A Mild Reduction of Azomethines with Zinc Borohydride. Synthetic Application to Tandem Alkylation–Reduction of Nitriles

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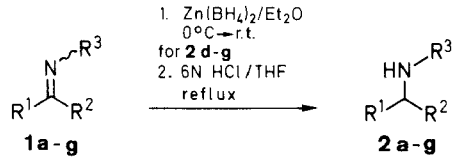
The reduction of Schiff bases; *N*-benzylidene- and *N*-(1-phenylethylidene)arylamines with zinc borohydride in diethyl ether gave the corresponding amines in excellent yield. *N*-benzylidene-benzyl- and cyclohexylamine, *N*-(1-phenylethylidene)- and *N*-(cyclohexylidene)cyclohexylamines, however, require additional treatment with 6N HCl to liberate the amine–borane complex to give the corresponding amines in quanitative yield. The procedure was also applied in the tandem alkylation–reduction of nitriles to yield 1-phenylalkylamines in good yield.

The preparation of amines from ketone or aldehyde derivatives via azomethine formation is a well-known and convenient procedure. Among the existing methods for effecting this transformation, sodium cyanoborohydride is most frequently used.[1] However, it is an expensive reagent. During our studies on the synthetic utility of zinc borohydride,[2] we noticed that zinc borohydride resembles sodium cyanoborohydride in its reducing ability. We describe herein the successful reduction of Schiff bases with zinc borohydride. Furthermore, the procedure was applied to the reduction of intermediate ketimines derived from nitriles through alkylation. The sequence constitutes a useful method for the synthesis of 1-phenylalkylamines from nitriles.



1, 2	R^1	R^2	R^3	1, 2	R^1	R^2	R^3
a	Ph	H	Ph	e	Ph	CH_3	c-C_6H_{11}
b	Ph	H	3-ClC_6H_4	f	Ph	H	c-C_6H_{11}
c	Ph	CH_3	Ph	g	$-(CH_2)_5-$		c-C_6H_{11}
d	Ph	H	CH_2Ph				

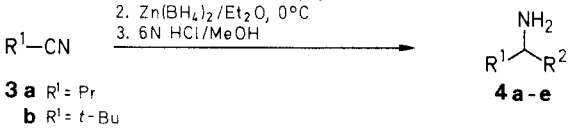
Table 1. Amines **2** and **2** · BH_3 Complexes Prepared

Product	Yield[a] (%)	mp (°C)[b] bp (°C)/Torr[c]	Molecular Formula[d] or Lit. mp (°C) or bp (°C)/Torr
2a	98	35–35.5	37–38[14]
2b	98	126–128/0.5	145–146/2.7[15]
2c	97	122–124/3	170–172/11[16]
2d	33	133–135/3	215/39[17]
2d · BH_3	65[e]	94.5–95.5	94–95[18]
2e	51	123–125/3	135/10[16]
2e · BH_3	42[e]	130 (sublimes)	$C_{14}H_{24}BN$
2f	10	146–148/15	145–147/15[19]
2f · BH_3	87[e]	73–73.5	$C_{13}H_{22}BN$
2g	27	117–119/12	113–115/9[14]
2g · BH_3	73[e]	141–141.5	$C_{12}H_{26}BN$

[a] Yields refer to pure isolated compounds. Yields of **2d–g** are from **1d–g**. All known compounds are characterized by IR and ^{1}H-NMR data.
[b] Uncorrected.
[c] Kugelrohr distillation bath temperature and uncorrected.
[d] Satisfactory microanalyses obtained: C ±0.12, H ±0.03, N ±0.06.
[e] The amine · borane complex is quantitatively converted into its free amine by the treatment with 6N HCl (see text).

From the reaction mixture of aliphatic Schiff bases **1d–g** an appreciable amount of amine–borane complex was also isolated with variable yield. However, this is not surprizing as it is known that aliphatic amine–borane complexes are more stable than the complexes derived from the corresponding aromatic amines.[4] Treatment of the amine–borane complexes **2d–g** · BH_3 with 6N hydrochloric acid yielded quantitatively the corresponding free amines **2d–g**. Hence the use of zinc borohydride is effective for the reduction of Schiff bases. In contrast to sodium cyanoborohydride, zinc borohydride has an almost neutral character, and hence all attempts to realize the reductive amination of aldehydes or ketones via their Schiff bases were fruitless.

We then examined the reduction of intermediate ketimines derived from nitriles with zinc borohydride. For this type of transformation the use of lithium/ammonia[5] has recently been reported.



