Notes

Reduction of Imines with Zinc Borohydride Supported on Silica Gel. Highly Stereoselective Synthesis of Substituted Cyclohexylamines

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The reduction of imines to the corresponding amines is a very useful transformation in organic synthesis since amines constitute important precursors to compounds that are of much interest in pharmaceutical and agricultural industries.[1] The stereochemistry of such carbon−nitrogen π bond reduction is also of great importance in synthetic applications; unfortunately, only a few reports are available in the literature dealing with this aspect.[2] In general, it has been postulated that smaller reducing agents such as sodium borohydride[2c,i] and sodium cyanoborohydride[2g,h] provide stereoselective conversion to equatorial secondary amines, although mixtures usually result. On the other hand, bulky trialkylborohydrides reduce imines to the corresponding axial amines with excellent stereoselectivity.[2c] Thus, although axial amines are obtained in high purity, an efficient method to produce equatorial amines through simple operation is still appreciated. Our recent endeavor of utilizing zinc borohydride[3] for selective reduction of various sensitive functionalities including the carbon−nitrogen bond[31] prompted us to study this important transformation. We have discovered that zinc borohydride supported on silica gel reduces imines to the corresponding secondary amines very efficiently (Scheme 1).

Scheme 1

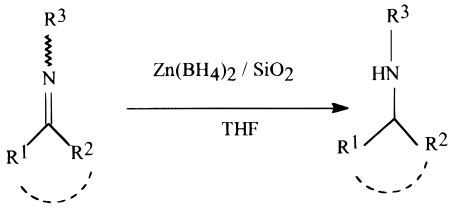

Table 1. Reduction of Imines with Zinc Borohydride Supported on Silica Gel

entry	R^1	R^2	R^3	time (h)	yield[a] (%)	ref
1	Ph	H	c-C_6H_{11}	12	92	2e
2	Ph	H	CH_2Ph	8	90	2e
3	Ph	H	$CH(CH_3)Ph$	10	92	2f
4	Ph	CH_3	CH_2Ph	12	90	2f
5	Ph	CH_3	c-C_6H_{11}	12	95	2e
6	Ph	CH_3	$CH(CH_3)Ph$	10	91	4
7	*n*-C_7H_{15}	H	CH_2Ph	8	94	5
8	*n*-C_7H_{15}	H	$CH(CH_3)Ph$	8	92	6
9	*n*-C_7H_{15}	H	c-C_6H_{11}	8	91	7
10	C_2H_5	H	$CH(CH_3)Ph$	10	94	8

[a] All yields refer to pure isolated products, fully characterized by IR and ^{1}H NMR.

In a simple procedure, the imine was stirred with a suspension of silica gel-supported zinc borohydride in THF at 0 °C under nitrogen for a certain period of time as required to complete the reaction (TLC). Usual workup and purification through a column of basic alumina furnished the corresponding amine. Several structurally varied aldimines and ketimines underwent reductions by this procedure to produce the corresponding secondary amines in high yields. Zinc borohydride without silica gel can also induce reduction,[2e] but in the case of aliphatic amines this requires treatment of the initially formed amine−borane complex with HCl in refluxing THF overnight to generate the free amine. On the other hand, reductions with silica gel-supported zinc borohydride directly lead to amines, avoiding this additional step of HCl treatment, and are comparatively clean and high yielding. Presumably, silica gel moderates the reactivity of zinc borohydride, making the process rather slow but cleaner compared to that with zinc borohydride alone. As is evident from the results summarized in Table 1, reductions of C=N by this reagent are uniform irrespective of the nature of substituents at N and C. The reductions of substituted

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(6) Experimental data: ^{1}H NMR δ 0.87 (3H, t, J = 6.6 Hz), 1.01−1.58 (12H, m), 1.34 (3H, d, J = 6.5 Hz), 2.46 (2H, m), 3.74 (1H, q, J = 6.6 Hz), 7.19−7.36 (5H, m); ^{13}C NMR δ 13.95, 22.53, 24.22, 27.27, 29.14, 29.40, 30.19, 31.71, 47.78, 58.31, 126.42, 127.51, 128.24, 145.82. Anal. Calcd for $C_{16}H_{27}N$: C, 72.33; H, 8.22. Found: C, 72.46; H, 8.16.

