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Nucleophilic and acid catalyst behavior of a protic ionic liquid in a molecular reaction media. Part 1

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This work presents a new approach using ionic liquids, namely ethylammonium nitrate. The aim was to analyze how the addition of small amounts of a protic ionic liquid to a pure molecular solvent, modifies the microscopic characteristics of a reaction medium. In order to achieve this, a kinetic study of nucleophilic aromatic substitution reactions between 1-fluoro-2,4-dinitrobenzene and 1-butylamine or piperidine was developed in this type of binary mixtures. We have detected nucleophiles competition originated by the presence of the ionic solvent at very low concentrations, observing the ethylamine derivative as the main substitution product. Moreover, in the light of previous results we have confirmed that the protic ionic liquid can act as both Brönsted acid and/or nucleophile. In this connection, we have selected the nucleophilic addition of amines to carbonyl compounds as reaction model. The protic ionic liquid in the presence of aromatic aldehydes substituted by electron-donating groups makes possible the formation of the corresponding imines with good yields. The results demonstrated that the influence of the protic ionic liquid is very important in the course of both reaction systems. Copyright © 2008 John Wiley & Sons, Ltd.

Keywords: protic ionic liquid; aromatic nucleophilic substitution; imine synthesis; ethylammonium nitrate; acid catalysts

INTRODUCTION

In the last few years designing solvents has become an important task for chemists, the challenge consisting in developing a "desired solvent" with particular properties for each application. In connection with this, ionic liquids (ILs) turn up as a new type of solvents suitable for developing physicochemical processes.[1–11]

IL technology has been successfully applied in several classic organic chemistry processes.[12,13] A great number of investigations are centered in characterizing ionic systems by measuring viscosity, boiling point, melting point, and additionally their microscopic properties. Other works were focused on modulating their physical and chemical properties through modifications in their anions or cations.[1–11] Recently, protic ionic liquids (PILs) have been extensively used in organic synthesis,[14–16] as catalysts,[17] and as self-assembly media.[18,19] Drummond and Greaves[20] published an extensive review on PILs, analyzing the goodness of these ILs as protic solvents in several reactions. Nevertheless, there are relatively few works based on kinetic studies. Even though some of these works analyze different reactive systems varying the nature of the IL, the data kinetic treatments result insufficient.[21–25]

In a recent work, we analyzed the microscopic features of binary solvent systems formed by a molecular solvent and an IL cosolvent (ethylammonium nitrate, EAN).[26] This study was focused on the identification of solvent mixtures with relevant solvating properties. We proposed three individual solvent mixtures, which were selected from the explored systems on the basis of their hydrogen-bonding ability, as "new liquids" suitable to provide a medium with particular microscopic solvent features. These results showed that it is possible to prepare strongly protic solvent mixtures of molecular solvent/ionic liquid type, as a new solvent.

The main purpose of this work is to study how a reaction medium is modified, at microscopic-molecular level, by adding small amounts of a PIL to a molecular solvent, in order to improve a reaction process. Hence, a specific aim is to evaluate if the presence of small amounts of a PIL could affect the course of a chemical reaction. In connection with this, our attention is drawn to analyze the possible participation of the ionic liquid both as acid catalyst and/or potential nucleophilie.

With these purposes in mind, we have selected two organic reactions as models: (i) the aromatic nucleophilic substitution reaction (S_NAr) between 1-fluoro-2,4-dinitrobenzene (FDNB) and 1-butylamine (BU) and piperidine (PIP), respectively, in order not only to highlight the possible nucleophiles competition but also to attempt the determination of the reaction rate constant for ethylamine (EA) as nucleophile; (ii) the addition of amines to substituted aromatic carbonyl compounds, in order to evaluate the behavior of EAN as dual acid catalyst and nucleophile.

