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# Application of 2-methylpyridinum *p*-toluenesulfonate ([2-MPy][*p*-TSA]) as an efficient catalyst for the one-pot synthesis of hexahydroquinoline-3-carboxamides

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**Abstract**

2-Methylpyridinum *p*-toluenesulfonate ([2-MPy][*p*-TSA]) as a novel room temperature ionic liquid was synthesized and evaluated as a recoverable catalyst for the one-pot synthesis of hexahydroquinoline-3-carboxamide derivatives by four-component reaction of arylaldehydes, dimedone, acetoacetanilide and ammonium acetate in high to excellent yield in ethanol at 50 $^{o}$C. The [2-MPy][*p*-TSA] catalyst was characterized via FT-IR, $^{1}$H NMR and $^{13}$C NMR spectroscopy. An environmentally benign procedure, four-component in one pot reaction, high yields and simple preparation of the catalyst are some advantages of this work.

***Keywords****: 2-Methylpyridinum p-toluenesulfonate, Ionic liquid, One-pot reaction, Hexahydroquinoline-3-carboxamide.*

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## Introduction

Nitrogen-containing heterocycles have attracted attention in modern organic synthesis due to they play a key role in the fields of natural products and medicinal chemistry. Quinolines including 1,4-dihydropyridines (1,4-DHPs) nucleus show a variety of pharmacological properties such as, antiangin [1], anti-inflammatory activity [2], antitumor [3], antitubercular activity [4], analgesic activity [5] and antithrombotic [6]. Furthermore, 1,4-DHPs exhibits several medicinal applications which include neuroprotectant [7] and cerebral antischemic activity in the treatment of Alzheimer's disease [8]. Acetoacetanilide is an important building block in the synthesis of heterocyclic compounds with antimicrobial activity [9,10] and analgesic activity [11]. The synthesis of hexahydroquinoline-3-carboxamides reported via the four component reaction of acetoacetanilide, aromatic aldehyde, and dimedone and ammonium acetate in the acidic conditions [12] and in high temperature at 150-160 °C [13]. However, some drawbacks still exist, such as, hard reaction condition, moderate yields, and non-recyclable catalyst. Ionic liquids have attracted attention as green media in organic synthesis, due to their unique properties such as good solvating capability, wide liquid range, negligible vapor pressure, and ease of recycling. Moreover, their hydrophobicity/hydrophilicity can be tuned by appropriate modification of the cation or anion, which has earned them the sobriquet of ''designer solvents'' [14].

## Experimental

*General*

All chemicals were purchased from the Merck chemical company. Melting points were recorded by an electrothermal 9100 apparatus. The NMR spectra were recorded in DMSO-$d_6$ with TMS as an internal standard on a Bruker Avance DRX 400 MHz spectrometer. FT-IR spectra were provided with potassium bromide pellets in the range 400–4000 $cm^{-1}$ with an SP-1100, Shimadzu instrument. Elemental analyses were done on a Carlo-Erba EA1110CNNO-S analyzer and agreed with the calculated values. Products were separated by simple filtration and identified by FT-IR, $^1$H NMR, $^{13}$C NMR spectra and elemental analysis.

*Preparation of 2-methylpyridinum p-toluenesulfonate [2-MPy][p-TSA]*

To 2-methyl pyridine (10 mmol), *p*-toluenesulfonic acid (10 mmol) was added and the mixture stirred for 1h at room temperature. The resulting liquid was separated to give 2-methylpyridinum *p*-toluenesulfonate [2-MPy][*p*-TSA] as a pale yellow ionic liquid. Spectral data: FT-IR (KBr): $\bar{\nu}$ = 3498 (N-H stretch), 3062 (aromatic C-H stretch), 2925 (aliphatic C-H stretch), 1635 (C=N stretch), 1541 (aromatic C=C stretch), 1203 and 1122 ($SO_2$ asymmetric and symmetric stretch) $cm^{-1}$; $^1$H NMR (400 MHz, DMSO-$d_6$):$\delta$ =8.70 (d, *J* = 5.6 Hz, 1H), 8.40 (td, *J* = 8, 1.6 Hz, 1H), 7.84 (t, *J* = 7.2

Hz, 2H),7.60 (d, *J* = 8 Hz, 2H), 7.10 (d, *J* = 8 Hz, 2H), 6.60 (br, 1H), 2.66 (s, 3H), 2.20 (s, 3H) ppm; $^{13}$C NMR (100 MHz, DMSO-$d_6$):$\delta$ = 153.7, 146.7, 144.2, 141.2, 139.4, 128.9, 128.2, 125.9, 124.6, 21.3, 19.5 ppm.

