Research article

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The green synthesis of *N*-hydroxyethyl-substituted 1,2,3,4-tetrahydroquinolines with acidic ionic liquid as catalyst

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Abstract: *N*-Hydroxyethyl-substituted 1,2,3,4-tetrahydroquinolines were synthesized by the reaction of 2-(phenylamino)ethanol with unsaturated ketone catalyzed by acidic ionic liquid *N*-methyl-2-pyrrolidonium dihydrogen phosphate [NMPH]H₂PO₄, obviating the need for toxic and expensive catalysts. The acidic ionic liquid not only showed superior performance over H₃PO₄ but also was stable and could be reused at least five times with a slight loss of activity. It provided a straightforward and efficient protocol for the synthesis of 1,2,3,4-tetrahydroquinoline derivatives.

Keywords: *N*-hydroxyethyl substituted 1,2,3,4-tetrahydroquinoline, ionic liquid, 2-(phenylamino)ethanol, unsaturated ketone

1 Introduction

1,2,3,4-Tetrahydroquinoline derivatives have attracted continuous attention due to their important physiological and biological properties [1,2]. A great deal of protocols for the preparation of 1,2,3,4-tetrahydroquinoline derivatives have been developed. Diels–Alder reaction catalyzed by Lewis acids (e.g., Yb(OTf)₃) is the most useful protocol for the synthesis of 1,2,3,4-tetrahydroquinoline derivatives [3–5]. In addition to the classical method, Khan et al. found

that 1,2,3,4-tetrahydroquinoline derivatives could also be synthesized by the Povarov reaction using [Fe₂(SO₄)₃·xH₂O as a catalyst [6]. Li et al. developed a domino reaction of aromatic amines, cyclic enol ethers and hemiacetals catalyzed by InCl₃ for the synthesis of 1,2,3,4-tetrahydroquinoline derivatives [7]. However, these metal-based catalysts own their drawbacks such as toxicity, corrosiveness and expensive cost. Recently, Chen and Li reported that the 1,2,3,4-tetrahydroquinoline derivatives could be prepared using acidic cation-exchange resin as a catalyst [8], and Wang and coworkers found that 2-methyl-4-anilino-1,2,3,4-tetrahydroquinoline derivatives could be synthesized by the tandem cyclization between anilines and *N*-vinyl amides with radical cation salt as a catalyst [9]. However, all the products obtained by the methods were a mixture of *cis*- and *trans*-isomers. Therefore, it is very necessary to develop effective and economical methodology for the synthesis of 1,2,3,4-tetrahydroquinoline derivatives.

Ionic liquids have emerged as green catalysts and reaction media in recent years [10–13]. They have been applied in many reactions such as the synthesis of methyl caprylate [14], extraction of Luteolin from Peanut Shells [15] and three-component cyclic condensation of aromatic aldehydes, malononitrile and dimesone [16]. To the best of our knowledge, relevant reports about the synthesis of 1,2,3,4-tetrahydroquinoline derivatives with ionic liquids have been demonstrated by several examples. Zhou et al. reported the regioselective reduction of quinolines in ionic liquid [BMIM]PF₆ with Ru/N-(*p*-toluenesulfonyl)-1,2-diphenylethylenediamine as a catalyst [17]. Li et al. found that quinolines could also be regioselectively reduced in ionic liquid [Rmim][*p*-CH₃C₆H₄SO₃] using [RuCl₂(TPPTS)₂] as a catalyst [18]. However, the synthesis of 1,2,3,4-tetrahydroquinoline derivatives catalyzed by ionic liquid still is an intriguing challenge. Herein, we, for the first time, present a straightforward and efficient protocol for the synthesis of novel 1,2,3,4-tetrahydroquinoline derivatives using acidic ionic liquid as a catalyst.

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2 Materials and methods

2.1 General

^1H and ^{13}C NMR spectra were recorded in CDCl_3 with a Bruker AVANCE DMX 500 spectrometer at 100 and 400 MHz, respectively. Chemical shifts are reported in ppm (δ), relative to tetramethylsilane (TMS) as the internal standard. IR spectra were measured with a Nicolet Nexus FTIR 670 spectrophotometer. All reactions were carried out with efficient stirring in a round bottom flask at 37°C , unless otherwise stated, and monitored by TLC. MVK was distilled before use, and other chemicals were obtained from commercial suppliers and were used without further purification. The acidic ionic liquid $[\text{NMPH}]\text{H}_2\text{PO}_4$ was prepared using an earlier reported procedure [19].