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RESULTS AND DISCUSSION

The selected PIL was EAN. This IL was chosen taking into account that it is a protic solvent and it has been extensively used. The molecular solvent selected was acetonitrile (AcN). The selection was done on the basis of its microscopic properties. This solvent is dipolar relatively strong hydrogen bond acceptor (HBA), with weak hydrogen bond donor (HBD) properties ($E_T^N = 0.46$, $\pi^* = 0.75$, $\alpha = 0.19$, and $\beta = 0.40$). It is important to remark that the binary solvent system [AcN + EAN], which molecular-microscopic properties have been determined recently, exhibits synergism on the acidity property.[26]

Solvent effect on chemical processes

Aromatic nucleophilic substitution reaction (S_NAr). Kinetic determinations

A kinetic study of the S_NAr reactions between FDNB with BU and PIP was developed in order to analyze the influence of EAN in the reaction system. The reactions were carried out at 25°C, in AcN, and in the presence of low EAN concentrations (6.25×10^{-4} M up to 0.3 M). They were performed under *pseudo*-first order conditions, and at constant amine concentration (0.002 M).

The mechanism of S_NAr reactions has been widely studied. Since the first pioneering studies,[27] different contributions have been made towards the understanding of solvent effects on S_NAr reactions[28,29] showing how extensive and complex the interactions of the substrate and/or the intermediates with the solvent molecules can be. We have analyzed the solvent effects on the S_NAr reactions carried out in molecular solvent mixtures, and we interpreted them by means of multiparametric correlation analysis between empirical solvent parameters and the k_A second-order rate constants.[30–34] Further, the *n*-butylammonium nitrate salt effects on rate constants for the reaction of 2,4-dinitrochlorobenzene with *n*-butylamine were previously studied in chloroform and ethanol. The results indicated that the addition of this salt has almost no effect on the reaction rate.[35]

The spectra of reaction with the studied S_NAr reactions for PIP and BU are presented in Figs. 1 and 2, respectively. For the reaction with PIP, a decrease in the absorbance values of the substitution product corresponding to this amine ($\lambda_{max} =$ 382 nm), can be observed at low EAN concentrations (from 0 to 0.025 M). In contrast, the formation of a new species with λ_{max} at 350 nm was detected at EAN concentrations $\geq$0.05 M. The above result can be understood by taking into account that EAN can act as a Brönsted acid and it can establish an acid–base equilibrium with amines, making possible to predict nucleophiles competition.

For the reaction with BU, the above differences in the absorbance values with the increase of the EAN concentrations, cannot be observed because the wavelengths of absorption for both products are similar (Fig. 2). As it can be observed, the spectra for the products from both amines at high EAN concentrations are coincident. This result is the expected one.

In the light of these results, we carried out the corresponding reactions with both amines at preparative scale. The *N*-(2,4-dinitrophenyl) ethylamine substitution product was observed in both cases, which was confirmed by ^{1}H NMR, ^{13}C NMR, and mass spectroscopy.

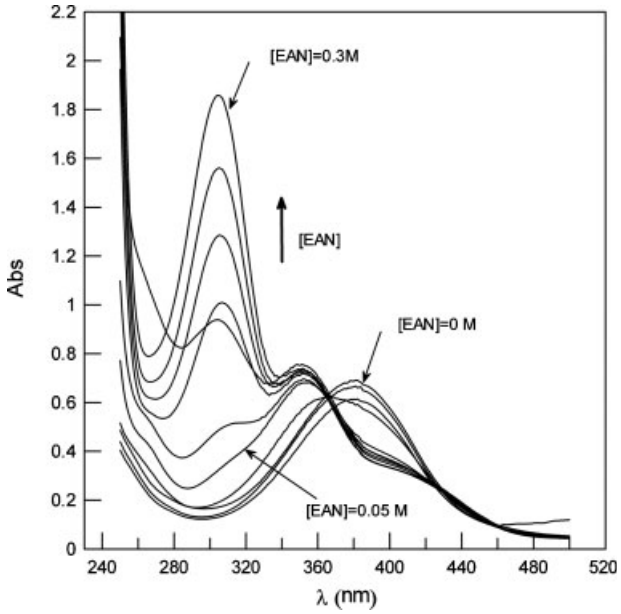


Figure 1. Spectra of S_NAr reaction between FDNB (5×10^{-5} M) and PIP (0.002 M) at variable concentrations of EAN (corresponding to Table 1)

Scheme 1 presents the equilibrium between EAN and PIP. The values corresponding to the equilibrium constants for PIP and EA in AcN were obtained from the literature.[36,37] This equilibrium modifies the reaction system and the quantitative yield of the product will depend on the equilibrium constant values proposed in Scheme 1.

In order to confirm the non-participation of the nitrate ion in this equilibrium, we selected the ethylammonium acetate (EAAc) as ionic solvent and applied the same methodology previously cited. In this experiment, only the *N*-(2,4-dinitrophenyl) ethylamine was observed as product.

