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An Easy Approach to Obtain Alcohol-Amines by Reduction of Alcohol Functionalized Imines †

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Abstract: The reduction of functionalized imines to yield amines is often an intricate task, since most of the methods described in the literature to reduce imines to amines do not take into account that many reducing agents have also basic character. In this way, iminic compounds that have phenol functions usually produce the phenolic salt of the precursor when they are treated with a basic reducing agent, but not the desired amine. In this work, we describe an easy way of isolating very pure aminic compounds with alcoholic functions in its structure from the corresponding iminic compounds, by using $NaBH_4$ as a reducing agent, and avoiding tedious chromatography or multiple solvent extraction steps.

Keywords: alcohol-amine; imine reduction; $NaBH_4$

1. Introduction

Polydentate organic compounds containing amines in their structures are useful Lewis bases in coordination chemistry. Nevertheless, this kind of polydentate amine is often difficult to prepare. However, the analogous imine ligands are usually easier to obtain, by simple condensation of a carbonyl and an amine precursor [1,2]. Accordingly, an advantageous approach to isolate polydentate amines is by the reduction of the corresponding imine analogous.

The reduction of imines to isolate amines is a well-known field of study. In fact, it is one of the central reactions in organic chemistry, and the search for more efficient and practical synthetic methods for carrying out this reduction is a theme of constant interest [3–5]. Many reduction agents have been tested in order to produce the mentioned transformation, and H_2 [6], silanes [7,8], boranes [9], and borohydrides [10] are maybe the most popular ones. Among them, sodium borohydride is commonly chosen to reduced polydentate Schiff bases to amines, because it is cheap and its excess is easily destroyed by an acid medium [11,12]. Nevertheless, success in the reduction process depends on many factors. Thus, the basic character of this reduction agent and the fact that some of the $NaBH_4$ present in the reaction medium can be consumed by acid groups present in the Schiff base, like phenolic functions, are features that are often not considered, preventing the isolation of the desired amine. Besides, the time of the reaction, the election of the solvents of reaction and extraction are also critical. In addition, in numerous synthetic related methods, many steps for adjusting the pH of the medium, drying the reaction media, extracting and purifying the obtained amine are necessary, and sometimes the isolation of amines from imines becomes a cumbersome process.

With these considerations in mind, and as a result of many attempts of isolating a new alcohol-amine ligand from the corresponding imine, we describe herein an easy method to reduce an aromatic imine-alcohol precursor.

2. Materials and Methods

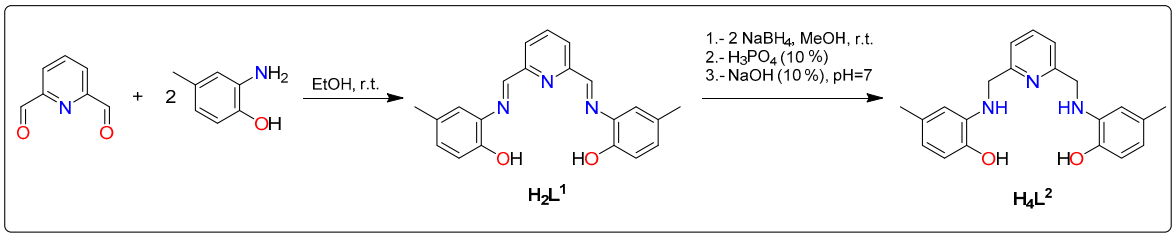
2.1. Materials and General Methods

All chemical reagents and solvents were purchased from commercial sources and used as received without further purification. Elemental analyses of C, H, and N were performed on a FISONS EA 1108 analyzer. Infrared spectra were recorded in the ATR mode on a Varian 670 FT/IR spectrophotometer in the range 4000–500 cm^{-1}. ^1H NMR spectra were recorded on a Bruker DPX-250 spectrometer, using DMSO-d_6 as a solvent. Selective NOEs spectra were recorded in DMSO-d_6 as a solvent on a Varian Inova 400 spectrometer.

2.2. Syntheses of the Alcohol-Imine and Its Reduction to Alcohol-Amine

Bis{2,6-bis[(2-hydroxy-5-methylphenyl)-iminomethyl]pyridine} (H_2L^1, Scheme 1) was obtained as a non-hydrated compound by a small modification of a procedure previously reported in the literature [13], by using absolute ethanol instead of ethanol, and by drying the compound in a laboratory oven. H_2L^1 was fully characterized by elemental analysis, IR and ^1H NMR spectroscopy. Yield: 79%. MW: 345.39. Anal. calcd. for $C_{21}H_{19}N_3O_2$: C 72.86, H 5.54, N 12.16%. Found: C 72.17, H 5.62, N 12.43%. IR (ATR, $\tilde{\nu}/cm^{-1}$): 3392, 3346 (OH), 1623 ($C{=}N_{imine}$), 1595 ($C{=}N_{Py}$). ^1H NMR (250 MHz, DMSO-d_6): δ 9.07 (s, 2H, OH), 8.79 (s, 2H, H4), 8.48 (d, 2H, H2,), 8.09 (t, 1H, H1), 7.16 (s, 2H, H6), 6.96 (d, 2H, H10), 6.83 (d, 2H, H9), 2.25 (s, 6H, CH_3).

