Revue Roumaine de Chimie, **2006**, *51*(7-8), 839–842

Dedicated to the memory of
Professor Mircea D. Banciu (1941–2005)

RAPID AND CONVENIENT APPROACH TO AMINES: REDUCTION OF IMINES USING METALLIC CALCIUM IN ETHYLALCOHOL

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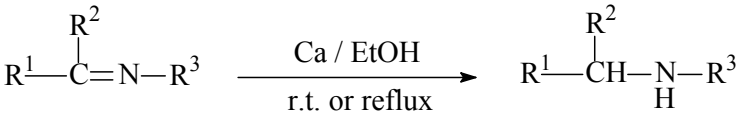
Received February 16, 2006

The reduction of imines using metallic calcium in alcohol rapidly gave the corresponding secondary amines, in good yields.

The reduction of imines is one of the most significant and useful methods for preparation of the corresponding amines.[1] Many reduction processes were therefore widely investigated,[2] which include catalytic reduction[3] as well as the use of metal hydrides ($LiAlH_4$, $NaBH_4$ or others),[1b,4] transition metals complexes (such as Ir,[5] Rh,[6] Mo,[7] Ni,[8] Sn,[9] Ti,[10] Ru,[11] Sm[12]), different boron compounds or complexes[13] or metal reduction systems – metal (Na, Zn, Al or Mg) in alcohols, alkaline or acidic *aq.* solution.[14] Most of the general methods of imine reduction present several disadvantages in the view of cost, safety and operations. As a solution to these problems, we paid much attention to the reduction of imines in water or alcohol as both hydrogen source and solvent. We have previously reported that the use of zinc powder in aqueous 5% NaOH solution was effective for the reduction of imines to corresponding amines.[15] Now, we wish to report the reduction of aromatic and aliphatic imines using metallic calcium in ethanol (Scheme 1) as a rapid and convenient method for formation of secondary amines in high yields without any undesired by-product, such as reductive coupling or hydrolysis products. To the best of our knowledge, there is no literature report about the use of calcium in alcohol in a reduction process involving amine formation. Therefore, our aim is to reveal the scope and limitations of this particular method. We have previously succeeded in using the system Ca / ethanol in dehalogenation processes of aromatic cloroderivatives such as PCB, dioxine or polychlorinated dibenzofuranes.[16]



R^1 : *p*-CH_3-C_6H_4-, *m*-CH_3O-C_6H_4-, *p*-F-C_6H_4-, C_5H_{11}-, C_6H_5-;
R^2 : H-, C_6H_5-, CH_3-;
R^3 : C_6H_5-, *p*-CH_3-C_6H_4-, *p*-F-C_6H_4-, C_6H_5-CH_2-, $(CH_3)_3C$-, C_3H_7-;

Scheme 1 – Reduction of imines using calcium in ethanol.

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RESULTS AND DISCUSSION

Several low aliphatic alcohols were tested in this reduction process. The effect of methanol, ethanol, *n*-propanol or *iso*-propanol on the formation of N-benzylideneaniline **2a**, at room temperature, is shown in Tab. 1.

Table 1

Effect of alcohol on the yield of **2a**[a]

Entry	Alcohol / 10 ml	GC Ratio of **2a**[b] (%)
1	MeOH	58
2	EtOH	100
3	*n*-PrOH	5
4	*iso*-PrOH	0

[a] Reagents amounts are: substrate, 5 mmole and calcium, 20 mmole, respectively. The reaction was carried out at room temperature for 24h. [b]GC program: initial temperature was kept at 60ºC for 3 minutes, the ratio of increasing temperature was 25ºC/min. up to 250ºC and kept for 10 minutes. The retention time of imines was smaller than the one of amines on this GC program. The GC ratio was estimated by the use of ethylbenzene as internal standard.

In *n*-propanol or *iso*-propanol (entries 3 and 4), the reduction of imine **1a** was difficult. However, in methanol, **1a** underwent reaction to afford the product (**2a**) in 58% yield, with partial recovery of **1a**. All reactions in Tab. 1 were carried out for 24h. Under these conditions, violent generation of hydrogen occurred during the initial 3h and reaction mixtures are very viscous. Differently from the other alcohols, the reaction in ethanol proceeded slowly to give the amine in 100% (GC ratio) and 91% isolated yield (after work-up, entry 2). Under reflux conditions, the reaction time (required for complete conversion of **1a**) was far shorter than the one of room temperature (Tab. 2).