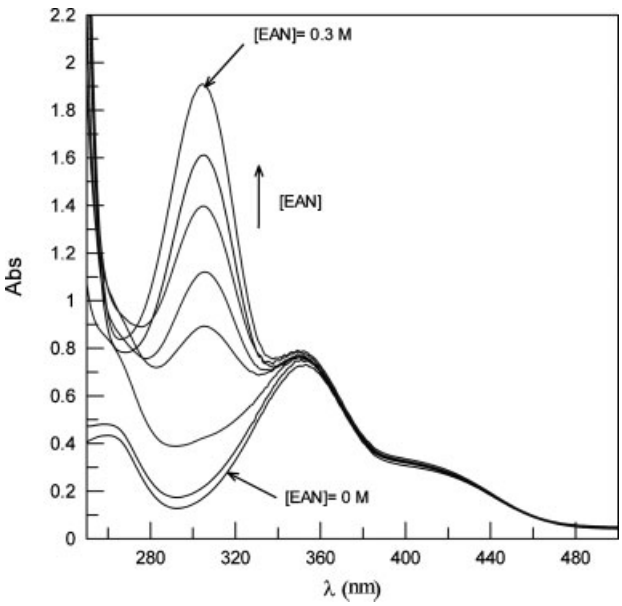
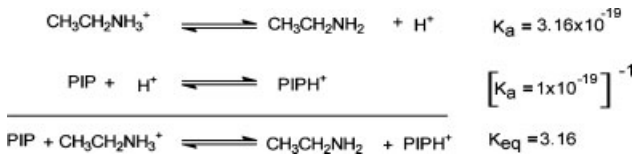


Figure 2. Spectra of S_NAr reaction between FDNB (5×10^{-5} M) and BU (0.002 M) at variable concentrations of EAN (corresponding to Table 1)



Scheme 1.

In this direction, we have calculated the amine effective molar concentration through Equation (1). Where x is the advance grade, C_{EAN} the EAN molar concentration, which is variable, and C_{Amine} is the constant amine (PIP or BU) molar concentration.

$$K_{eq} = \frac{X^2}{(C_{EAN} - x)(C_{Amine} - x)} \quad (1)$$

Table 1 shows the results obtained from Equation (1), varying the EAN concentration and at 0.002 M of BU or PIP. It can be deduced that, for concentrations of EAN $\geq$0.05 M, the effective concentrations of PIP^{eff} or BU^{eff} are similar to the substrate concentration. At this point, the EA concentration is close to 0.002 M, being this amine the only effective nucleophile. Moreover, under the present conditions, these reactions are not base catalyzed. We support this assumption based on the abundant evidence of strong hydrogen-bonding interactions between amines and protic solvents. Several contributions have revealed that the strong solvation of the amine molecule by protic solvent is responsible for the observed decrease in rate.[30]

Scheme 2 shows the reaction mechanism in all solvents when primary amines are the nucleophiles. In this type of S_NAr reactions base catalysis is not operative so the formation of the zwitterionic intermediate is rate limiting and the k_A second-order rate constants is simplified to $k_A = k_1$.

Pseudo-first order rate constants, k^T_{obs}, for the S_NAr reaction with EA as nucleophile in the presence of PIP (k^{PIP}_{obs}) or BU (k^{BU}_{obs}) are listed in Table 2. As it can be observed, at low concentrations of EAN, two processes are taking place simultaneously as consequence of the competition of both nucleophiles, EA with PIP or BU, respectively.

At this point and considering the protic characteristic of EAN, the *pseudo*-first order constant derives in Equation (2).

$$k^T_{obs} = k^{EA}_A[EA] + k^{Amine}_A[Amine] \quad (2)$$

At EA concentration of 0.002 M, the k^{PIP}_{obs} and k^{BU}_{obs} (s^{-1}) values are very similar, corresponding wholly to the reaction with EA. For this condition, the k^{EA}_A value is 2.62 ($l\,mol^{-1}\,s^{-1}$). It is interesting to note that, for the reaction with BU in AcN pure solvent and at the same concentration of amine, the k^{BU}_A value is approximately 7.54 ($l\,mol^{-1}\,s^{-1}$).[32]