Syntheses of bis{2,6-bis[(2-hydroxy-5-methylphenyl)-aminomethyl]pyridine (H_4L^2, Scheme 1). This ligand was obtained by a modification of a method previously reported [14], and that is detailed as follows: To a suspension of H_2L^1 (0.214 g, 0.616 mmol) in methanol (20 mL), $NaBH_4$ (0.050 g, 1.232 mmol) is added in small portions during 30 min, and a very pale yellow solution is obtained. The solution is concentrated to dryness and the oily residue obtained is dissolved in 15 mL of 10% H_3PO_4. The solution is basified with NaOH 10% up to pH = 7, and a yellow solid precipitate. The mixture is extracted with ethyl acetate (150 mL), and the organic phase is dried with Na_2SO_4 during 1 h, and filtered. The solution is concentrated to dryness, and the obtained yellow residue is treated with hexane. After stirring the mixture for 30 min, a pale yellow solid precipitate; this is filtered and dried in air. Yield: 0.11 (51%). MW: 349.43. Anal. calcd. for $C_{21}H_{23}N_3O_2$: C 72.18, H 6.63, N 12.03%. Found: C 71.90, H 6.87, N 11.89%. IR (ATR, $\tilde{\nu}/cm^{-1}$): 3437 (OH), 3267 (NH), 1600 ($C{=}N_{Py}$). ^1H NMR (250 MHz, DMSO-d_6): δ 9.05 (s, 2H, OH), 7.67 (t, 1H, H1), 7.19 (d, 2H, H2), 6.56 (d, 2H10), 6.24–6.20 (m, 4H, 2H6 + 2H9), 5.45 (s, 2H, NH), 4.37 (s, 4H, CH_2), 2.07 (s, 6H , CH_3).



Scheme 1. Synthetic route to the isolation of the alcohol-imine H_4L^2.

3. Results and Discussion

3.1. Synthesis

H_4L^2 could be obtained from H_2L^1, according to Scheme 1, after various attempts to reduce the imine bond of H_2L^1 with different reducing agents, and under different reaction conditions. Accordingly, the treatment of diimine H_2L^1 with $NaBH_4$ in 1:4 molar ratio, followed by acidification

with hydrochloric acid, in line with a synthetic method previously described [15], was unsuccessful. Nevertheless, a second approach using $NaBH_4$, followed by treatment with phosphoric acid, and with control of the reaction time, allows isolating the alcohol-amine H_4L^2 with high purity. This method supposes a modification of an already related one [14], where both diimine precursor and $NaBH_4$ are mixed in 1:1 molar ratios. In our case study, when the diimine H_2L^1 is treated with the reducing agent in 1:1 molar ratio, H_2L^1 does not lose its yellow color, suggesting that the reduction of the imine group does not take place. Nevertheless, if H_2L^1 and $NaBH_4$ are mixed in 1:2 molar ratios, the reduction proceeds.

H_4L^2 was unequivocally identified by a combination of elemental analysis, IR and ^1H NMR spectroscopy techniques.

3.2. Spectroscopic Characterization

IR Spectroscopy

The IR spectroscopy was a useful technique for detecting the reduction of the imine group of H_2L^1. Thus, when the IR spectrum of H_4L^2 was compared with that of H_2L^1, some changes that became apparent unequivocally point to the reduction of the imine group. In this sense, the following facts are observed:

1. The $\nu(C{=}N_{imine})$ band, present in the spectrum of H_2L^1 at 1623 cm^{-1}, is absent in the spectrum of H_4L^2.
2. The spectrum of H_4L^2 shows a sharp band at 3437 cm^{-1}, which can be assigned to an N-H vibration, and that is absent is the spectrum of H_2L^1.

Accordingly, both facts, i.e., the disappearance of the imine vibration and the appearance of a new band assigned to an N-H vibration, agree with the reduction of the imine group and the isolation of the alcohol-amine H_4L^2.

The ^1H NMR studies are even more conclusive. First of all, the ^1H NMR spectra of both H_2L^1 and H_4L^2 suggest their isolation with high purity. In addition, the comparison of the ^1H NMR spectra of both samples (Figure 1) shows some remarkable differences, which agree with the reduction of the imine functional group by $NaBH_4$. In this way, the following is observed:

1. The singlet at 8.79 (2H) ppm, assigned to the imine nitrogen atoms H_4 in the spectrum of H_2L^1, is absent in the spectrum of H_4L^2.
2. All the aromatic hydrogen atoms are displaced to a higher field in the spectrum of H_4L^2 with respect to that of H_2L^1, in agreement with less delocalization of the charge.
3. The spectrum of H_4L^2 shows two new singlets with respect to that of H_2L^1. These singlets are located at 5.45 (2H) and 4.37 (4H) ppm, and can be assigned to the protons of NH and CH_2 groups, respectively.