*General procedure for the synthesis of hexahydroquinoline-3-carboxamides (**5a-l**)*

A mixture of aromatic aldehyde (1mmol), dimedone (1mmol, 0.14 g), acetoacetanilide (1 mmol, 0.177 g) and ammonium acetate (1.2 mmol, 0.092 g) in the presence of [2-MPy][*p*-TSA] (0.053 g, 0.2 mmol) was stirred in ethanol (3 mL) at 50 °C for the appropriate time, as shown in Table 1. Completion of the reaction was indicated by TLC monitoring. The crude solid residue was recrystallized from ethanol to afford pure crystals of the proper hexahydroquinoline-3-carboxamide in 88-96% yields. The products were characterized by FT-IR, $^1$H NMR,$^{13}$C NMR, elemental analysis and by comparison with authentic samples reported in the literature.

*Spectral data of the some products*

*4-(2-Chlorophenyl)-2,7,7-trimethyl-5-oxo-N-phenyl-1,4,5,6,7,8-hexahydro quinoline-3-carbox amide* (**5c**)

White solid, m.p =225-227 °C; FT-IR (KBr): $\bar{\nu}$ = 3265 (N-H stretch), 2956 (aliphatic C-H stretch), 1677 (C=O), 1645 (C=O), 1498 (C=C stretch), 752 (aromatic C-H out of plane bending) cm$^{-1}$; $^1$H NMR (400 MHz, $CDCl_3$):$\delta$ = 0.96 (s, 3H, $CH_3$), 1.06 (s, 3H, $CH_3$), 1.95 (s, 3H, $CH_3$), 1.98 (d, *J* = 13.2 , 1H), 2.13 (d, *J* = 16, 1H), 2.32 (d, *J* = 16.8, 1H), 2.41 (d, *J* = 17.2, 1H), 5.35 (s, 1H, CH), 6.97-7.29 (m, 7H), 7.53 (d, *J*= 7.6, 2H), 8.74 (s. 1H, NH), 9.72 (s, IH, NHCO). $^{13}$C NMR (100 MHz, $CDCl_3$):$\delta$ = 19.5, 27.1, 29.3, 32.6, 35.3, 41.2, 50.5, 108.6, 110.9, 120.3, 124.0, 127.7, 128.3, 128.9, 129.7, 131.0, 131.6, 138.1, 140.4, 143.5, 148.6, 165.8, 194.9. Elemental analysis: Calculated (%) for $C_{25}H_{25}ClN_2O_2$ (420.93): C, 71.33; H, 5.99, N, 6.66. Found: C, 71.13; H, 6.04, N, 6.59.

*4-(4-(Dimethylamino)phenyl)-2,7,7-trimethyl-5-oxo-N-phenyl-1,4,5,6,7,8-hexahydroquinoline-3-carboxamide* (**5k**)