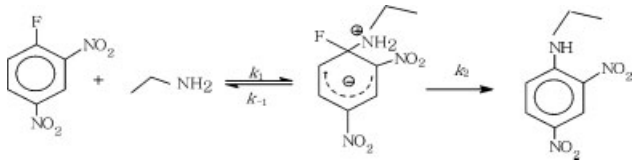
The three-dimensional space, plotted from the data corresponding to Tables 1 and 2, presents the k^{PIP}_{obs} and k^{BU}_{obs} values as a function of the concentrations of EA, BU, and PIP, respectively (Fig. 3). As it can be observed, the variation of the k^T_{obs} values corresponding to both amines (PIP and BU) in pure AcN (plane YZ) is due to the fact that the S_NAr reaction with PIP is base catalyzed while the corresponding to BU is not base catalyzed.[32] Additionally, the plot shows a decrease of the k^T_{obs} values until both reactive processes converge to a single value, the k^T_{obs} value corresponding to the reaction with the EA.

Table 1. Values of effective amine molar concentration obtained by Equation (1). The conditions are: 0.002 M of BU or PIP, concentration of variable EAN, and 5×10^{-5} M of FDNB

		[EAN] $\times 10^{-4}$ (M)								
$Amine_{eff}$	K_{eq}	6.25	12.5	50	250	500	1000	1500	2000	2500	3000
PIP	3.16	1.44×10^{-3}	1.03×10^{-3}	2.84×10^{-4}	5.21×10^{-5}	5.21×10^{-5}	2.57×10^{-5}	1.28×10^{-5}	6.35×10^{-6}	5.08×10^{-6}	4.23×10^{-6}
BU	0.72[a]	1.55×10^{-3}	1.29×10^{-3}	6.70×10^{-4}	1.95×10^{-5}	1.04×10^{-4}	5.37×10^{-4}	3.62×10^{-5}	2.73×10^{-6}	2.19×10^{-6}	1.83×10^{-6}
EA		5.5×10^{-4}	9.46×10^{-4}	1.69×10^{-3}	1.95×10^{-4}	1.97×10^{-3}	1.99×10^{-3}	1.99×10^{-3}	1.99×10^{-3}	1.99×10^{-3}	2.00×10^{-3}

[a] $k^{BuH^+}_A = 5.46 \times 10^{-19}$ [36,37].

Journal of Physical Organic Chemistry



Scheme 2.

Table 2. *Pseudo*-first order rate constants, k^T_{obs} (s^{-1}) for the S_NAr reaction between FDNB (5×10^{-5} M) and ethylamine in the presence of PIP (k^{PIP}_{obs}) and BU (k^{BU}_{obs}), measured at 25°C

	[EA]/10^3 M					
$k^T_{obs}(s^1)$	0.55	0.946	1.69	1.95	1.97	2
k^{PIP}_{obs}	0.1349	0.0848	0.0286	0.0112	0.01	0.0051
k^{BU}_{obs}	0.0127	0.0128	0.0099	0.0081	0.0087	0.0054

Addition reactions of carbonyl compound with a nitrogen nucleophile: Imine formation

While the employ of pure ILs as reaction media have been investigated in a great variety of chemical processes, reactions in which ILs take part as reagents were less investigated. Taking into account that EAN is a Brönsted acid and so, it can act as an acid catalyst generating at the same time a nucleophilic specie, it was interesting to explore the dual behavior of EAN in nucleophilic addition reactions to carbonyl compounds. An important number of chemical and biochemical processes are initiated by the addition of a nitrogen nucleophile to a carbonyl group. These processes have been the subject of extensive study.[38–40] Due to their diverse reactivity, imines are common substrates in a wide range of chemical transformations. However, the equilibrium in these reactions usually lies in favor of the free carbonyl compound and amine, in consequence, it is generally necessary to remove water and/or employ an excess amount of the reactants for satisfactory conversion to product. At weakly acidic pH, the addition of amines to carbonyl compounds can follow either a concerted or a stepwise mechanism. The predominant mechanism depends on the basicity of the amine and the mutual equilibrium affinity for adduct formation between the carbonyl compound and the amine. Recently, a series of solid-state reactions between gaseous amines and aldehydes to render imines have been reported.[41]

