Reductive amination of aromatic aldehydes and ketones with nickel boride

Ira Saxena, Ruli Borah† and Jadab C. Sarma *

Regional Research Laboratory, Jorhat 785006, Assam, India

Reactions of aromatic aldehydes and ketones with primary amines give the corresponding secondary amines in the presence of *in situ* generated nickel boride.

The reductive amination of aldehydes and ketones is one of the significant transformations in biological as well as chemical systems.[1] The importance of the reductive amination process may be judged from the enormous number of its synthetic uses in various reaction schemes.[2] The process may be termed as direct or indirect depending upon the number of operational steps involved.[3] The commonly used direct amination methods mostly use either a catalytic hydrogenation procedure or a hydride reducing agent.[4] Since the introduction of sodium cyanoborohydride as the reagent of choice for this transformation by Borch *et al.*[5] many more new and modified hydride reagents have been developed. Borane–pyridine,[6] borohydride exchange resin,[7] sodium borohydride–sulfuric acid,[8] zinc–acetic acid,[9] zinc borohydride–zinc chloride,[10] sodium cyanoborohydride–titanium isopropoxide,[11] sodium borohydride–magnesium chlorate[12] and sodium cyanoborohydride–zinc chloride[13] are some of the hydride reagents used for this purpose. Recently Abdel-Magid *et al.*[14] have

reported the use of sodium triacetoxyborohydride for this direct reductive amination process. Due to the recent trend in developing solid phase reactions for combinatorial chemistry, different solid supported reagents and reactions have also been developed for this type of transformation.[15]

Although several reagents are available for reductive amination most of the reagents have one drawback or another. Hydrogenation is not compatible with compounds that contain a double or a triple bond and several other reducible functional groups. Sodium cyanoborohydride requires up to a 5 fold excess of the amine and may result in the contamination of the product with cyanide. Moreover, this reagent is highly toxic and generates toxic byproducts HCN and NaCN upon work up. Although sodium triacetoxyborohydride is free from these drawbacks, it has limitations with aromatic and unsaturated ketones. Herein, we wish to present a new direct reductive amination method using nickel boride.

During the course of our studies on *in situ* generated nickel boride,[16] it was observed that a carbonyl group remains unaffected under appropriate reaction conditions. Since generation of nickel boride from sodium borohydride and nickel chloride is accompanied by a sufficient amount of hydrogen evolution,[17] it was argued that the system could be a suitable one for reductive amination of aldehydes and ketones. Since its discovery in Brown's laboratory in the early sixties,[17] nickel boride has been developed by different research groups

† Present address: Department of Polymer Chemistry, Tezpur University, Tezpur 784 028, India.