2.2 Typical procedure for the synthesis of 2-(phenylamino)ethanol

To a mixture of aniline (0.1 mol, 9.3 g) and 2-chloroethanol (0.05 mol, 4 g), Et_3N (15 mL) was added. Then, the mixture was heated to reflux and stirred for 8 h. After the completion of reaction, the mixture was neutralized with the saturated NaHCO_3 solution, extracted with ethyl acetate and dried over anhydrous sodium sulfate. Then, the solvent was evaporated, and the product was isolated by column chromatography. A yellow oil; ^1H NMR (400 MHz, CDCl_3): δ = 3.27 (t, J = 4 Hz, 2H), 3.79 (t, J = 4 Hz, 2H), 6.63–6.76 (m, 3H), 7.16–7.20 (m, 2H); ^{13}C NMR (100 MHz, CDCl_3): δ = 46.1, 61.0, 113.3, 117.9, 129.3, 148.0.

2.3 Typical procedure for the synthesis of *N*-hydroxyethyl substituted 1,2,3,4-tetrahydroquinolines

To a mixture of 2-(phenylamino)ethanol (0.5 mmol, 68 mg) in $[\text{NMPH}]\text{H}_2\text{PO}_4$ (0.5 mmol), MVK (0.5 mmol, 35 mg) and CH_2Cl_2 (1 mL) were added. After addition, the mixture reacted for 12 h at 37°C . The reaction was monitored by TLC [solvent system–PE:EA (1:1)]. After the completion of reaction, the reaction mixture was extracted with CH_2Cl_2 for several times. The solvent was evaporated, and the product was isolated by column chromatography. Yellow oil; IR (neat): 3384, 2956, 2929, 2868, 1602, 1503, 1338, 1287, 1047 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3): δ = 1.29 (d, J = 7.2 Hz, 3H), 1.69–1.72 (m, 1H), 2.00–2.02 (m, 1H),

2.87–2.94 (m, 1H), 3.36–3.45 (m, 2H), 3.46–3.48 (m, 2H), 3.83 (t, J = 5.6 Hz, 2H), 6.63–6.70 (m, 2H), 7.06 (t, J = 7.6 Hz, 2H); ^{13}C NMR (100 MHz, CDCl_3): δ = 22.5, 29.6, 30.8, 46.9, 54.1, 59.7, 111.3, 116.4, 126.9, 127.9, 128.2, 145.0; HRMS: calculated for $\text{C}_{12}\text{H}_{17}\text{NO}$ (M^+) 191.131, found 191.131.

3 Results and discussion

3.1 Effects of ionic liquids

Initial studies were carried out using the reaction of 2-(phenylamino)ethanol with methyl vinyl ketone (MVK) as a model reaction. Table 1 presents the effect of different ionic liquids on the reaction. In a first set of experiments, ionic liquids of the general $[\text{cation}][\text{BF}_4]$ and $[\text{BMIM}]\text{PF}_6$ were tested as catalysts and a reaction medium (Table 1, entries 1–3). The results showed that the 1,2,3,4-tetrahydroquinoline derivative could not be obtained in these ionic liquids. To obtain 1,2,3,4-tetrahydroquinoline derivative, some acidic ionic liquids were used to catalyze the reaction (Table 1, entries 4–7). Although the acidic ionic liquids could promote the reaction and produce the corresponding 1,2,3,4-tetrahydroquinoline derivative, the best yield was only 30% when ionic liquid $[\text{NMPH}]\text{H}_2\text{PO}_4$ was used as a catalyst (Table 1, entry 7).

Although better result could be obtained in ionic liquid $[\text{NMPH}]\text{H}_2\text{PO}_4$, the result still could not meet our needs. To obtain higher yield, the reaction of 2-(phenylamino)ethanol with MVK was carried out in the ionic liquid/solvent two phase system. It was found that the 1,2,3,4-tetrahydroquinoline derivative could not be produced in $[\text{NMPH}]\text{H}_2\text{PO}_4/\text{DMSO}$ and $[\text{NMPH}]\text{H}_2\text{PO}_4/\text{DMF}$.