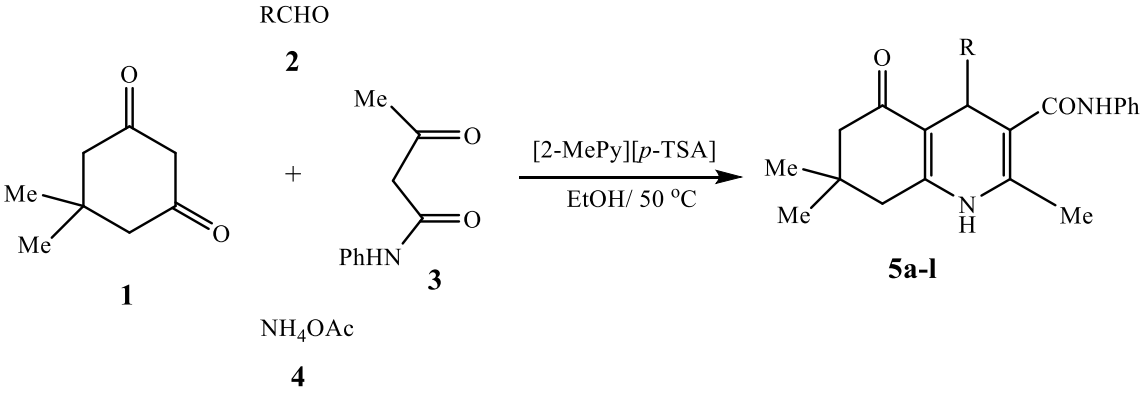
Orange solid; m.p =248-250 °C; FT-IR (KBr): $\bar{\nu}$ = 3269 (N-H stretch),3066 (aromatic C-H), 2952 (C-H stretch),1674 (C=O stretch), 1637 (C=O stretch), 754 (aromatic C-H out of plane bending) cm$^{-1}$;$^1$H NMR: $\delta$ = 0.87 (s, 3H, $CH_3$), 1.03 (s, 3H, $CH_3$), 2.11–2.26 (m, 4H), 2.37 (s, 3H, $CH_3$), 2.39 (s, 6H, $2CH_3$), 4.82 (s, 1H, CH), 6.72 (d, *J* = 8 Hz, 2H), 6.94 (s, 1H, Ar), 7.04 (m, 1H, Ar), 7.23–7.34 (m, 4H, Ar), 7.36 (d, *J* = 4 Hz, 2H, Ar), 7.52 (s, 1H, NH), 9.72 (s, 1H, NHCO) ppm; $^{13}$C NMR: $\delta$ = 18.0, 27.2, 29.2, 32.5, 37.0, 40.1, 40.5, 50.7, 76.8, 77.1, 77.4, 108.3, 111.0, 111.05, 112.9, 119.8, 123.8, 128.7, 128.8, 133.6, 138.3, 141.3, 149.1, 167.0, 195.0 (C=O) ppm. Elemental

analysis: Calculated (%) for $C_{27}H_{31}N_3O_2$ (429.55) C, 75.50; H, 7.27, N, 9.78. Found: C, 75.33; H, 7.35, N, 9.69.

*4-Isopropyl-2,7,7-trimethyl-5-oxo-N-phenyl-1,4,5,6,7,8-hexahydroquinoline-3-carboxamide* (**5l**)
Yellow solid, m.p =234-236°C; FT-IR (KBr): $\bar{\nu}$ = 3296 (N-H stretch), 2956 (aliphatic C-H stretch), 1664 (C=O), 1637 (C=O), 1490 (C=C stretch), 752 (aromatic C-H out of plane bending)$cm^{-1}$;$^1$H NMR (400 MHz, $CDCl_3$):$\delta$ = 0.74 (d, *J* = 4.4, 3H), 0.758 (d, *J* = 4.4, 3H, $CH_3$), 1.05 (s, 6H, $2CH_3$), 1.62-1.66 (m, 1H), 2.01 (s, 3H, $CH_3$), 2.07 (d, *J* = 16, 1H), 2.160 (d, *J* = 16, 1H), 2.22 (d, *J* = 1.68, 1H), 2.33 (d, *J* = 4.8, 1H), 3.81 (d, *J* = 2.8, CH), 7.00 (t, *J* = 14, 1H), 7.26 (t, *J* = 0.4, 2H), 7.62 (d, *J* = 8.04, 2H), 8.48 (s, 1H, NH), 9.62 (s, 1H, NHCO) ppm; $^{13}$C NMR (100 MHz, $CDCl_3$):$\delta$ =17.3, 18.2, 197, 27.01, 30.1, 32.3, 35.3, 38.2, 51.2, 107.1, 109.0, 120.1, 123.3, 128.9, 136.2, 140.1, 152.1, 169.7, 194.6 (C=O) ppm. Elemental analysis: Calculated (%) for $C_{22}H_{27}N_2O_2$ (351.46 ) C, 75.18; H, 7.74, N, 7.97. Found: C, 75.06; H, 7.85, N, 8.05.

