

## Cu-exchanged heteropoly acids as efficient and reusable catalysts for preparation of 1-amidoalkyl-2-naphthols

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MS received 13 November 2008; revised 4 February 2009; accepted 10 February 2009

**Abstract.** A series of amidoalkyl naphthols were prepared in high yields using various aldehydes and urea or amides. The reaction was catalysed by  $\text{Cu}_{1.5}\text{PMo}_{12}\text{O}_{40}$  (CuPMo) and  $\text{Cu}_{1.5}\text{PW}_{12}\text{O}_{40}$  (CuPW) and conducted in molten tetrabutylammonium bromide as an ionic liquid.

**Keywords.** Amidoalkyl naphthol; heteropoly acid; Cu-exchanged salts; ionic liquid; tetrabutylammonium bromide.

### 1. Introduction

Compounds bearing 1,3-amino oxygenated functional groups are ubiquitous to a variety of biologically important natural products and potent drugs including a number of nucleoside antibiotics and HIV protease inhibitors, such as ritonavir and lipinavir.<sup>1</sup> In this research, we represent an advance in the context of synthetic methodology towards mentioned class of biologically important molecules. It is noteworthy that 1-amidomethyl-2-naphthols can be converted to important biologically active 1-aminomethyl-2-naphthol derivatives by amide hydrolysis reaction. The hypotensive and bradycardiac effects of these compounds have been evaluated.<sup>2</sup>

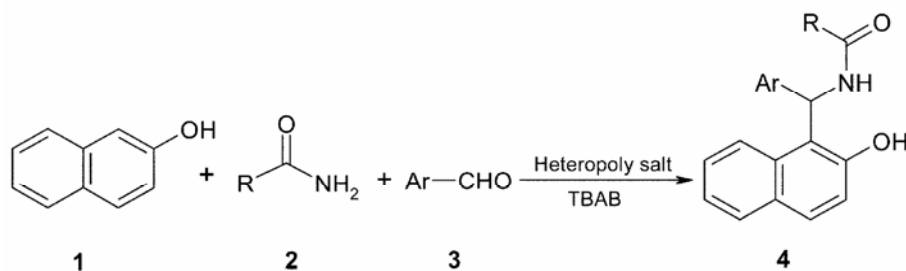
In recent years, the use of solid acids as heterogeneous catalysts has received considerable interest in different areas of organic synthesis.<sup>3</sup> The heterogeneous solid acids are advantageous over conventional homogeneous acid catalysts as they can be easily recovered from the reaction mixture by simple filtration and can be re-used after activation or without activation, thereby making the process economically viable. In many cases, heterogeneous catalysts can be recovered with only minor change in activity and selectivity so that they can be conveniently used in continuous flow reactions. Among various heterogeneous catalysts, heteropoly acids are most attractive, because of their unique properties such as well-defined structure, Bronsted acidity, possibility to

modify their acid–base and redox properties by changing their chemical composition (substituted HPAs), ability to accept and release electrons, high proton mobility, etc.<sup>4–7</sup> However, they are readily soluble in polar solvents. The solubility problem can be overcome by changing these HPAs into their corresponding salts, which are generally insoluble in polar solvents. Salts of heteropoly acids have been studied in different organic transformations under heterogeneous conditions.<sup>8,9</sup>

Multicomponent reactions (MCRs) have attracted considerable attention since they are performed without need to isolate the any intermediate during their processes; this reduces time and saves both energy and raw materials.<sup>10</sup> They have merits over two-component reactions in several aspects including the simplicity of a one-pot procedure, possible structural variations and building up complex molecules.

The preparation of 1-amidoalkyl-2-naphthols can be carried out by multi-component condensation of aryl aldehydes, 2-naphthol and an amide in the presence of Lewis or Bronsted acid catalysts such as montmorillonite K10 clay,<sup>11</sup>  $\text{Ce}(\text{SO}_4)_2$ ,<sup>12</sup> Iodine,<sup>13</sup>  $\text{K}_5\text{CoW}_{12}\text{O}_{40}\cdot 3\text{H}_2\text{O}$ ,<sup>14</sup> *p*-TSA<sup>15</sup> and Sulfamic acid.<sup>16</sup> However, some of these catalysts suffer from the drawback of green chemistry such as prolonged reaction times, low yields, toxicity and recovery and reusability of the catalyst. Therefore, introducing clean processes and utilizing eco-friendly and green catalysts which can be simply recycled at the end of reactions have been under permanent attention. The

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Scheme 1.

demand for environmentally benign procedure with heterogeneous and reusable catalyst<sup>17</sup> promoted us to develop a safe alternate method for the synthesis of amidoalkyl naphthols.