Therefore, the ^1H NMR spectra clearly confirm the isolation of the desired alcohol-amine. In addition, selective NOE experiments were performed for H_4L^2, with the aim of unequivocally assigning the three kinds of aromatic protons that lead to doublet signals (H2, H9, and H10, Figure 1), information that has also been useful to assign the protons in the region 8.5–6.8 for H_2L^1. Accordingly, selective irradiation of the triplet peak corresponding to H1 allows identifying the doublet at 7.19 ppm as that corresponding to H2. In the same way, selective irradiation of H8, allows locating both H9 protons in the multiplet at 6.20–6.24 ppm. Therefore, the only remaining doublet at 6.56 ppm is assigned to H10.

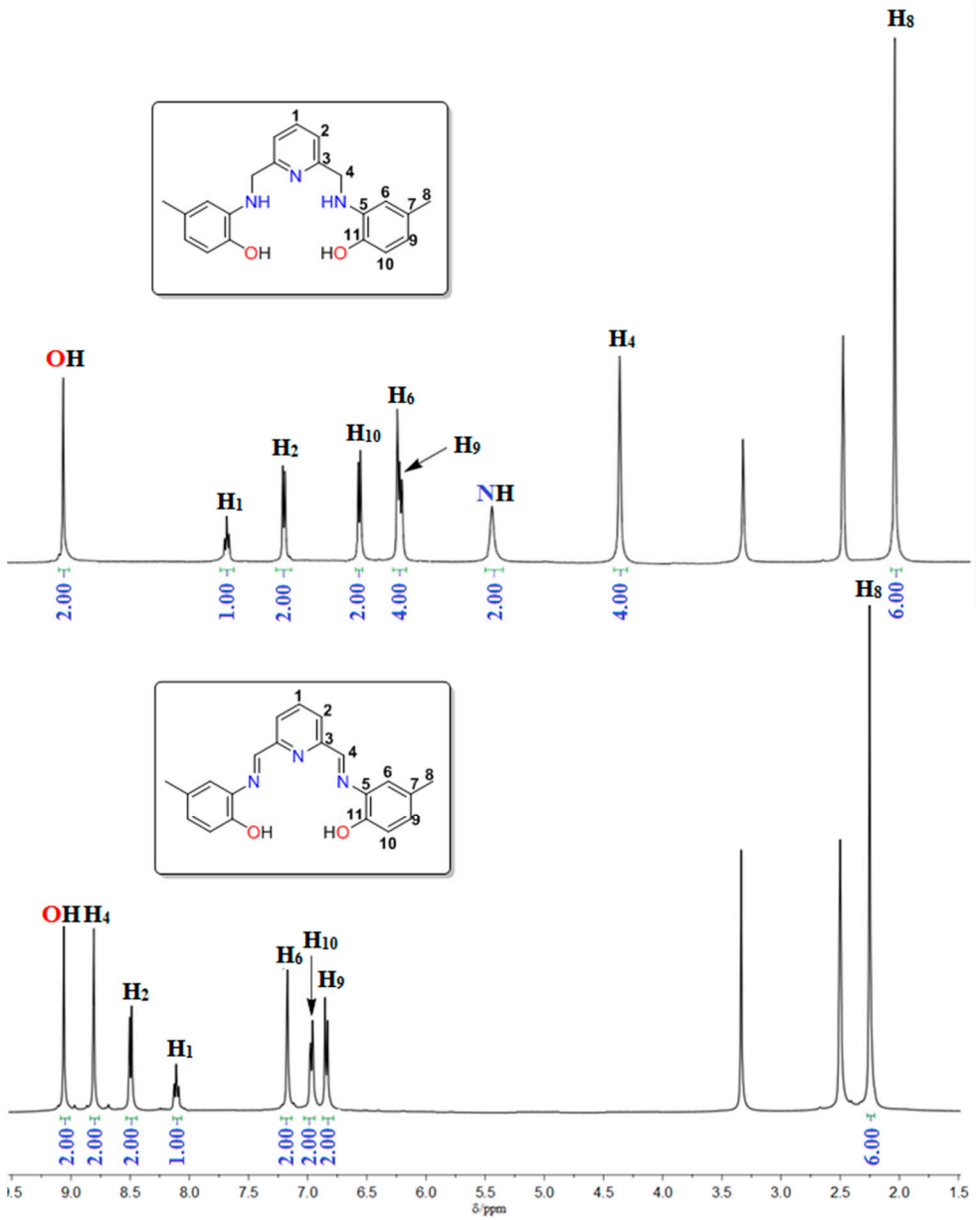


Figure 1. ^{1}H NMR spectra of H_2L^1 (down) and its reduced product H_4L^2 (up) in DMSO-d_6.

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Conflicts of Interest: The authors declare no conflict of interest.

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