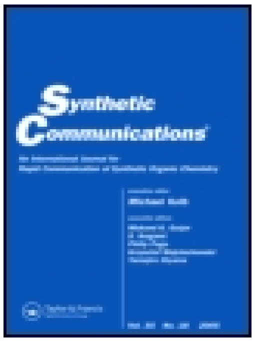

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# Green synthesis of *N*-(2-hydroxyethyl)anilines by the selective alkylation reaction in $H_2O$

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# Green synthesis of *N*-(2-hydroxyethyl)anilines by the selective alkylation reaction in $H_2O$

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**ABSTRACT**

Based on our previous work, a safer and more sustainable protocol for the synthesis of *N*-(2-Hydroxyethyl)anilines has been developed. The synthesis included the selective alkylation reaction of aniline with 2-chloroethanol in $H_2O$, eliminating the need for any catalysts and solvents during synthesis. Comparing with our previous work, the salient features of this methodology are eco-friendliness, economic benefit, and the ease of obtaining target compounds. The selective alkylation reaction in $H_2O$ is amenable to scale-up for the synthesis of *N*-(2-Hydroxyethyl)anilines.

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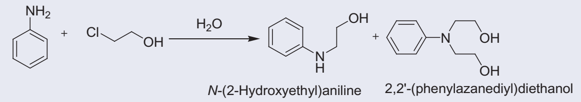
**KEYWORDS**
Alkylation reaction; $H_2O$; N-(2-Hydroxyethyl)anilines; selectivity

**GRAPHICAL ABSTRACT**



A green and efficient alternative way for the industrial synthesis of N-hydroxyethyl anilines was developed, eliminating the need for toxic and expensive catalysts and volatile organic solvents. The selectivity of *N*-hydroxyethyl anilines obtained in H2O are significantly increased in comparison to those traditional methods.

## Introduction

Replacement or elimination of toxic reagents or volatile organic solvents in chemical processes is one of the main goals of green chemistry. In order to achieve the goals, it is necessary to develop greener and more sustainable synthetic strategies.[1,2] Nitrogen-containing compounds are widely applied in organic synthesis and pharmaceutical chemistry.[3–5] *N*-(2-Hydroxyethyl)anilines, which are one kind of important nitrogen-containing compounds, continue to attract interest due to their importance as substances and intermediates of polymeric dye, organic pigments, hair dye, and other fine chemicals. The alkylation reaction of aniline has been shown to be a very common method for synthesis of the *N*-(2-Hydroxyethyl)anilines, however, the yield of objective compound was low because of the exist of the byproduct.[6,7] Numerous attempts to

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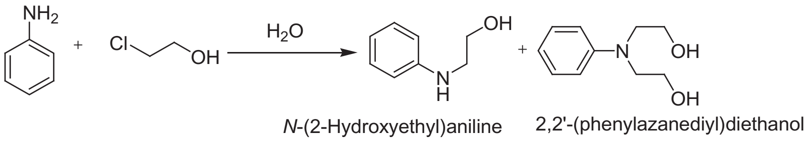
overcome these drawbacks, $Cu^0$ powder,[8] $Fe_3O_4$ magnetic nanoparticles-supported EDTA–copper(II) complex ($Fe_3O_4$-EDTA–Cu(II)),[9] a heterogeneous catalyst system composed of CuI and polystyrene-supportedN(-(4-(aminomethyl)naphthalen-1-yl)-N(-phenyl-1H-pyrrole-2-carbohydrazide(PSAP),[10] and ruthenium pincer complex(Ru-MACHO-BH)[11]have been used as catalysts, but these synthetic methods are limited due to their drawbacks, such as violent reaction conditions, toxic and expensive catalysts and hazardous results to environment. Therefore, green and controlled synthesis method for the preparation of the *N*-(2-Hydroxyethyl)anilines are still highly desirable. Although we recently reported a synthesis of such compounds through the reaction of aniline with 2-chloroethanol in ionic liquid [BMIM]$BF_4$ (1-butyl-3-methylimida zolium tetrafluoroborate),[12] the concept of green chemistry encouraged us to develop a safer and more sustainable synthetic method, meanwhile, achieve the goal of control of the reaction depth at the one-time alkylation, and avoidance of the generation of the two-time alkylation by-product.

$H_2O$ is not only environmentally friendly but also has many economic advantages.[13–16] In addition to being an environmentally benign reaction medium,[17–20] $H_2O$ has unique chemical and physical properties that allow it to promote many organic reactions, such as synthesis of navenone B,[21] synthesis of quinazoline-2,4(1H,3H)-diones,[22] synthesis of sulfonylated *N*-Heteroaromatics,[23] aerobic oxidation of sulfides to sulfoxides.[24] Inspired by these important breakthrough and following our continued pursuit of developing effective and environmentally benign synthetic strategies, herein we reported a safer and more sustainable method for the synthesis of *N*-(2-Hydroxyethyl)aniline by the controllable selective alkylation reaction in $H_2O$. Good conversion and high selectivity could be obtained, eliminating the need for any additional catalyst and volatile organic solvent.