A series of amidoalkyl naphthols were prepared in high yields using various aldehydes and urea or amides (scheme 1). The reaction was catalysed by  $\text{Cu}_{1.5}\text{PMo}_{12}\text{O}_{40}$  (CuPMo) and  $\text{Cu}_{1.5}\text{PW}_{12}\text{O}_{40}$  (CuPW) and conducted in molten tetrabutylammonium bromide as an ionic liquid.

## 2. Experimental

All compounds were identified by comparison of their spectral data and physical properties with those of the authentic samples. NMR spectra were recorded on a BRUKER DRX-500 AVANCE NMR spectrometer using  $\text{DMSO}-d_6$  as solvent. Aldehydes,  $\beta$ -naphthol, urea, acetamide, benzamide and  $\text{Bu}_4\text{NBr}$  were purchased from Merck chemical company.  $\text{Cu}_{1.5}\text{PMo}_{12}\text{O}_{40}$  and  $\text{Cu}_{1.5}\text{PW}_{12}\text{O}_{40}$  were synthesized according to the literature.<sup>18,19</sup>

### 2.1 General procedure for the CuPMo catalysed synthesis of 1-amidoalkyl-2-naphthols in molten salt media

A mixture of appropriate aldehyde (1 mmol),  $\beta$ -naphthol (1 mmol), amide/urea (1 mmol),  $\text{Bu}_4\text{NBr}$  (1 mmol) and CuPMo (5 mol%) was heated in an oil bath at 100°C for 90 min. After completion of the reaction, 10 ml of ethanol was added. The catalyst was removed by filtration and reused. The solution was poured into water and the resulting precipitate recrystallised from ethanol to give pure product 4.

### 2.2 Spectral data for the selected compounds

2.2a *N*-[(2-Hydroxynaphthalen-1-yl)phenylmethyl]acetamide (4a): White solid; IR (KBr): 1520,

**Table 1.** Optimization of amounts of Cu exchange heteropoly salts and reaction time of benzaldehyde,  $\beta$ -naphthol and acetamide.

Entry	Catalyst (mol%)	Time (min)	Yield (%)
1	CuPMo (1)	180	60
2	CuPMo (2)	120	70
3	CuPMo (3)	120	80
4	CuPMo (4)	100	86
5	CuPMo (5)	90	92
6	CuPMo (6)	90	92
7	CuPW (1)	110	85
8	CuPW (2)	80	94
9	CuPW (3)	80	94

1660, 3063, 3251, 3390  $\text{cm}^{-1}$ .  $^1\text{H}$  NMR ( $\text{DMSO}-d_6$ ):  $\delta$  (ppm) = 1.99 (s, 3H), 7.15–7.37 (m, 9H), 7.76–7.82 (m, 3H), 8.45 (d,  $J$  = 8.32 Hz, 1H), 9.99 (s, 1H).

2.2b *N*-[(2-Hydroxynaphthalen-1-yl)-*p*-tolylmethyl]-acetamide (4c): White solid; IR (KBr): 1519, 1659, 2970, 3063, 3391  $\text{cm}^{-1}$ .  $^1\text{H}$  NMR ( $\text{DMSO}-d_6$ ):  $\delta$  (ppm) = 1.99 (s, 3H), 2.23 (s, 3H), 7.06–7.36 (m, 8H), 7.75–7.85 (m, 3H), 8.42 (d,  $J$  = 8.12 Hz, 1H), 9.97 (s, 1H).

2.2c *N*-[(2-Hydroxynaphthalen-1-yl)-(4-nitrophenyl)-methyl]-acetamide (4d): Pale yellow solid; IR (KBr): 1520, 1660, 2975, 3080, 3380  $\text{cm}^{-1}$ .  $^1\text{H}$  NMR ( $\text{DMSO}-d_6$ ):  $\delta$  (ppm) = 2.03 (s, 3H), 7.19–7.24 (m, 4H), 7.41 (d,  $J$  = 7.1 Hz, 2H), 7.80 (m, 3H), 8.14 (d,  $J$  = 7.2 Hz, 2H), 8.60 (d,  $J$  = 6.15 Hz, 1H), 10.12 (s, 1H).

