Synthesis of amidoalkyl naphthol via Ritter-type reaction catalysed by heteropolyanion-based ionic liquid

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Abstract. A facile and efficient procedure for the preparation of amidoalkyl naphthols via a Ritter-type reaction of 2-naphthol, aromatic aldehydes and amide in the presence of heteropolyanion-based functionalized ionic liquid has been described. The one-pot solvent-free three-component reaction is accomplished at 110°C for 5–10 min in reasonable to good yield ranging from 73% to 94%. The catalyst could be recovered and reused at least six times without noticeably decreasing the catalytic activity.

Keywords. Ritter-type reaction; heteropolyanions ionic liquid; amidoalkyl naphthol; multi-component reaction

1. Introduction

Multi-component reactions (MCRs) play an important role in organic synthesis since they generally occur in a single pot and exhibit a high atom-economy and selectivity. Ritter-type reaction is an important MCR in organic synthesis for C–N bond forming to afford N-alkyl amide compounds, which are ubiquitous to a variety of biologically important natural products and potent drugs, including a number of nucleoside antibiotics and HIV protease inhibitors.[1] Ritter-type reaction is usually accomplished with the condensation of aryl aldehydes, 2-naphthol and acetonitrile or amide in the presence of Lewis acid, Brønsted acid, solid acid, or organic compounds catalysts such as $Ce(SO_4)_2$,[2] $FeCl_3 \cdot SiO_2$,[3] I_2,[4] *p*-TSA and sulphamic acid,[5] silica sulphuric acid,[6] $HClO_4–SiO_2$,[7] Zeolite H-BEA,[8] $Al(H_2PO_4)_3$,[9] cation-exchanged resins,[10] $K_5CoW_{12}O_{40} \cdot 3H_2O$,[11] polymer-supported sulphonic acid,[12] acidic ionic liquid/silica gel,[13] heteropoly acids,[14] 2,4,6-trichloro-1,3,5-triazine,[15] as well as under the irradiation of ultrasound or microwave.[16]

Heteropoly acids (HPAs) and their salts have been extensively investigated as solid acid catalysts,[14,17] it was inferred that the combination of organic
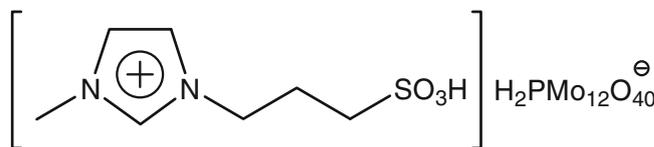

**Figure 1.** Structure of heteropolyanion-base [MIMPS] $H_2PMo_{12}O_{40}$.

cations with heteropolyanions could form a different kind of HPA salts, which might be a novel member of ionic liquids (ILs) family. In continuation of our study on MCRs, and considering the importance of combined catalytic systems,[18] we synthesized the heteropolyanion-based SO₃H-functional ionic liquid [MIMPS]$H_2PMo_{12}O_{40}$ (figure 1) that bear a propane sulphonic acid group in a*N*-methylimidazolium cation. Its use as a novel catalyst for the synthesis of amidoalkyl naphthol (scheme 1) has also been explored.

2. Experimental

2.1 *Materials and methods*

Melting points were determined on an X-6 microscope melting apparatus. The IR spectra were run on a Bruker Vector 22 spectrometer and expressed in cm⁻¹ (KBr). ¹H Nuclear Magnetic Resonance (NMR) spectra were recorded on a Bruker DRX300 (300 MHz) spectrometer. ¹³C NMR spectra were recorded on a Bruker

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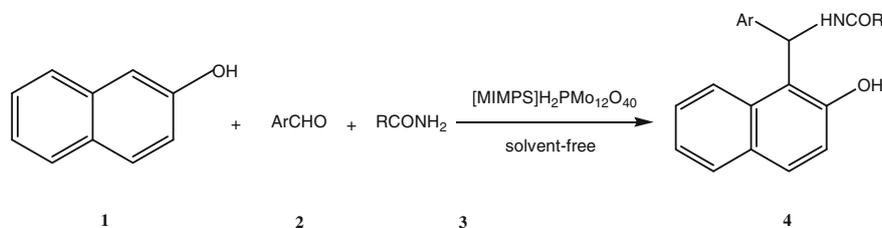
Scheme 1. Synthesis of amidoalkyl naphthol derivatives.