Table 1: The effect of solvent on the reaction

Entry	Ionic liquid	Yield ^b (%)
1	$[\text{BMIM}]\text{BF}_4$	0 ^a
2	$[\text{BMIM}]\text{PF}_6$	0 ^a
3	$[\text{OMIM}]\text{BF}_4$	0 ^a
4	$[\text{HMIM}]\text{HSO}_4$	12 ^a
5	$[\text{BMIM}]\text{HSO}_4$	18 ^a
6	$[\text{NMPH}]\text{HSO}_4$	19 ^a
7	$[\text{NMPH}]\text{H}_2\text{PO}_4$	30 ^a

^aReaction conditions: 0.5 mmol MVK, 0.5 mmol 2-(phenylamino)ethanol, 0.5 mmol ionic liquid, 37°C , 24 h. ^bYield determined by HPLC.

(Table 2, entries 1 and 2), and the reactions were less efficient in $[\text{NMPH}]\text{H}_2\text{PO}_4/\text{THF}$ and other ionic liquid/solvent systems (Table 2, entries 3–8). To our delight, a promising result (89% yield) was achieved when the $[\text{NMPH}]\text{H}_2\text{PO}_4/\text{CH}_2\text{Cl}_2$ system was employed (Table 2, entry 10). The good result could be due to the extraction ability of CH_2Cl_2 for the product.

A control experiment was designed to demonstrate that the reaction was an acidic ionic liquid-catalyzed process. In the absence of the acidic ionic liquid, the reaction of 2-(phenylamino)ethanol with MVK could not produce the 1,2,3,4-tetrahydroquinoline derivative even in CH_2Cl_2 (Table 2, entry 11). Moreover, the reaction with H_3PO_4 as a catalyst was also carried out, but the yield was

significantly lower even under the same reaction conditions (Table 1, entry 12).

3.2 Effects of time

The effect of the reaction time was presented in Table 3. The yield increased as time prolonged, and the best result was obtained when the reaction was carried out for 12 h. Longer reaction time could not increase the yield.

3.3 Effects of different substrates

With the optimal reaction conditions in hands, we then examined the scope and the limitation of this strategy for other structurally diverse substrates, and the results were summarized in Table 3. The reaction of 2-(phenylamino)ethanol with MVK produced 1-(2-hydroxyl-ethyl)-4-methyl-1,2,3,4-tetrahydroquinoline with high yield (Table 4, entry 1). A series of substituted 2-(phenylamino)ethanols could also react with MVK to produce the corresponding 1,2,3,4-tetrahydroquinoline derivatives (Table 4, entries 2 and 3), albeit in lower yield. 2-(3-Chlorophenylamino)ethanol reacted with sterically hindered unsaturated ketone, such as pent-1-en-3-one, and produced the 1-(2-hydroxyl-ethyl)-7-chloro-4-ethyl-1,2,3,4-tetrahydroquinoline with lower yield (Table 4, entry 4).

2-(2-Nitrophenylamino)ethanol was examined under the same reaction conditions, but the corresponding 1,2,3,4-tetrahydroquinoline derivatives could not be obtained (Table 4, entries 5 and 6), and it could be due to the steric effect of the substituent group. Aniline and *N*-ethylbenzenamine were also examined under the same reaction conditions, but the corresponding 1,2,3,4-tetrahydroquinoline derivatives could not be obtained (Table 4, entries 7 and 8). The results showed that the existence of hydroxyl in the 2-(phenylamino)ethanol moiety could have an important effect on the synthesis of 1,2,3,4-tetrahydroquinoline derivatives.