## 3. Results and discussion

Benzaldehyde was selected as a representative aldehyde along with of  $\beta$ -naphthol, acetamide and CuPMo or CuPW were reacted in presence of tetrabutylammonium bromide at 100°C in order to

**Table 2.** Preparation of 1-amidoalkyl-2-naphthols.

Entry	Ar	Urea/amide	Product <b>4</b>	Yield (%)		mp <sup>ref</sup>
				CuPW <sup>a</sup>	CuPMo <sup>b</sup>	
1	C <sub>6</sub> H <sub>5</sub>	CH <sub>3</sub> CONH <sub>2</sub>	<b>4a</b>	94	92	238–240 <sup>11</sup>
2	4-CH <sub>3</sub> O-C <sub>6</sub> H <sub>4</sub>	CH <sub>3</sub> CONH <sub>2</sub>	<b>4b</b>	82	75	180–182 <sup>20</sup>
3	4-CH <sub>3</sub> -C <sub>6</sub> H <sub>4</sub>	CH <sub>3</sub> CONH <sub>2</sub>	<b>4c</b>	88	85	220–223 <sup>20</sup>
4	4-Cl-C <sub>6</sub> H <sub>4</sub>	CH <sub>3</sub> CONH <sub>2</sub>	<b>4d</b>	78	76	224–226 <sup>20</sup>
5	4-NO <sub>2</sub> -C <sub>6</sub> H <sub>4</sub>	CH <sub>3</sub> CONH <sub>2</sub>	<b>4e</b>	92	92	245–246 <sup>20</sup>
6	3-NO <sub>2</sub> -C <sub>6</sub> H <sub>4</sub>	CH <sub>3</sub> CONH <sub>2</sub>	<b>4f</b>	90	87	238–240 <sup>20</sup>
7	2,4-Di-Cl-C <sub>6</sub> H <sub>3</sub>	CH <sub>3</sub> CONH <sub>2</sub>	<b>4g</b>	84	80	225–228 <sup>11</sup>
8	2-Cl-C <sub>6</sub> H <sub>4</sub>	CH <sub>3</sub> CONH <sub>2</sub>	<b>4h</b>	75	70	196–198 <sup>16</sup>
9	2-CH <sub>3</sub> -C <sub>6</sub> H <sub>4</sub>	CH <sub>3</sub> CONH <sub>2</sub>	<b>4i</b>	74	70	200–201 <sup>20</sup>
10	C <sub>6</sub> H <sub>5</sub>	NH <sub>2</sub> CONH <sub>2</sub>	<b>4j</b>	95	93	170–173 <sup>16</sup>
11	4-Cl-C <sub>6</sub> H <sub>4</sub>	NH <sub>2</sub> CONH <sub>2</sub>	<b>4k</b>	86	82	166–168 <sup>16</sup>
12	3-NO <sub>2</sub> -C <sub>6</sub> H <sub>4</sub>	NH <sub>2</sub> CONH <sub>2</sub>	<b>4l</b>	92	90	186–188 <sup>16</sup>
13	C <sub>6</sub> H <sub>5</sub>	PhCONH <sub>2</sub>	<b>4o</b>	85	82	233–236 <sup>16</sup>
14	4-Cl-C <sub>6</sub> H <sub>4</sub>	PhCONH <sub>2</sub>	<b>4p</b>	85	80	175–177 <sup>16</sup>
15	4-CH <sub>3</sub> -C <sub>6</sub> H <sub>4</sub>	PhCONH <sub>2</sub>	<b>4q</b>	82	76	190–193 <sup>16</sup>
16	3-NO <sub>2</sub> -C <sub>6</sub> H <sub>4</sub>	PhCONH <sub>2</sub>	<b>4r</b>	85	80	214–216 <sup>16</sup>

<sup>a</sup>Reaction conditions: aldehyde (1 mmol),  $\beta$ -naphthol (1 mmol), amide/urea (1 mmol), Bu<sub>4</sub>NBr (1 mmol) and CuPW (2 mol%)

<sup>b</sup>Reaction conditions: aldehyde (1 mmol),  $\beta$ -naphthol (1 mmol), amide/urea (1 mmol), Bu<sub>4</sub>NBr (1 mmol) and CuPMo (5 mol%)

**Table 3.** Re-usability of catalysts.

Entry	Catalyst	Number of recycles	Yield (%)
1	CuPMo	Fresh	92
2	CuPMo	1	88
3	CuPMo	2	85
4	CuPW	Fresh	94
5	CuPW	1	90
6	CuPW	2	88

optimize the reaction conditions. As can be seen from table 1, it was found that the reaction in the presence of 5 mol% of CuPMo and 2 mol% of CuPW needs shorter reaction time and gives best yields. Using higher amounts of catalysts did not have considerable effect on the yield and reaction time. So the best condition was that the reaction was catalysed by 5 mol% of CuPMo and 2 mol% of CuPW in 90 and 80 minutes respectively.