## Results and discussion

To establish the feasibility of this strategy as well as to optimize the reaction conditions, the reaction of aniline with 2-chloroethanol was employed as the model (Scheme 1). Initially, the effects of the amount of $H_2O$ on the reaction were tested. Among the different amount of the $H_2O$ surveyed, 1 ml was found to be the most suitable amount for the model reaction (Table 1, Entries 1–4).

In order to maximize the product conversion and selectivity, we then tested the different reactant ratios (Table 1, Entries 2 and 5–8). Conversions would increase when the ratio (2-chloroethanol/aniline) increased from 0.5:1 to 3:1, while the selectivity of *N*-(2-Hydroxyethyl)aniline would decrease. The ideal ratio for the synthesis of *N*-(2-Hydroxyethyl)aniline was 1:1. Other reaction temperatures including 60 and 100 °C were screened (Table 1, Entries 9 and 10), but no better result was got. It seemed that



Scheme 1. The alkylation reaction of aniline with 2-chloroethanol in $H_2O$.

**Table 1.** Optimization of the reaction conditions for the model reaction[a].

| Entry | Amount of $H_2O$ (ml) | Ratio (2-chloroethanol/aniline) | Temperature (°C) | Time (h) | Conversion (%) | Selectivity (%) |
|---|---|---|---|---|---|---|
| 1 | 2 | 1:1 | 80 | 6 | 70 | 90 |
| 2 | 1 | 1:1 | 80 | 6 | 80 | 95 |
| 3 | 0.5 | 1:1 | 80 | 6 | 65 | 90 |
| 4 | 0.1 | 1:1 | 80 | 6 | 50 | 90 |
| 5 | 1 | 3:1 | 80 | 6 | 95 | 55 |
| 6 | 1 | 2:1 | 80 | 6 | 91 | 75 |
| 7 | 1 | 1.5:1 | 80 | 6 | 87 | 85 |
| 8 | 1 | 0.5:1 | 80 | 6 | 72 | 95 |
| 9 | 1 | 1:1 | 60 | 6 | 30 | 95 |
| 10 | 1 | 1:1 | 100 | 6 | 92 | 76 |
| 11 | 1 | 1:1 | 80 | 1 | 15 | 100 |
| 12 | 1 | 1:1 | 80 | 2 | 25 | 100 |
| 13 | 1 | 1:1 | 80 | 3 | 40 | 97 |
| 14 | 1 | 1:1 | 80 | 8 | 85 | 95 |
| 15 | 1 | 1:1 | 80 | 10 | 81 | 87 |
| 16 | 1 | 1:1 | 80 | 12 | 77 | 82 |

[a]Conversion and selectivity determined by HPLC.

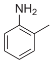
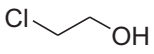
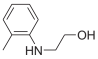
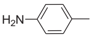
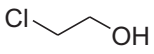
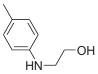
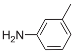
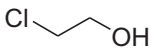
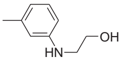
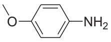
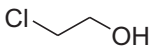
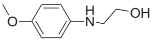
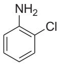
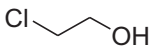
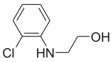
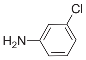
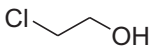
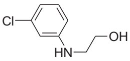
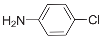
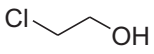
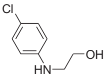
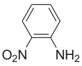
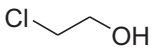
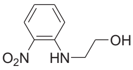
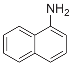
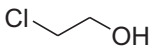
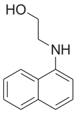
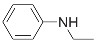
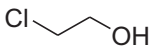
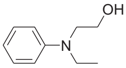
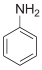
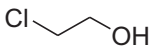
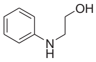
high temperature would lead the selectivity of *N*-(2-Hydroxyethyl)aniline decrease, while low temperature would lead the conversion of *N*-(2-Hydroxyethyl)aniline decrease. It should be noted that time has an important impact on the reaction. The conversion increased as time prolonged. The best result was obtained when the reaction was carried out for 8 h. Continuing to prolong the reaction time could not increase the conversion (Table 1, Entries 2 and 11–16). Overall, the best reaction conditions for synthesizing *N*-(2-Hydroxyethyl)aniline are achieved by employing the reaction of aniline with 2-chloroethanol in $H_2O$ (1 ml) at 80 °C for 8 h.