DRX300 (75 MHz) spectrometer. Mass spectra were obtained with an automated Fininigan TSQ Quantum Ultra AM (Thermal) LC/MS spectrometer. Elemental analyses were recorded on a Perkin-Elmer 240°C spectrometer. *N*-Propane sulphone pyridinium (PPS) was purchased from Wuhan Fengfan Chemical Co., Ltd., Wuhan, China. All other chemicals (AR grade) were commercially available and used without further purification unless otherwise stated.

2.2 *Synthesis of heteropolyanion-based ionic liquid ([MIMPS]H_2PMo_{12}O_{40})*

The heteropolyanion-based SO_3H-functional ionic liquid [MIMPS]H_2PMo_{12}O_{40} was synthesized according to earlier methods.[17,18] The [MIMPS]H_2PMo_{12}O_{40} was analysed by [1]H Nuclear Magnetic Resonance (NMR), IR and the spectral data agreed with their structures.

[MIMPS]H_2PMo_{12}O_{40} [1]*H NMR (300 Mz, D_2O)*: δ ppm 2.03 (m, $J = 7.2$ Hz, 2H, CH$_2$), 2.64 (t, $J = 7.5$ Hz, 2H, CH$_2$), 3.62 (s, 3H, CH$_3$), 4.08 (t, $J = 6.9$ Hz, 2H, CH$_2$), 7.17 (d, $J = 1.5$ Hz, 1H, CH), 7.24 (d, $J = 1.5$ Hz, 1H, CH), 8.47 (s, 1H, CH). ^{13}C NMR (75 Mz, D_2O): δ ppm 25.48, 36.46, 47.66, 48.13, 122.57, 124.32, 136.53. Anal. Calcd. for $C_7H_{15}N_2O_{43}SPMo_{12}$: C, 4.14; H, 0.75; N, 1.38. Found: C, 4.28; H, 0.79; N, 1.40.

2.3 *General procedure for the synthesis of amidoalkyl naphthols catalysed by [MIMPS]H_2PMo_{12}O_{40}*

In a typical experiment (scheme 1), to a round-bottomed flask charged with β-naphthol (1 mmol), aldehyde (1 mmol), and amide (1 mmol) were added [MIMPS]H_2PMo_{12}O_{40} (0.1 mmol) under stirring respectively. The mixture was then stirred for a length of time at 110°C. After completion of the condensation (monitored by Thin Layer Chromatography (TLC)), water (2 mL) was added to the reaction mixture and stirred continually for 5 min and then filtered. The solid crude product was recrystallized from 95% ethanol

to afford pure amidoalkyl naphthol derivatives, the products obtained were identified by ^{1}HNMR, and physical data (m.p.) with those reported in literature. [MIMPS]H_2PMo_{12}O_{40}, contained in the filtrate, could be recovered and reused for the next run after the removal of water.

2.4 *Selected spectral data for amidoalkyl naphthol derivatives*

N-((2-chloro-phenyl)-(2-hydroxynaphalen-1-yl)-methyl)-acrylamide (table 4, entry 14): White solid, mp 220–222°C; IR(KRr) 3419, 3060, 3022, 1629, 1571, 1515, 1450, 1434, 1394, 1270, 1257, 1242, 1076, 943, 823, 696, 582 cm^{-1}. ^{1}H NMR (300 MHz, DMSO-d$_6$) δ: 5.56–5.60 (m, 2H), 6.09–6.12 (d, 1H), 6.49–6.55 (m,1H), 7.14–7.47 (m, 7H), 7.74–7.99 (m, 3H), 8.84–8.87 (d, 1H), 9.89 (s, 1H). ^{13}C NMR (75 MHz, DMSO-d$_6$) δ: 167.0, 153.5, 143.4, 133.6, 133.5, 131.1, 129.7, 129.4, 129.0, 128.8, 128.3, 128.2, 127.7, 127.4, 126.3, 123.2, 122.5, 118.9, 115.4, 40.1. MS: $m/z = 338$ (M$^+$). Anal. Calcd. for $C_{20}H_{16}NO_2Cl$: C, 71.11; H, 4.77; N, 4.15. Found: C, 71.32; H, 4.78; N, 4.27.