Table 1 Reductive amination with nickel boride

Carbonyl compounds	Amines	Time/min	Products	Yield (%)	Ref.
PhCHO	Bu^{n}NH$_2$	10	PhCH$_2$NHBu^n	80	24
PhCHO	PhNH$_2$	5	PhCH$_2$NHPh	75	24
PhCHO	PhCH$_2$NH$_2$	10	PhCH$_2$NHCH$_2$Ph	85	6
PhCHO	C$_5$H$_{11}$N	10	NR		
4Cl-PhCHO	Bu^{n}NH$_2$	5	4Cl-PhCH$_2$NHBu^n	80	
4Cl-PhCHO	PhNH$_2$	5	4Cl-PhCH$_2$NHPh	75	
4Cl-PhCHO	PhCH$_2$NH$_2$	5	4Cl-PhCH$_2$NHCH$_2$Ph	85	9
4NO$_2$-C$_6$H$_4$CHO	Bu^{n}NH$_2$	10	4NO$_2$-PhCH$_2$NHBu^n	58^b	
4NO$_2$-C$_6$H$_4$CHO	PhNH$_2$	10	4NO$_2$-PhCH$_2$NHPh	40^b	
4NO$_2$-C$_6$H$_4$CHO	PhCH$_2$NH$_2$	10	4NO$_2$-PhCH$_2$NHCH$_2$Ph	65^b	
4MeO-C$_6$H$_4$CHO	Bu^{n}NH$_2$	10	4MeO-PhCH$_2$NHBu^n	83	
4MeO-C$_6$H$_4$CHO	PhNH$_2$	10	4MeO-PhCH$_2$NHPh	90	
4MeO-C$_6$H$_4$CHO	PhCH$_2$NH$_2$	10	4MeO-PhCH$_2$NHCH$_2$Ph	85	24
Cyclohexanone	Bu^{n}NH$_2$	10	C$_6$H$_{11}$NHBu^n	90	
Cyclohexanone	PhNH$_2$	10	C$_6$H$_{11}$NHPh	98	
Cyclohexanone	PhCH$_2$NH$_2$	10	C$_6$H$_{11}$NHCH$_2$Ph	95	
Cyclohexanone	C$_5$H$_{11}$N	15	NR		
PhCOCH$_3$	Bu^{n}NH$_2$	15	NR		
PhCOCH$_3$	PhNH$_2$	15	PhCH(Me)NHPh	76	
PhCOCH$_3$	PhCH$_2$NH$_2$	15	PhCH(Me)NHCH$_2$Ph	97	
α-Ionone^c	Bu^{n}NH$_2$	10	C$_{13}$H$_{20}$NHBu^n	85	
α-Ionone^c	PhNH$_2$	15	NR		
α-Ionone^c	PhCH$_2$NH$_2$	10	C$_{13}$H$_{20}$NHCH$_2$Ph	80	
PhCOPh	Bu^{n}NH$_2$	15	NR		
PhCOPh	PhNH$_2$	10	PhCH(Ph)NHPh	52	
PhCOPh	PhCH$_2$NH$_2$	10	PhCH(Ph)NHCH$_2$Ph	50	

^{a} All the products were characterized by spectroscopic (NMR, IR, MS) methods as well as direct comparison with authentic materials. ^{b} Another product obtained was the compound in which the group was reduced. ^{c} The IUPAC name for α-ionone is 4-[2,6,6-trimethylcyclohex-2-en-1-yl]but-3-en-2-one.

as an important catalyst for various transformations. The moistened reagent is nonpyrophoric in nature relative to many metal hydrogenation catalysts. It was reported to be an efficient catalyst for reduction of azides to amines [16] as well as reduction of aromatic nitro compounds to anilines.[18] It is also reported to perform reduction of carboxylic acid anhydrides,[19] hydrochlorination of chloroaromatics,[20] reduction of allylic hydroperoxides to hydroxides,[21] deoximercuration of organic mercurials,[22] reductive removal of allylic functional groups,[23] *etc.*

In the present method nickel boride generated *in situ* from nickel chloride hexahydrate and sodium borohydride was used for reductive amination of aldehydes and ketones. Four different aldehydes and four different ketones were reductively aminated with *n*-butylamine, benzylamine and aniline respectively to give the corresponding secondary amines within a few minutes. Our observations are reported in Table 1.

It is clear from Table 1 that both aliphatic and aromatic primary amines react with aromatic aldehydes as well as ketones to give an appreciable yield of the corresponding secondary amines, but the secondary amines (*e.g.* piperidine) remain inert in this system. Moreover acetophenone and benzophenone also remained unreactive with *n*-butylamine. In the case of *p*-nitrobenzaldehyde, reduction of the aromatic nitro group was also observed, giving a mixture of products. Unlike sodium triacetoxyborohydride, nickel boride is also well suited to α,β-unsaturated ketones.

Experimental

To a solution of 1.6 mmol (379 mg) of nickel chloride hexahydrate in 3 ml of methanol was added 3 mmol (111 mg) of sodium borohydride under stirring at rt. Formation of nickel boride was indicated by instant indication of black precipitate with evolution of gases. Immediately a premixed solution of 1 mmol of aldehyde/ketone and 1.5 mmol of amine in 2 ml of methanol was added. Stirring was continued at rt with intermittent monitoring by TLC. On completion the reaction mixture was diluted with chloroform (25 ml) and filtered. The precipitate was washed well with chloroform (3 × 10 ml). The combined organic layer was washed with water, dried over anhydrous sodium sulfate and evaporated at reduced pressure to get the crude product. Purification was performed by preparative TLC if needed.

Notes and references

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