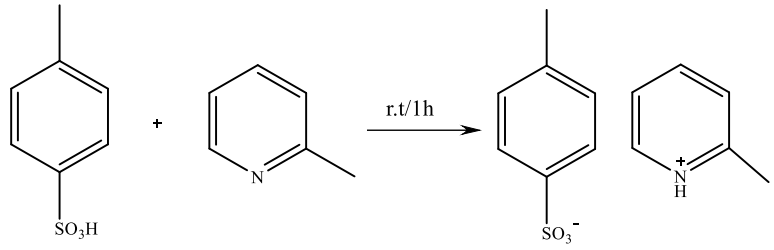
## Results and discussion

In this study, 2-methylpyridinum *p*-toluenesulfonate ([2-MPy][*p*-TSA]) ionic liquid was successfully applied in the reaction of arylaldehydes, dimedone, acetoacetanilide and ammonium acetate at 50 $^o$C to provide a series of hexahydroquinoline-3-carboxamides in excellent yields (Scheme 1).




**Scheme 1.** Synthesis of hexahydroquinoline-3-carboxamides by [2-MPy][*p*-TSA].

2-methylpyridinum *p*-toluenesulfonate ([2-MPy][*p*-TSA]) ionic liquid was obtained by simple reaction of 2-methylpyridine with *p*-toluene sulfonic acid (Scheme 2). The structure of the [2-MPy][*p*-TSA] was identified by FT-IR, $^1$H NMR, and $^{13}$C NMR. The corresponding spectral data are reported in the experimental section.




**Scheme 2.** Preparation of 2-methylpyridinum *p*-toluenesulfonate ([2-MPy][*p*-TSA]).

Characterization of the ionic liquid was performed by recording the Fourier transform infrared spectroscopy (FT-IR). In the FT-IR spectrum, the N–H stretching near 3498 $cm^{-1}$, the aromatic and aliphatic C-H stretching at 3062 and 2925 respectively, the C=N stretching at 1635 $cm^{-1}$, the C=C stretching at 1481 and 1541 $cm^{-1}$, the $SO_2$ asymmetric and symmetric stretching at 1203 and 1122 $cm^{-1}$ respectively, were observed (Figure 1c). The comparison of the FT-IR spectrum of [2-MPy][*p*-TSA] (Figure 1c) with FT-IR spectrum of 2-methylpyridine (Figure 1a) and *p*-TSA (Figure 1b), showed the evidences that the catalyst was successfully prepared.