3. Results and discussion

The synthesis approach is made up of two-step atom economic reactions. The zwitterionic-type precursor MIMPS (N-methyl-imidazolium propane sulphonate) of the [MIMPS]H_2PMo_{12}O_{40} was prepared according to our earlier work.[18] The synthesis of heteropolyanion-based SO_3H-functional catalyst was carried out by mixing of MIMPS with heteropoly acids $H_3PMo_{12}O_{40}$. The result is the transformation of the zwitterion into a cation bearing an appended sulphonic acid group, combined with a heteropolyanion. The fresh new heteropolyanion-based [MIMPS]H_2PMo_{12}O_{40} is a somewhat green solid at room temperature. [MIMPS]H_2PMo_{12}O_{40} is soluble in water, methanol, ethanol, partly soluble in acetone, and nearly insoluble in ethers, alkanes and aromatic hydrocarbons.

The Fourier Transform Infrared Spectroscopy (FTIR) spectra for $H_3PMo_{12}O_{40}$ and $[MIMPS]H_2PMo_{12}O_{40}$ were compared. The featured peaks of the Keggin anion at 1064, 963, 869 and 790 cm^{-1} indicate that the Keggin structure of the heteropolyanion in $H_3PMo_{12}O_{40}$ is well-retained after one of the protons in the HPAs is substituted by the large organic cation to form $[MIMPS]H_2PMo_{12}O_{40}$. There are also some characteristic peaks at 1193, 1157 (S=O), and 2940, 1573, 1457, 1390 cm^{-1} (imidazole ring) for the cation, which are consistent with that of MIMPS.

In case of the model Ritter-type condensation reaction, 2-naphthol, benzaldehyde and acetamide were employed as model reactants at 110°C in the presence of $[MIMPS]H_2PMo_{12}O_{40}$ for a length of time to explore the catalytic performance. TLC indicated that the starting materials had disappeared, water was then added to the reaction mixture and stirred to extract the catalyst, and then filtered. The ionic liquid, contained in filtrate, could be recovered and reused as catalyst for the next run after the removal of water (table 1).

It showed that the Ritter-type reaction of 2-naphthol, benzaldehyde and acetamide could be accomplished smoothly in $[MIMPS]H_2PMo_{12}O_{40}$. In comparison, the $[MIMPS]H_2PMo_{12}O_{40}$ gave the best result (entry 5). In addition, the catalyst could be reused several times without appreciable decrease in yield and reaction rate.

After selection of catalyst, the optimal amount of $[MIMPS]H_2PMo_{12}O_{40}$ for the model reaction was subsequently explored, and the results are summarized in table 2.

In the absence of catalysts, no product was obtained even after 5 h (entry 1). Excellent yield could be obtained with 10 mol% catalyst (entry 3). No significant impact was found on the yield when the amount of catalyst increased from 10% to 20% mol. Thus, 10 mol% was chosen as the optimal dosage of $[MIMPS]H_2PMo_{12}O_{40}$.

To optimize the reaction conditions, different polar solvents were then selected as the reaction medium. The results are summarized in table 3.

Among the six reaction conditions, Ritter-type reaction was accomplished in polar solvents such as ethanol and acetonitrile, gave a higher yield than in weaker polar solvents such as tetrahydrofuran and dichlormethane. Considering the reaction rate and yield, solvent-free condition was confirmed to be the best, additionally, it is an eco-friendly and economic procedure under solvent-free conditions.

Using our experimental data, a Ritter-type condensation reaction with various aldehydes and amides in the presence of $[MIMPS]H_2PMo_{12}O_{40}$ was then explored and the results are presented in table 4. It can be

Table 1. Ritter-type condensation of 2-naphthol, benzaldehyde and acetamide in different systems[a].