To explore the scope of the model reaction, we firstly substituted 2-methylaniline, 3-methylaniline, 4-methylaniline, and 4-methoxybenzenamine under optimal reaction conditions. The reactions of 3-methylaniline, 4-methylaniline and 4-methoxybenzenamine with 2-chloroethanol in $H_2O$ proceeded smoothly and the desired *N*-(2-Hydroxyethyl)anilines were obtained with good conversion and high selectivity (Table 2, Entries 2–4). But the reactions conversion of 2-methylaniline with 2-chloroethanol was lower under the same reaction conditions because of the steric effect of substituent (Table 2, Entry 1).

To further explore the scope of the procedure reported in Table 1, the methodology was evaluated by using 2-chloroaniline, 3-chloroaniline, 4-chloroaniline, and 2-nitrobenzenamine under the same conditions. Although these reactions could proceed smoothly, the conversions were lower due to the electrophilic effect of substituent (Table 2, Entries 5–8). More complicated substrates, such as *N*-ethylbenzenamine and α-naphthyl amine also could undergo the selective alkylation reaction and give the desired *N*-(2-Hydroxyethyl)anilines (Table 2, Entries 9 and10).

A large scale reaction was attempted with 1 mol of aniline and 1 mol of 2-chloroethanol in $H_2O$. As shown in Table 2, high conversion and selectivity were obtained; this result revealed this protocol was practical even for large scale reaction (Table 2, Entry 11).

**Table 2.** The alkylation reaction in ionic liquid[a].

| Entry | Substrate1 | Substrate2 | Product | Conversion(%)[b] | Selectivity(%)[b] |
|---|---|---|---|---|---|
| 1 |  |  |  | 62 | 95 |
| 2 |  |  |  | 75 | 95 |
| 3 |  |  |  | 78 | 95 |
| 4 |  |  |  | 70 | 95 |
| 5 |  |  |  | 50 | 95 |
| 6 |  |  |  | 58 | 95 |
| 7 |  |  |  | 55 | 95 |
| 8 |  |  |  | 52 | 95 |
| 9 |  |  |  | 60 | 95 |
| 10 |  |  |  | 50 | 95 |
| 11 |  |  |  | 80 | 95[c] |

[a] Reaction conditions: 1 mmol substrate 1, 1 mmol substrate 2, 1 ml $H_2O$, 80 °C, 8 h; [b] Conversion and selectivity determined by HPLC; [c] Reaction conditions: 1 mol substrate 1, 1 mol substrate 2, 3 ml $H_2O$, 80 °C, 8 h.

## Conclusion

In this study, we developed an efficient, green, and sustainable approach for the synthesis of *N*-(2-Hydroxyethyl)anilines. This synthetic method involves a selective alkylation reaction of aniline with 2-chloroethanol under a catalyst-free condition in $H_2O$. Comparing with our previous work, advantages of this method include a significant reduction in the amount of toxic 2-chloroethanol needed, increase of selectivity of objective product, eliminating the need for any additional catalysts and the ease of obtaining target compounds, thus it can provide a better alternative way for the industry synthesis of *N*-(2-Hydroxyethyl)anilines.

# Experimental

## Materials and general methods

$^1H$ spectra and $^{13}C$ NMR were recorded in $CDCl_3$ with a Bruker AVANCE DMX 500 spectrometer at 400 and 100 MHz, respectively. Chemical shifts are reported in ppm ($\delta$), relative to tetramethylsilane (TMS) as the internal standard. IR spectra were measured with a Nicolet Nexus FTIR 6700 spectrophotometer. All reactions were carried out with efficient stirring in a round bottom flask, unless otherwise stated, and monitored by TLC. All chemicals were obtained from commercial suppliers and were used without further purification.

## Typical procedure for alkylation of hydroxybenzenes

To a mixture of aniline (1 mmol, 93 mg) in $H_2O$ (1 ml), 2-chloroethanol (1 mmol, 80 mg) was added. After addition, the reaction was stirred for 8 h at 80 °C. The reaction was monitored by TLC. After the completion of reaction, reaction mixture was extracted with ethyl acetate. The solvent was evaporated and the product was isolated by column chromatography. Pale yellow oil; IR (neat) $\nu$: 3397, 3052, 3025, 2944, 2879, 1605, 1507, 1461, 1434, 1325, 1261, 1182, 1124, 1058, 995, 914, 898, 873, 754, 692, 504 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$): $\delta = 2.12$(br. s, 1H), 3.27(t, $J = 4$Hz, 2H), 3.79 (t, $J = 4$Hz, 2H), 3.96–3.98 (br, 1H), 6.63–6.66 (m, 2H), 6.72–6.76 (m, 1H), 7.16–7.20 (m, 2H). $^{13}C$ NMR (100 MHz,$CDCl_3$): $\delta = 46.1$, 61.2, 113.2, 117.9, 129.3, 148.1. HRMS: calcd for $C_8H_{11}NO$ ($M^+$) 137.084, found 137.084.

Full experimental detail, IR, $^1H$ spectra, $^{13}C$ NMR, HRMS. This material can be found *via* the "Supplementary Content" section of this article's webpage.

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