In this direction, we analyzed the behavior of 4-(dimethyl)-aminobenzaldehyde, 4-hidroxy benzaldehyde, benzaldehyde, and 4-nitrobenzaldehyde in the presence of EAN. The aromatic aldehydes were selected in view of the electronic effects of the *p*-substituents: electron-donating and electron-withdrawing groups. Benzaldehyde was chosen as reference. The reactions were carried out at preparative level and the formation of the expected products was confirmed. The experimental results showed that the electronic nature of the substituent groups in the aromatic ring played a key role in the quantitative conversion to imine product. The experimental yields followed the order: 4-(dimethyl)aminobenzaldehyde > 4-hidroxy benzaldehyde > benzaldehyde ≅ 4-nitrobenzaldehyde (97%, 64, 14, and 10%, respectively). For benzaldehyde and 4-nitrobenzaldehyde, the corresponding imines were obtained with poor yields. It is interesting to note that the above reactivity trend for the selected aldehydes followed an opposite direction to the one expected if reactions would be carried out under usual conditions. As a result, in the presence of EAN, the imine product formation is promoted by electron-donating substituents in the aromatic ring. In these cases, these substituent groups favor the acid–base equilibrium between EAN and aldehydes.

In order to get a deeper insight of the reaction feature, we analyzed the influence of small amounts of EAN (0.05 M ≤ [EAN] ≤ 0.3 M) to a solution of 4-(dimethyl)aminobenzaldehyde in pure AcN, following the methodology previously applied for S_NAr reactions. Figure 4 shows the following plots: (a) the

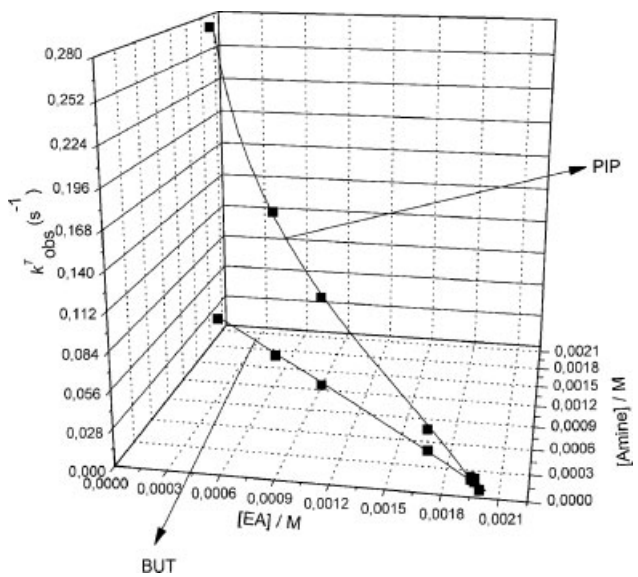


Figure 3. *Pseudo*-first order rate constants, k^T_{obs} for the S_NAr reaction in the presence of PIP (k^{PIP}_{obs}) and BU (k^{BU}_{obs}), at 25°C

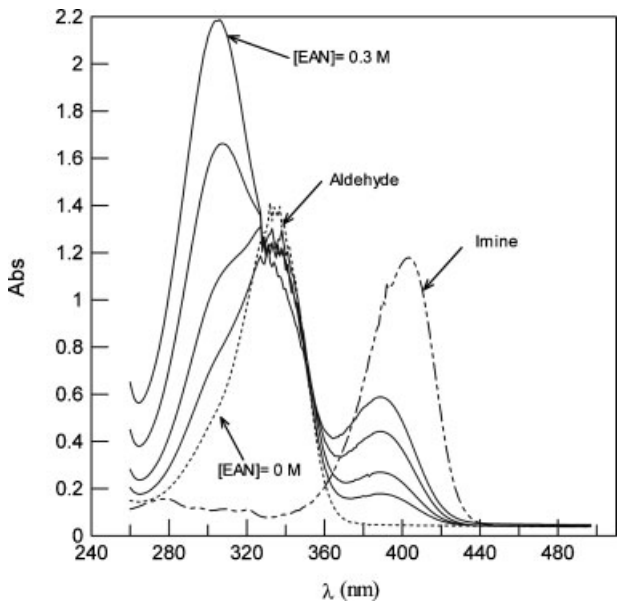
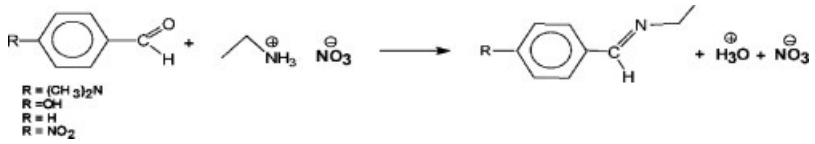