Table 2: The effect of ionic liquid/solvent two phase system on the reaction

Entry	Ionic liquid/solvent two-phase system	Yield ^b (%)
1	$[\text{NMPH}]\text{H}_2\text{PO}_4/\text{DMSO}$	0 ^a
2	$[\text{NMPH}]\text{H}_2\text{PO}_4/\text{DMF}$	0 ^a
3	$[\text{NMPH}]\text{H}_2\text{PO}_4/\text{THF}$	19 ^a
4	$[\text{NMPH}]\text{H}_2\text{PO}_4/\text{CH}_3\text{CN}$	27 ^a
5	$[\text{NMPH}]\text{H}_2\text{PO}_4/\text{Et}_2\text{O}$	25 ^a
6	$[\text{NMPH}]\text{H}_2\text{PO}_4/\text{acetone}$	31 ^a
7	$[\text{NMPH}]\text{H}_2\text{PO}_4/1,4\text{-dioxane}$	43 ^a
8	$[\text{NMPH}]\text{H}_2\text{PO}_4/\text{toluene}$	35 ^a
9	$[\text{NMPH}]\text{H}_2\text{PO}_4/\text{CHCl}_3$	72 ^a
10	$[\text{NMPH}]\text{H}_2\text{PO}_4/\text{CH}_2\text{Cl}_2$	89 ^a
11	CH_2Cl_2	0 ^c
12	$\text{H}_3\text{PO}_4/\text{CH}_2\text{Cl}_2$	40 ^d

^aReaction conditions: 0.5 mmol MVK, 0.5 mmol 2-(phenylamino)ethanol, 1 mL solvent, 0.5 mmol ionic liquid $[\text{NMPH}]\text{H}_2\text{PO}_4$, 37°C, 24 h. ^bYield determined by HPLC. ^cReaction conditions: 0.5 mmol MVK, 0.5 mmol 2-(phenylamino)ethanol, 1 mL solvent, 37°C, 24 h.

^dReaction conditions: 0.5 mmol MVK, 0.5 mmol 2-(phenylamino)ethanol, 1 mL solvent, 0.5 mmol H_3PO_4 , 37°C, 24 h.

Table 3: The effect of time on the reactions^a

Entry	Time (h)	Yield ^b (%)
1	1	15
2	3	29
3	5	51
4	8	78
5	12	89
6	24	89

^aReaction conditions: 0.5 mmol MVK, 0.5 mmol 2-(phenylamino)ethanol, 1 mL CH_2Cl_2 , 1 mmol ionic liquid $[\text{NMPH}]\text{H}_2\text{PO}_4$, 37°C.

^bYield determined by HPLC.

3.4 Reuse of the ionic liquid

In order to test the reuseability of $[\text{NMPH}]\text{H}_2\text{PO}_4$, the reaction of 2-(phenylamino)ethanol with MVK was repeated five times under the same reactions, and the results were presented in Table 5. The results showed that the acidic ionic liquid $[\text{NMPH}]\text{H}_2\text{PO}_4$ was stable and could be reused at least 5 times with a slight loss of activity. Graph: use this for the first paragraph in a section, or to continue after an extract.

Table 4: The synthesis of 1,2,3,4-tetrahydroquinoline derivatives with acidic ionic liquid as catalyst^a

Entry	Substrate 1	Substrate 2	Product	Yield ^b (%)
1			3a	89
2			3b	85
3			3c	80
4			3d	65
5			3e	78
6			3f	73
7			3g	85
8			3h	78

^a Reaction conditions: 0.5 mmol substrate 1, 0.5 mmol substrate 2, 0.5 mmol acidic ionic liquid [NMPH]H₂PO₄, 1 mL CH₂Cl₂, 37°C, 12 h.^b Yield determined by HPLC.**Table 5:** The recycling of [NMPH]H₂PO₄^a

Run	Yield ^b
1	89
2	89
3	89
4	87
5	87

^a Reaction conditions: 0.5 mmol MVK, 0.5 mmol 2-(phenylamino) ethanol, 1 mmol ionic liquid [NMPH]H₂PO₄, 1 mL CH₂Cl₂, 37°C, 12 h. ^b Yield determined by HPLC.

4 Conclusions

Novel *N*-hydroxyethyl-substituted 1,2,3,4-tetrahydroquinolines were synthesized with the acidic ionic liquid as a catalyst for the first time. The acidic ionic liquid showed superior performance over H₃PO₄ under the same condition, and the acidic ionic liquid could be reused for at least five times with the consistent activity. The developed protocol provided a simple and efficient alternative for the synthesis of tetrahydroquinoline derivatives.

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