Table 2

Reduction of imines **1a-k** using metallic calcium in ethanol.[a]

Entry	Compound	Temperature	Reaction time (min.)	Amine	Structure			Yield[b] %
					R^1	R^2	R^3	
1	**1a**	**reflux**	10	**2a**[17]	C_6H_5-	-H	C_6H_5-	89
2	**1b**	**reflux**	10	**2b**[18]	4-CH_3-C_6H_4-	-H	C_6H_5-	92
3	**1c**	**reflux**	15	**2c**[19]	4-CH_3O-C_6H_4-	-H	C_6H_5-	96
4	**1d**	**reflux**	10	**2d**[20]	4-F-C_6H_4-	-H	C_6H_5-	99
5	**1e**	**reflux**	10	**2e**[21]	C_6H_5-	-H	4-CH_3-C_6H_4-	97
6	**1f**	**reflux**	10	**2f**[22]	C_6H_5-	-H	4-F-C_6H_4-	99
7	**1g**	**reflux**	40	**2g**[23]	C_6H_5-	-H	-$C(CH_3)_3$	73
8	**1h**	**reflux**	10	**2h**[24]	C_6H_5-	-H	C_6H_5-CH_2-	59
9	**1i**	**reflux**	20	**2i**[25]	C_6H_5-	-CH_3	C_6H_5-	80
10	**1j**	**reflux**	10	**2j**[25]	C_6H_5-	C_6H_5-	C_6H_5-	89
11	**1k**	**r.t.**	24 h	**2k**[26]	C_2H_5-	-H	C_3H_7-	55
12	**1a**	**r.t.**	24 h	**2a**[17]	C_6H_5-	-H	C_6H_5-	95

[a] Same ratio of reagents: 5 mmole substrate for 20 mmole of calcium. EtOH (10ml) was used as a solvent. [b.]The structure of products was determined by ^{1}H NMR and GC-MS analysis.

In a typical experimental procedure, a mixture of metallic calcium (0.8g, 20 mmol), the imine **1** (5 mmol) and ethanol (10 mL) are stirred under reflux for the required time (see Tab. 2). Cold water (10 mL) was added carefully to the mixture to quench the remaining calcium. After cooling, ether (10 mL) was poured into the mixture. The mixture was centrifuged (1500 rpm, 10 min.) and the organic layer was separated. The extraction process was repeated 3 times. The combined organic layers were dried on anhydrous $MgSO_4$ and the ether was removed *in vacuo*. The crude residue was purified by Kugelrohr distillation (150ºC, 1.2 torr). The final reaction product was analyzed by GC, GC-MS and NMR; all isolated amines presented analytical data according to their structure (MS, ^{1}H- and ^{13}C-NMR spectra). The results are summarized in Tab. 2. The treatment of

N-benzilideneaniline **1a** and its derivatives with metallic calcium in ethanol, under reflux, rapidly gave the corresponding secondary amines in excellent yields (entries 1~6). Disappearance of starting materials and formation of the secondary amine within 10 min was confirmed by GC (usually, retention times for amines are higher than those for imines). Reduction process is also effective for imines bearing bulky groups (*e.g.* **1g** – entry 7), although it required longer reaction time (up to 40 min.). In the case of less hindered imines, the amount of calcium required can be reduced to half (e.g., **1a**~**1f**). The reaction of aliphatic imine **1k** at reflux gave complex compounds. However, the treatment of **1k** at room temperature (entry 11) formed the corresponding amine **2k** in a 55% yield. Under reflux conditions, the reaction time for **1a** was far shorter compared as the one at room temperature (entry 12).

Advantages of the Ca – ethanol system for the reduction of imines over other specific reagents is due to the availability of the reductive system (and low cost), very short reaction time, lack of secondary by-products and high yields. Although the reduction process was effective for a large number of different aldimines (generated from aromatic aldehydes and aromatic amines, aromatic aldehydes and aliphatic amines, aliphatic aldehydes and aliphatic amines) the use of refluxing conditions is not always suitable: for example, aliphatic aldimines are much too sensitive to high temperatures – in this case the reaction is carried at room temperature, the disadvantage being the long reaction time. There were no attempts to reduce ketimines obtained from aromatic or aliphatic ketones with aliphatic amines, with the exception of compounds **1i** and **1j**, which are aromatic ketimines.

ACKNOWLEDGMENT. We express our gratitude to Dr. Thomas Mathew, University of Southern California for his kind suggestion about this paper.

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