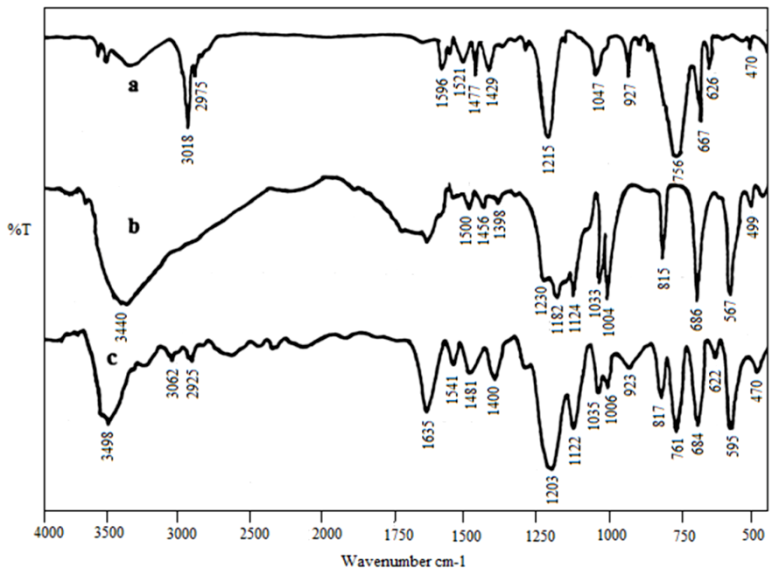



**Figure 1.** FT-IR spectrum of 2-methylpyridine (a) and *p*-TSA (b) and [2-MPy][*p*-TSA] (c).

To optimize the reaction conditions and get the best catalytic activity, the four-component reaction of benzaldehyde, dimedone, acetoacetanilide and ammonium acetate was examined as a sample reaction in several solvents. In this investigation, it was perceived that 2methylpyridinum *p*-toluenesulfonate in ethanol at room temperature is more efficient with respect to the efficiency of the desired product (Table 1).

**Table 1.** Synthesis of **5a** by [2-MPy][*p*-TSA] in different solvents[a]

| Entry | Solvent | Yield (%) |
|---|---|---|
| 1 | EtOH (96%) | 94 |
| 2 | $H_2O$ | 48 |
| 3 | EtOH/$H_2O$ (1:1) | 70 |
| 4 | $CH_3CN$ | 60 |
| 5 | $CH_2Cl_2$ | 40 |
| 6 | solvent-free | 80 |

[a]Reaction conditions: benzaldehyde (1 mmol), dimedone (1 mmol), acetoacetanilide (1 mmol) and ammonium acetate (1.2 mmol), and [2-MPy][p-TSA] (0.2 mmol) at 50 °C after 30minute.

In order to investigate the effect of the catalyst, the model reaction was also carried out by different amounts of [2-MPy][*p*-TSA]. It was considered that the variation of the catalyst had an effective influence on the reaction yields. The results showed the best amount of [2-MPy][*p*-TSA] is 20 mol%, which afforded the required product in good yields. By these optimized reaction conditions, a diversity of hexahydroquinoline-3-carboxamide derivatives were prepared in the presence of [2-MPy][*p*-TSA] as a novel ionic liquid catalyst (Table 2). All synthesized products were characterized by using infrared spectroscopy, $^1$H and $^{13}$C-NMR spectroscopy and elemental analysis. For example, the FT-IR spectra of **5e** product revealed the N-H stretch band at 3281 cm$^{-1}$, CH aromatic and aliphatic stretch band at 3070 cm$^{-1}$, 2964 cm$^{-1}$ respectively, ketone C=O stretch band at 1668 cm$^{-1}$, amid C=O stretch band at 1650 cm$^{-1}$, C=C stretch band at 1602 cm$^{-1}$, and asymmetric and symmetric $NO_2$ stretch band at 1500 and 1384 cm$^{-1}$ respectively. The $^1$H NMR spectrum of compound **5e** showed a singlet at 0.92 ppm for methyl protons ($CH_3$) and a singlet at 1.06 ppm for other methyl protons ($CH_3$) of the dimedone ring. One of the methylene proton (H-C-H) of the dimedone ring was observed as a doublet at 2.04 ppm ($J$ = 16 Hz). Another methyl protons ($CH_3$) attached to pyridine ring appeared as a singlet at 2.10 ppm. Another methylene proton (H-C-H) of the dimedone ring was observed as a doublet at 2.22 ppm ($J$ = 16 Hz). A methylene protons ($CH_2$) of the dimedone ring was observed as a doublet at 2.39 ppm ($J$ = 16 Hz) and 2.43 ppm ($J$ = 16 Hz). The methyn proton (C-H) was observed as a singlet at 5.12 ppm. An aromatic proton was observed as triplet at 7.03 ppm ($J$ = 8 Hz). Two aromatic protons were observed as multiplet at 7.23-7.27 ppm. Three aromatic protons were observed as multiplet at 7.53-7.55 ppm. A aromatic proton was observed as doublet at 7.63 ppm ($J$ = 8 Hz). Two aromatic protons were observed as multiplet at 7.98-8.03 ppm. The NH proton of pyridine ring was observed as singlet at 8.92 ppm. The NH proton of amid functional group was observed as singlet at 9.67 ppm. In the $^{13}$C NMR spectrum of **5e**, the aliphatic carbons were observed at 17.6, 19.0, 27.0, 29.5, 32.6, 50.6, and 56.5 ppm. The aromatic carbons were exhibited at 107.6, 110.4, 120.1, 120.2, 121.3, 123.6, 128.5, 129.8, 134.7, 136.1, 139.6, 148.0, 149.7, and 151.6 ppm. In addition, the carbon of the carbonyl of an amide