Entry	Catalytic system	Time (min)	Yield (%)[b]
1	[TMPSA][HSO_4]	5	60
2	[PyPS][HSO_4]	5	73
3	[MIMPS][HSO_4]	5	76
4	PEG_{1000}-DAIL	5	72
5	[MIMPS]H_2PMo_{12}O_{40}	5	92, 89[c]

[a]Reaction conditions: naphthol (1 mmol), benzaldehyde (1 mmol), acetamide (1 mmol), catalyst (0.1 mmol), 110°C
[b]Isolated yield
[c]After six recycles

Table 2. Influence of the catalytic amounts of $[MIMPS]H_2PMo_{12}O_{40}$ on the model reaction[a].

Entry	Catalytic amounts (mol%)	Time (min)	Yield (%)[b]
1	/	5	/
2	2	5	71
3	5	5	92
4	10	5	92
5	15	5	92

[a]Reaction conditions: naphthol (1 mmol), benzaldehyde (1 mmol), acetamide (1 mmol), catalyst (0.1 mmol), 110°C
[b]Isolated yield

Table 3. $[MIMPS]H_2PMo_{12}O_{40}$-catalysed model reaction in different solvents[a].

Entry	Solvents (mol%)	Time (min)	Yield (%)[b]
1	Solvent-free	5	92
2	Ethanol	60	78
3	Acetonitrile	60	76
4	Tetrahydrofuran	60	65
5	Dichlormethane	60	52
6	Water	60	86

[a]Reaction conditions: naphthol (1 mmol), benzaldehyde (1 mmol), acetamide (1 mmol), catalyst (0.1 mmol), 110°C
[b]Isolated yield

easily seen that this one-pot, three-component Ritter-type reaction was completed within 5–10 min and the products were isolated in moderate to good yields. Aromatic aldehydes carrying either electron-donation or electron-withdrawing substituents could afford good yields of amidoalkyl naphthol. It is noteworthy that aromatic aldehydes with electron-withdrawing groups reacted as fast as aromatic aldehydes with electron-releasing groups which was not expected. In case

Table 4. [MIMPS]$H_2PMo_{12}O_{40}$-catalysed three-component reaction of naphthol, amides and various aromatic aldehydes[a].

Entry	Ar	R	Time/min	Yield/%[b]	mp/°C[Lit]
1	C_6H_5	Me	5	92	236–238 [7]
2	2-ClC_6H_4	Me	10	93	193–195 [7]
3	4-ClC_6H_4	Me	5	90	224–226 [7]
4	$2,4\text{-Cl}_2C_6H_3$	Me	5	91	200–202 [15]
5	$2\text{-NO}_2C_6H_4$	Me	10	91	215–217 [15]
6	$3\text{-NO}_2C_6H_4$	Me	5	93	239–241 [7]
7	$4\text{-NO}_2C_6H_4$	Me	5	94	234–236 [16]
8	$4\text{-CH}_3C_6H_4$	Me	5	91	218–220 [9]
9	C_6H_5	Ph	5	92	232–234 [7]
10	2-ClC_6H_4	Ph	5	94	252–254 [15]
11	$3\text{-NO}_2C_6H_4$	Ph	5	93	212–214 [7]
12	$4\text{-NO}_2C_6H_4$	Ph	5	93	232–234 [7]
13	$4\text{-CH}_3C_6H_4$	Ph	5	93	194–196 [7]
14	2-ClC_6H_4	$CH_2{=}CH$	5	91	220–222
15	$4\text{-CH}_3OC_6H_4$	$CH_2{=}CH$	5	92	218–220 [15]
16	$3\text{-NO}_2C_6H_4$	NH_2	10	73	176–178 [15]

[a]Reaction conditions: naphthol (1 mmol), benzaldehyde (1 mmol), amides (1 mmol), catalyst (0.1 mmol), 110°C
[b]Isolated yield; products were confirmed by ^{1}H NMR, MS

of amides, alkyl, alkene, phenyl amides as well as pyrrolidin-2-one could afford reasonable to good yields.

4. Conclusion

In summary, an efficient procedure for preparation of a variety of amidoalkyl naphthol by one-pot, three-component Ritter-type reaction was carried out. The methodology provides advantages such as short reaction time, recyclability of catalyst and operational simplicity in the isolation of the products in good yield.

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