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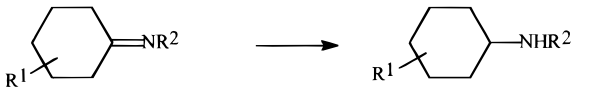
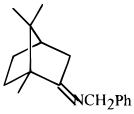
Table 2. Reduction of Cyclohexylimines with Zinc Borohydride Supported on Silica Gel



entry	R^1	R^2	time(h)	yield(%)[a]	trans : cis ratio[b]	ref
1	2 -CH_3	CH_2Ph	12	90	95: 5	2c ,9
2	2 -CH_3	$CH(CH_3)Ph$	12	88	70 : 30	10
3	3 -CH_3	Ph	8	91	75 : 25	11
4	3 -CH_3	CH_2Ph	12	90	100 : 0	9
5	3 -CH_3	$CH(CH_3)Ph$	12	86	80 : 20	10
6	4 -CH_3	Ph	8	92	100 : 0	2c
7	4 -CH_3	CH_2Ph	12	88	100 : 0	9
8	4 - t-Bu	Ph	8	90	100 : 0	2c
9	4 - t-Bu	CH_2Ph	12	92	100 : 0	9
10			14	85	endo	12

[a] All yields refer to pure isolated products, fully characterized by IR, ^{1}H NMR, ^{13}C NMR, mp, and mp of derivatives. [b] The ratio of isomers has been determined by GC and NMR.

cyclohexylimines (Table 2) are highly stereoselective, providing exclusively (Table 2, entries 4 and 6−9) or predominantly (Table 2, entries 1−3 and 5) trans amine products. *N*-Benzylbornimine (Table 2, entry 10) also undergoes stereoselective reduction to produce the corresponding endo bornamine.[12] Evidently, in analogy with small reducing agents,[2c] axial hydride attack is preferred, in general, for substituted cyclohexylimines. Steric factors do seem to influence the stereochemistry as mixtures of trans and cis product are formed when certain 2- or 3-substituted cyclohexylimines (Table 2, entries 2, 3, and 5) are reduced. This is possibly because of the steric hindrance imposed by the combination of the particular alkyl substituent present and its proximity to the imino group.

In conclusion, zinc borohydride supported on silica gel thus appears to be a very efficient reagent for the reduction of imines to the corresponding amines in high yields. Moreover, the easy availability of the reagent, operational simplicity, generality, and superior stereoselectivity make this procedure extremely attractive and a practical alternative to the existing methods,[2] and we believe this will find general acceptance in organic synthesis.

(12) A similar stereochemical outcome was also observed in the reduction of *N*-benzyl bornimine by $NaBH_4/NiCl_2$ in MeOH: Jian, L.; Aiqiao, M.; Guishu, Y.; Yaozhong, J. *Synth. Commun.* **1992**, *22*, 1497.

Experimental Section

General Methods. General information regarding instruments and techniques used are the same as mentioned in our previous paper.[3b]

The aldimines and cyclohexylimines were prepared by treatment of the corresponding aldehydes and cyclohexanones with the appropriate amines in ether in the presence of sodium sulfate following a reported procedure.[13] However, the corresponding imines from acetophenone and comphor were obtained by reactions catalyzed with *p*-toluenesulfonic acid/molecular sieves[14] and zinc chloride,[15] respectively.

Zinc borohydride in DME was prepared from zinc chloride and sodium borohydride according to a reported procedure,[16] and the crude solution was used without any purification. Silica gel-supported zinc borohydride was obtained[3b] by adding activated (heated at 200 °C for 4 h at reduced pressure) silica gel HF 254 (1 g) to the crude solution of $Zn(BH_4)_2$ (3 mmol) in DME (3 mL) followed by stirring at room temperature for 30 min. Solvent was evaporated under reduced pressure at room temperature to give the reagent, which was used on the same or next day.

General Procedure for Reduction. Representative Procedure. 4-(Methylcyclohexyl)phenylimine (187 mg, 1 mmol) in THF (3 mL) was added to the silica gel-supported zinc borohydride (1.3 g, 3 mmol) at 0 °C under nitrogen, and stirring was then continued at room temperature for a certain period of time (Tables 1 and 2) as required to complete the reaction (TLC). The reaction mixture was then decomposed by careful dropwise addition of water and extracted with ether (3 × 10 mL). The extract was washed with brine, dried (Na_2SO_4), and evaporated to leave the crude product, which was purified by column chromatography over basic alumina to provide the pure (>99%; TLC, ^{1}H and ^{13}C NMR) trans amine (174 mg, 92%) as an oil.

This procedure is followed for reduction of all imines. The products (Table 1 and Table 2) are all known compounds and have been easily characterized by their spectral (^{1}H and ^{13}C NMR) and other physical data.

Although the results reported in Tables 1 and 2 were based on mmol-scale reactions, gram-scale reactions also afforded the corresponding products in analogously excellent yields.

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