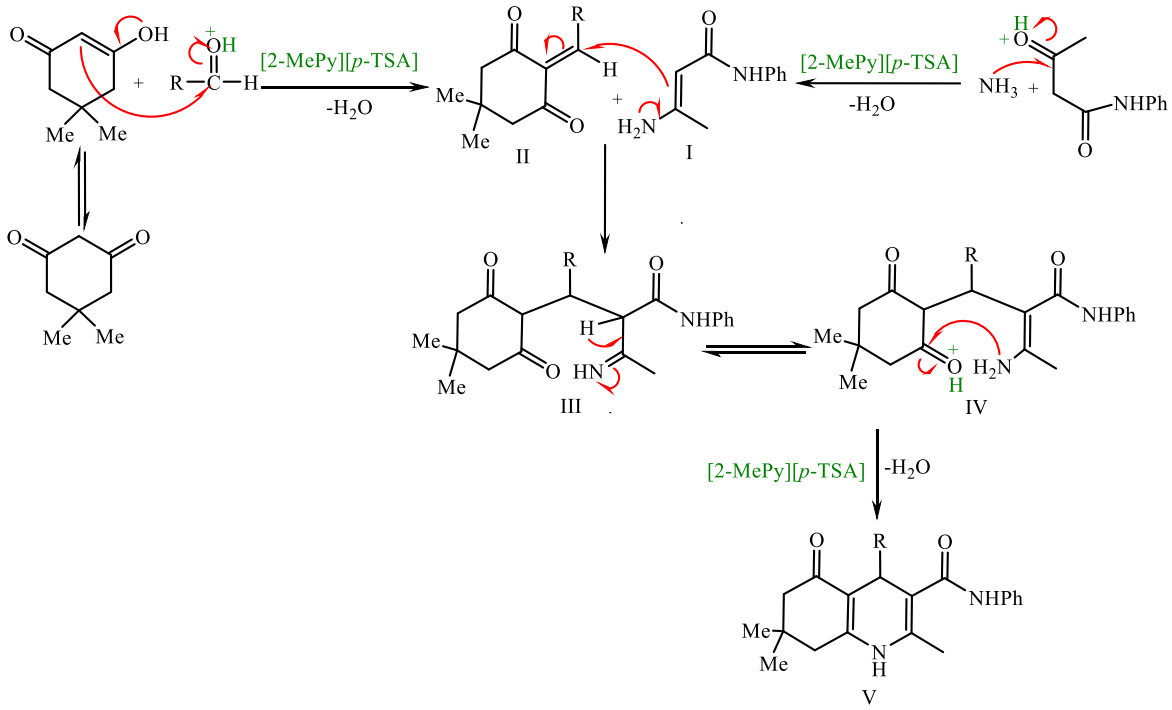
group was observed at d 167.3 ppm. Also, the carbon of the carbonyl of cyclohexenone ring was observed at 194.2 ppm.