4	R^1	R^2	4	R^1	R^2
a	Pr	Ph	d	Ph	Bu
b	t-Bu	Ph	e	Ph	Ph
c	Ph	Et			

The alkylation of alkyl nitriles with phenylmagnesium bromide or benzonitrile with ethyl- or phenylmagnesium bromide, or butyllithium, and reduction of the intermediate ketimines afforded the desired 1-phenyl-1-alkylamines **4** in fair yield in a one-pot procedure. In the case of the reaction of benzonitrile with phenylmagnesium bromide, the intermediate ketimine salt was slightly soluble in tetrahydrofuran. Therefore it was necessary[5] to quench the salt with one equivalent of absolute methanol before the introduction of zinc borohydride.

The advantages zinc borohydride as a reducing agent are

Table 2. Compounds **4** Prepared

Substrate	Alkylating Agent	Reaction Conditions[a]	Product	Yield[b] (%)	bp (°C)/Torr[c]	Lit. bp (°C)/Torr
3a	PhMgBr	1. reflux, 1.5 h 2. 0°C, 2 h	**4a**	91	73–75/0.7	102/14[20]
3b	PhMgBr	1. reflux, 20 h 2. 0°C, 1 h	**4b**	82	75–77/0.5	115/22[21]
3c	EtMgBr	1. reflux, 15 min 2. 0°C, 20 min	**4c**	59	89–91/15	88/16[22]
3c	BuLi	1. r.t., 1 h 2. r.t., 2 h	**4d**	80	62–64/0.5	150/20[23]
3c	PhMgBr	1. reflux, 1.5 h[d] 2. 0°C, 14 h[d]	**4e**	86	114–116/3	176/23[14]

[a] Reaction conditions: 1. Reaction with 1.2 equiv of alkylating agent, 2. Reduction with 1.2 equiv of $Zn(BH_4)_2$.
[b] Yields refer to pure isolated compounds. All known compounds are characterized by IR and ^{1}H-NMR data.
[c] Kugelrohr distillation bath temperature and uncorrected.
[d] First step was performed in THF and 1 equiv of absolute MeOH was added before the reduction with $Zn(BH_4)_2$ (see text).

its ease of handling as a solution in diethyl ether, and the mildness of the reagent. This simple method for the reduction of Schiff bases and also for the tandem alkylation–reduction of nitriles has a potential utility in the field of amine synthesis.

The Schiff bases, **1a**,[6] **1b**,[7] **1c**,[8] **1d**,[9] **1e**,[10] **1f**,[11] and **1g**,[12] were prepared as previously reported. An ethereal solution of zinc borohydride was prepared from $NaBH_4$ and $ZnCl_2$ according to the literature method.[13]

Reduction of Schiff Bases; General Procedure:
To an solution of azomethine (**1**; 1 mmol) in Et_2O (2 mL) is added 0.15 M Et_2O solution of $Zn(BH_4)_2$ (1 mmol) at 0°C and the mixture is stirred at r.t. After completion of the reaction (ca. 1 h) TLC monitoring, the mixture is quenched with 2 N NaOH (2 mL) and extracted thoroughly with EtOAc. The combined extracts are dried and evaporated. The residue is purified by preparative TLC to afford the corresponding amines, **2a–f**, respectively. The aliphatic amine–borane complexes **2d–g** · BH_3 obtained by this procedure are treated with excess 6 N HCl in refluxing THF overnight and extracted with EtOAc. The solvent is evaporated to give the free amine in quantitative yield (Table 1).

Tandem Alkylation–Reduction of Nitriles 3; General Procdure:
To a solution of Grignard reagent (2.4 mmol) in Et_2O (2 mL) is added nitrile **3** (2 mmol) at r.t. and the mixture is refluxed for ~1 h. After completion of the reaction GC monitoring, the resulting white turbid solution is cooled to 0°C and 0.15 M Et_2O solution of $Zn(BH_4)_2$ (2.4 mmol) is added. After completion of the reduction TLC monitoring, the mixture is evaporated to remove most of Et_2O and quenched with 6 N HCl (3 mL) and MeOH (3 mL). After evaporation of most of the MeOH, the residue is basified with 2 N NaOH and saturated with NaCl, and extracted with Et_2O. The Et_2O extract is dried, the solvent evaporated, and the residue is purified Kugelrohr distillation to afford the pure amine as a colorless oil.

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