Figure 4. Spectra of 4-(dimethyl)aminobenzaldehyde (---) at 10^{-4} M in pure AcN; product of the reaction (—·---·—) and influence of EAN concentration (—)



Scheme 3.

spectrum corresponding to the aldehyde in pure AcN ([aldehyde] = 10^{-4} M) (dot line); (b) the spectra obtained as EAN is added to the aldehyde solution, at different concentrations of the IL (solid line), and (c) the spectrum corresponding to the pure imine product in AcN. (dash-dot line). From the analysis of the plots, it can be concluded that, as EAN concentration in the media is increased, a new species appears at λ_{max} near to 400 nm, corresponding to the formation of the imine product.

In the light of these results, a simplified reaction scheme is presented in Scheme 3.

CONCLUSIONS

Based on the overall results presented in this work, we can conclude the following:

- For the S_NAr reactions studied, it was possible to confirm that EAN can take part in an acid–base equilibrium with amines, even at very low concentrations ([EAN] $\geq$ 0.05 M), generating a nucleophile species which can participate in the reaction. The substitution product, *N*-(2,4-dinitrophenyl) ethylamine was obtained and therefore the k_A second-order rate constant for ethylamine could be determinated.
- For the nucleophilic addition reactions of amines to substituted aromatic aldehydes, where acid catalysis is required, the use of EAN seems to be convenient. The EAN can take part in an acid–base equilibrium with aromatic aldehydes substituted by electron-donating group. The imine products from the selected aldehyde could be obtained, confirming the dual behavior of EAN as Brönsted acid and potential nucleophile. The participation of these salts as potential nucleophiles in this type of process allows developing new synthesis routes.

The model reactions presented in this work constitute suitable examples of how the microscopic feature of a reactive system can be modified by adding aliquots of a protic ionic liquid to a molecular solvent. The acidity of the resultant binary mixtures plays a key role in acid-catalyzed reactions with the possibility of replacing traditional acid reagents. Moreover, the whole reactive system can be modulated with the aim of not only to promote acid-catalyzed reactions but also to generate nucleophilic species *in situ*. In connection with this, the design of ionic liquids can be formulated according to the particular requirements of a reactive system.

EXPERIMENTAL

Materials

All the amines, reagents and the solvents were prepared and/or purified as reported previously.[30–34] The EAN was prepared from a concentrated aqueous solution of ethylamine (70%) and nitric acid (70%).[12,13]

General methods

All the products were obtained stirring the reaction mixture over night at room temperature. Yields were determined by weight, purity by ^{1}H and ^{13}CNMR and mass spectroscopy. All NMR spectra were taken at a 500 MHZ Bruker Unity instrument in $CDCl_3$. These values were verified with those previously reported.[41,42]

The spectrophotometric measurements and kinetic experiments were preformed on PerkinElmer Lambda 40 UV/Vis spectrophotometer, equipped with a thermostatic cell holder.

The kinetics of the reactions was run under *pseudo*-first order conditions with the substrate (FDNB) as a minor component at 25°C.

***N*-(2,4-dinitrophenyl) ethylamine** was obtained by the reaction of FDNB, PIP, and EAN (1:10:20, respectively). The reaction was followed by TLC (Hexane/EtOAc, 10:1). The reaction mixture was cleaned up by chromatography silica gel column.

4-[(Ethylimino) methyl]-*N,N*-dimethylbenzenamine was obtained as yellow solids by the reaction of 4-(dimethyl)-aminobenzaldehyde and with EAN (1:7), measured pH value for this mixture was about 6. The solid obtained was washed repeatedly with diethyl ether (2 × 5 ml) to give a 97% yield.

4-[(ethylimino) methyl] phenol was obtained by the reaction of 4-(hydroxy)benzaldehyde and with EAN (1:8) measured pH value for this mixture was about 6. The imine was extracted from the reaction mixture with dichlomethane, and purified by chromatography silica gel column. This product was obtained with a 64% yield.

Acknowledgements

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