**Table 2.** Synthesis of hexahydroquinoline-3-carboxamides by [2-MPy][*p*-TSA][a].

| Entry | R | Product | Time (min) | Yield (%)[b] | m.p. °C | |
|---|---|---|---|---|---|---|
| | | | | | Found | Reported |
| 1 | $C_6H_5$ | **5a** | 20 | 94 | 242-244 | 243-245[13] |
| 2 | 4-Cl-$C_6H_4$ | **5b** | 15 | 96 | 251-253 | 252-254[13] |
| 3 | 2-Cl-$C_6H_4$ | **5c** | 20 | 92 | 225-227 | ---- |
| 4 | 3-Cl-$C_6H_4$ | **5d** | 20 | 93 | 240-241 | 238-240[12] |
| 5 | 3-$NO_2$-$C_6H_4$ | **5e** | 20 | 94 | 244-246 | 245-247[13] |
| 6 | 4-$NO_2$-$C_6H_4$ | **5f** | 20 | 95 | 209-211 | 208-210[13] |
| 7 | 2-$NO_2$-$C_6H_4$ | **5g** | 15 | 91 | 254-256 | 255-257[12] |
| 8 | 3-Br-$C_6H_4$ | **5h** | 15 | 95 | 211-213 | ---- |
| 9 | 4-HO-$C_6H_4$ | **5i** | 30 | 88 | >300 | >300 [12] |
| 10 | 4-MeO-$C_6H_4$ | **5j** | 30 | 89 | 247-249 | 248-250[13] |
| 11 | 4-$N(Me)_2$-$C_6H_4$ | **5k** | 30 | 91 | 249-251 | ---- |
| 12 | $CH(CH_3)_2$ | **5l** | 45 | 90 | 234-236 | ---- |

[a]Reaction and conditions: aldehyde (1 mmol), dimedone (1 mmol), acetoacetanilide (1 mmol), ammonium acetate (1.2 mmol) and [2-MPy][p-TSA] (0.05 g) in EtOH (3 mL) at 50 °C. [b]All yields refer to isolated products.

A reasonable mechanism for the synthesis of hexahydroquinoline-3-carboxamides catalyzed by [2-MPy][*p*-TSA] is shown in Scheme 3. Formation of the hexahydroquinoline-3-carboxamides **V** takes place through a Hantzsch-type mechanism via conjugate addition of the enamine intermediate **I** obtained from acetoacetanilide and ammonium acetate. Then, intermediate **III** is converted to **IV** by imino-enamino tautomerization. Finally, hexahydroquinoline-3-carboxamides **V** forms by an intramolecular nucleophilic attack of the $NH_2$ group to the activated carbonyl group and then removes one molecule $H_2O$.




**Scheme 3.** Plausible mechanism for the synthesis of hexahydroquinoline-3-carboxamides catalyzed by [2-MPy][*p*-TSA].

In order to explore the efficiency of the present method for the synthesis of hexahydroquinoline-3-carboxamides, compound **5a** was compared with some of those reported in the literature (Table 3). As one can see, our results show a very good comparison with previously reported data when all terms, including yields, reaction times, and reaction conditions are taken into account.

**Table 3.** Comparison of verjuice with some other catalysts for synthesis of **5a**.

| Entry | Catalyst | Reaction conditions | Time/ min | Yield (%) | Ref. |
|---|---|---|---|---|---|
| 1 | *p*-TSA | Grinding/EtOH (1 mL) | 15 | 78 | [12] |
| 2 | ----- | 150-160 °C | 10-20 | 89 | [13] |
| 3 | ([2-MPy][*p*-TSA] | EtOH/50 °C | 20 | 94 | This work |

To study the recyclability of the catalyst, the synthesis of compound **5a** was utilized after five runs under the optimized conditions. After completion of the reaction, the crude residue was filtered and the ionic liquid was recovered after evaporation of the solvent and washed with dichloromethane (2 × 10 ml), and then used in the subsequent preparation of **5a**. The results indicated that the catalyst can be reused five sequential times without considerable lack of its catalytic activity (Table 4).

**Table 4.** The recycling of [2-MPy][*p*-TSA] for the synthesis of **5a**[a].

| Run | 1 | 2 | 3 | 4 | 5 |
|---|---|---|---|---|---|
| Yield (%) | 94 | 93 | 91 | 90 | 89 |

[a]All yields refer to isolated products.

## Conclusion

An efficient procedure for the synthesis of hexahydroquinolines using [2-MPy][*p*-TSA] as a reusability of the catalyst was developed. Environmentally friendly conditions, easy preparation of the catalyst and, simple performance and high yields are some of the advantages of this method.

## Acknowledgements

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