometric reduction with sodium borohydride in combination with $CeCl_3$ (Luche reduction),[14] or oxazaborolidines[15] has led to satisfactory results. It is also worth mentioning that DIBAL-H has been used for highly chemoselective reduction of conjugated aldehydes and ketones, leading to the corresponding allylic alcohols.[16] In view of the literature reports, there is a need to develop novel reducing agents that are easy to use, are inexpensive and environmentally benign.



Entry	Substrate **4**	Product **5**	Yield (%) **5**
a			88
b			93
c			100
d			81
e			79
f			93

Scheme 2. 1,2-Selective reduction of unsaturated aldehydes and ketones.

On the basis of the encouraging results obtained on the regioselective reductive amination of α,β-unsaturated carbonyl compounds, it seemed logical to investigate the possibility of extending this method to the preparation of allylic alcohols via selective 1,2-reduction of α,β-unsaturated aldehydes and ketones. We first examined the reduction of cinnamyl aldehyde using $H_3PW_{12}O_{40}$ (0.5 mol %)/$NaBH_4$ in methanol. We tested various α,β-unsaturated carbonyls, the reactions were highly regioselective and afforded only the corresponding allyl alcohols (Scheme 2). Furthermore, treatment of oxycodone **4f** with $H_3PW_{12}O_{40}$ (0.5 mol %)/$NaBH_4$ led to the corresponding 6β-alcohol **5f** as the sole epimer. The stereochemical assignment of the epimeric 6β-alcohol **5f** has been previously deduced based on the relative magnitude of the ^{1}H NMR vicinal coupling constants of $J_{5,6}$[17].

In summary, we have developed the $H_3PW_{12}O_{40}$ (0.5 mol %)/$NaBH_4$ promoted direct reductive N-alkylation methodology which is both selective and efficient. This methodology also proved to be a general protocol for the syntheses of allyl alcohols.

2. General procedure I: reductive amination of carbonyl compounds

To a solution consisting of reagent grade methanol (4 mL), carbonyl compound (2 mmol) and amine (2.2 mmol) was added $H_3PW_{12}O_{40}$ (30 mg, 0.5 mol %) and the mixture vigorously stirred for 10 min at room temperature. $NaBH_4$ (20 mg, 2 mmol, 1 equiv) was added and the mixture was stirred for an additional 30 min. The reaction mixture was washed with water followed by brine then extracted with CH_2Cl_2. The combined organics were dried over Na_2SO_4, concentrated under vacuum and the crude mixture was purified by column chromatography on silica gel (hexane/ethyl acetate, 2:1) to afford pure products.

3. General procedure II: selective 1,2-reduction of α,β-unsaturated aldehydes and ketones

An analogous procedure was used for 1,2-reduction to that described above. Spectroscopic data for selected examples follow. Compound **3f**: ^{1}H NMR (90 MHz, $CDCl_3$): δ 3.61 (br s, 1H), 4.33 (s, 2H), 6.52–6.81 (m, 5H), 7.13 (d, $J = 9$ Hz, 2H), 8.54 (d, $J = 9$ Hz, 2H); ^{13}C NMR (22.5 MHz, $CDCl_3$): δ 48.3 (CH_2), 113.0 (CH), 117.9 (CH), 122.4 (CH), 128.9 (CH), 148.1 (CH), 149.5 (C), 159.3 (C). Compound **3i**: ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.64 (s, 3H), 1.72 (s, 3H), 1.75 (s, 3H), 2.04–2.13 (m, 4H), 3.63–3.74 (m, 2H), 5.12 (m, 1H), 5.33 (m, 1H), 6.61–6.64 (m, 2H), 6.74 (m, 1H), 7.13–7.25 (m, 2H); ^{1}H NMR (122 MHz, $CDCl_3$): δ 16.3 (CH_3), 17.6 (CH_3), 25.7 (CH_3), 26.4 (CH_2), 39.4 (CH_2), 41.9 (CH_2), 112.8 (CH), 117.2 (CH), 121.5 (H), 122.2 (C), 123.9 (CH), 129.1 (CH), 138.9 (C), 148.9 (C). Compound **5f**: ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.82 (m, 1H), 2.44 (t, $J = 8.14$ Hz, 2H), 2.47 (s, 3H), 2.55 (m, 2H), 2.97 (d, $J = 10.16$ Hz, 1H), 3.10 (br s, 1H), 3.22 (d, $J = 18.66$ Hz, 1H), 3.88 (s, 3H), 4.67 (m, 1H), 4.93 (d, $J = 6.61$ Hz, 1H), 5.02 (br s, 1H), 5.54 (dd, $J = 9.89$, 3.04 Hz, 1H), 5.96 (d, $J = 8.74$ Hz, 1H), 6.62 (d, $J = 8.2$ Hz, 1H), 6.70 (d, $J = 8.2$ Hz, 1H); ^{13}C NMR (122 MHz, $CDCl_3$): δ 22.6 (CH_2), 32.0 (CH_2), 43.2 (NCH_3), 45.6 (CH_2), 47.1 (C), 56.7 (OCH_3), 64.4 (CH), 65.6 (C), 69.1 (C), 90.3 (CH), 113.6 (CH), 119.7 (CH), 126.0 (C), 129.1 (C), 132.6 (C), 138.4 (CH), 143.0 (C), 145.9 (C).

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