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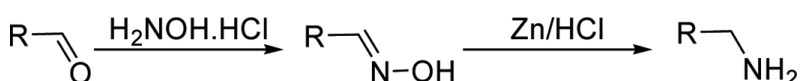
SYNTHESIS OF PRIMARY AMINES BY ONE-POT REDUCTIVE AMINATION OF ALDEHYDES

Mohamed Ali Ayedi,^{1,2} Yves Le Bigot,¹ Houcine Ammar,²
Souhir Abid,² Rachid El Gharbi,² and Michel Delmas¹

¹Université de Toulouse, INP-ENSIACET, Laboratoire de Génie Chimique (LGC), Toulouse, France

²Laboratoire de Chimie Appliquée, Faculté des Sciences de Sfax, Université de Sfax, Sfax, Tunisia

GRAPHICAL ABSTRACT



Abstract We report here a novel, one-pot, two-step reductive amination of aldehydes for the atom-economical synthesis of primary amines. The amination step has been carried out with hydroxylammonium chloride and does not require the use of a base. In the subsequent reduction step, a metal zinc/hydrochloric acid system has been used. This method is applicable to both aliphatic and aromatic aldehydes. The operational simplicity, the short reaction times, and the mild reaction conditions add to the value of this method as a practical alternative to the reductive amination of aldehydes.

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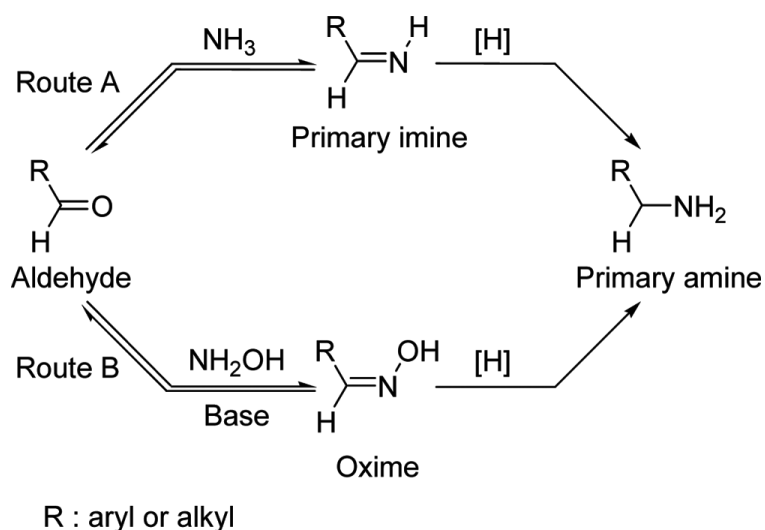
Keywords Hydroxylammonium chloride; primary amine; reductive amination; zinc

INTRODUCTION

Primary amines are important in view of their application in a variety of chemical industry sectors; hence their production processes are of great interest. These compounds are extensively used in the agrochemical and plastics industries and for the development of pharmaceuticals and fine chemicals.^[1–6] Among the amines, primary amines are the most useful; however, their synthesis is challenging because of their high reactivity.

Various methods allow the preparation of primary amines.^[7–10] Among those, reductive amination is the most extensively used. This method, which has been known for a long time, is based on the conversion of aldehydes into imines (route A)^[11–15] or oximes (route B)^[16–28] followed by a reduction step (Scheme 1).

Address correspondence to Houcine Ammar, Laboratoire de Chimie Appliquée, Faculté des Sciences de Sfax, Université de Sfax, BP 1170, 3000 Sfax, Tunisia. E-mail: houcine_fss@yahoo.fr



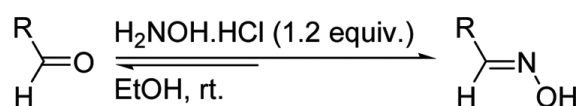
Scheme 1. General scheme for preparation of a primary amine.

However, route A does not allow the selective synthesis of primary amines. In fact, the primary imine intermediates are unstable and could self-condense to form secondary and tertiary imines at the end of the reduction step.^[15,29–32] Route B has the advantage that it leads to primary amines via a generally stable oxime intermediate. This step has been studied in aqueous,^[20,28] organic^[17,18,21,23–27] or hydro-organic^[15,16,19,22] media in the presence of hydroxylammonium chloride and a basic reagent. The oximes can then be reduced either by catalytic hydrogenation^[15,29] or with the aid of metal hydrides such as LiAlH_4 ,^[21,27,28] $\text{NaBH}_3(\text{CN})$,^[30] or NaBH_4 .^[33] These reducing agents allow us to selectively obtain the corresponding amines. However, these procedures are not convenient for large-scale synthesis because of the moisture-sensitive nature of most of the metal hydrides and the high cost of the catalysts. Alternatively, primary amines can be selectively synthesized by the reduction of the corresponding oximes using low-cost zinc metal in the presence of acetic acid^[22–24,26] or formic acid.^[25] However, these acids are very good solvents, making the separation of the amines from the reaction medium very difficult, if not impossible.

Herein, we report a new, efficient, one-pot route to primary amines. It is carried out in ethanol at room temperature under atmospheric pressure.

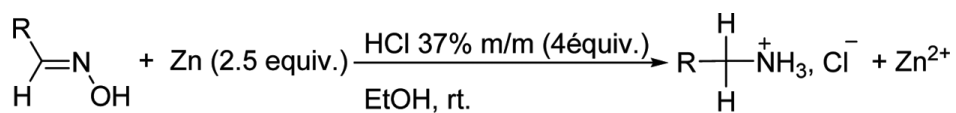
RESULTS AND DISCUSSION

The synthesis of primary amines from the corresponding aldehydes was carried out in two successive steps. In the first step, the aldehyde function was converted to oxime according to the reaction shown in Scheme 2.



R : aryl or alkyl

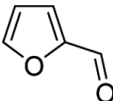
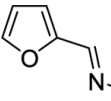
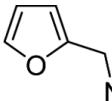
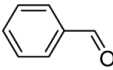
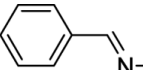
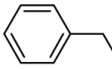
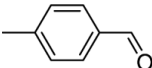

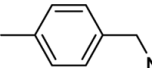
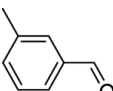
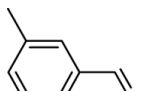
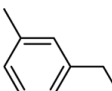
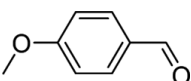
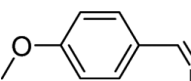
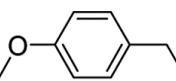
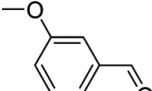
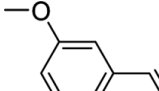
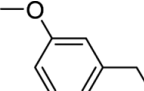
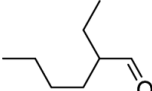
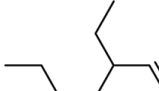
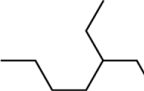

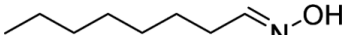
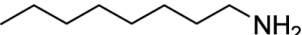
Scheme 2. Formation of oxime from aldehyde.



R : aryl or alkyl

Scheme 3. Formation of primary amine from oxime.

Table 1. Synthesis of primary amines from aldehydes^a

Aldehyde	Time (min)	Intermediate	Product	Yield ^b (%)
 1a	35	 1b	 1c	99
 2a	35	 2b	 2c	99
 3a	50	 3b	 3c	99
 4a	35	 4b	 4c	99
 5a	60	 5b	 5c	93
 6a	35	 6b	 6c	95
 7a	40	 7b	 7c	87
 8a	40	 8b	 8c	80

^aStep 1: aldehyde: 1 (equiv), H₂NOH · HCl: 1.2 (equiv), T: rt, solvent: EtOH. Step 2: Zn: 2.5 (equiv), HCl: 4 (equiv), T: rt, Solvent: EtOH, t: 15 min.

^bIsolated yields.

The second step involves the successive reduction of the nonisolated oxime into the corresponding primary amine according to the reaction shown in Scheme 3.

A series of aromatic and aliphatic primary amines have been thus synthesized. It is worth noting that the primary amines have been obtained in excellent yields. The results are given in Table 1.

Furthermore, the significance of this method is that it does not require a base to generate the oxime intermediate, in contrast to the methods reported in the literature. Thus, the amount of acid introduced to the reaction medium in the reduction step of the oxime is considerably limited. We also found that the solvent used has an influence on the progress of the reaction: The use of ethanol as solvent not only enables the total conversion but also reduces the reaction time as well as the amount of reagents used in the reduction step.

The analysis of the reaction mixture at the end of the reduction step showed that the resulting primary amines form a complex with Zn^{2+} . This phenomena has also been observed by Milligan.^[34] The free amines can be separated from the reaction mixture by treatment with ammonia in the presence of sodium hydroxide. The complex can be dissociated by NH_3 to release the primary amines. The amines can thus be obtained by simple extraction with an organic solvent. No further treatment is required to purify the amine. This method can be applied to the synthesis of relatively small quantities of product.

CONCLUSION

This convenient method, which is used at room temperature and under atmospheric pressure, should prove useful for the synthesis of a variety of primary amines from carbonyl compounds of various structures.

EXPERIMENTAL

All chemistry reagents were purchased from Acros Organics and Fisher Chemical. Commercially available starting reagents were used without further purification. All compounds were analyzed with a Perkin-Elmer Spectrum 100 Universal attenuated total reflectance-Fourier transform infrared analysis instrument equipped with a diamond/ZnSe crystal single reflection. The 1H NMR (300 MHz) and ^{13}C NMR (75 MHz) spectra were recorded on a Bruker Avance 300 spectrometer at 25 °C using $CDCl_3$ as solvent. Elemental microanalyses were performed on an EA1112 analyzer from CE Instruments.

General Procedure for the Preparation of Amines

A solution of carbonyl (aldehyde) compound (49 mmol, 1 equiv.) and hydroxylammonium chloride (4.1 g, 58.8 mmol, 1.2 equiv.) in ethanol (30 mL) was stirred for the times given in Table 1. Subsequently, hydrochloric acid (12 M, 16.33 mL, 4 equiv.) and zinc dust (8 g, 122.5 mmol, 2.5 equiv.) slowly were added to the solution and the mixture was stirred at room temperature for 15 min. A solution of ammonia (30%, 14 mL) and sodium hydroxide (6 M, 30 mL) was added dropwise to the resulting slurry, and the mixture was stirred at room temperature for 15 min. Then, the

resultant solution was extracted with dichloromethane, dried over anhydrous sodium sulfate, and filtered. The solvent was removed under vacuum to afford the amines without further purification in the yields given in Table 1. The purity determined by NMR was found to be superior to 95%.

Furfurylamine (1c)

IR: 3379 cm^{-1} (N-H); ^1H NMR (300 MHz, CDCl_3) δ = 1.30 (s, 2H; NH_2), 3.62 (s, 2H; CH_2), 5.95 (m, 1H; CH), 6.13 (m, 1H; CH), 7.17 (m, 1H; CH) ppm; ^{13}C NMR (75 MHz, CDCl_3) δ = 39.2, 104.8, 110.0, 141.3, 156.8 ppm. Calculated for $\text{C}_5\text{H}_7\text{NO}$: C, 61.84; H, 7.27; N, 14.42. Found: C, 61.83; H, 7.25; N, 14.45.

Supporting Information

Full experimental details and ^1H and ^{13}C NMR spectra can be found online in the Supplementary Material for this article.

ACKNOWLEDGMENTS

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