In order to evaluate the generality of the process, several examples illustrating the present method for the synthesis of amidoalkyl naphthols **4** were studied (table 2). The reaction of  $\beta$ -naphthol **2** with various aromatic aldehydes bearing electron withdrawing groups (such as nitro and halide), electron releasing groups (methyl and methoxy groups) and acetamide, benzamide or urea was carried out in the presence of

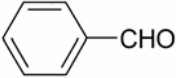
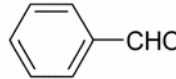
CuPMo and CuPW as catalyst. In all these reactions, clean and complete conversion was obtained leading to the corresponding amidoalkyl naphthols. The yields obtained were good to excellent without formation of any side products such as di-benzoxanthenes, which are normally observed under the influence of strong acids.

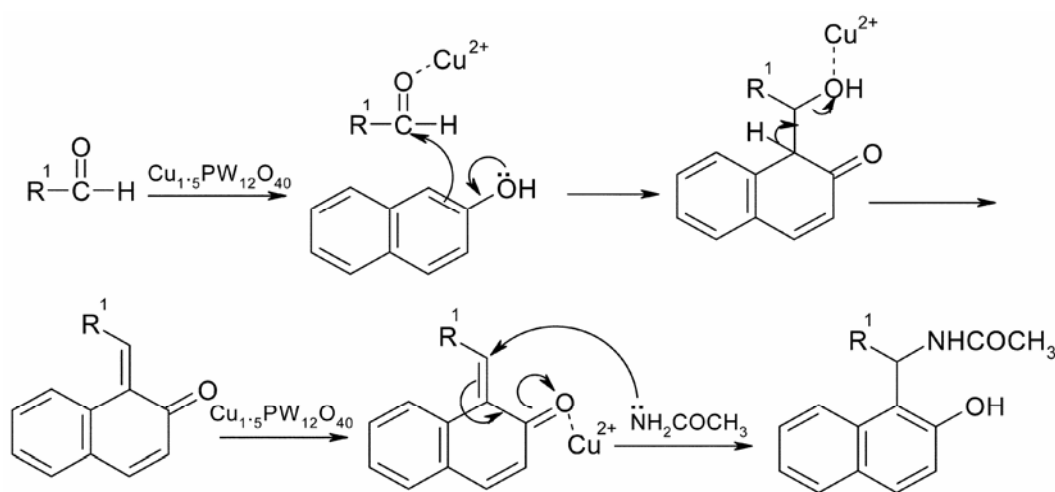
The reusability of the catalyst was also examined by treating benzaldehyde with  $\beta$ -naphthol and acetamide in the presence of 5 mol% and 2 mol% of CuPMo and CuPW for three consecutive reactions respectively. The reactions proceed smoothly with a few decrease in the yield and this result indicates that the catalyst can be reused without significant loss of activity (table 3).

To show the merit of the present work in comparison with reported results in the literature, we compared results of CuPMo and CuPW with montmorillonite K10 clay,<sup>11</sup> iodine,<sup>13</sup> and K<sub>5</sub>CoW<sub>12</sub>O<sub>40</sub>·3H<sub>2</sub>O<sup>14</sup> in the synthesis of 1-amidomethyl-2-naphthol derivatives. As shown in table 4, CuPMo and CuPW can act as effective catalysts with respect to reaction times and yields of the obtained products. Thus, the present protocol with Cu-exchanged heteropoly acids catalyst is convincingly superior to the previous reported catalytic methods.

As reported in the literatures,<sup>13,15</sup> the reaction of  $\beta$ -naphthol with aromatic aldehydes in the presence

**Table 4.** Comparison of the results of synthesis of 1-amidoalkyl-2-naphthols in the presence of CuPMo and CuPW in molten salt media with the literature.

Entry	Amide	Aldehyde	Catalyst	Mol ratio of catalyst	Time (min)	Yield (%)
1	CH <sub>3</sub> CONH <sub>2</sub>		K10	0.1 g	90	89
			I <sub>2</sub>	5 mol%	330	85
			K <sub>5</sub> CoW <sub>12</sub> O <sub>40</sub> ·3H <sub>2</sub> O	1 mol%	120	90
			Cu <sub>1.5</sub> PW <sub>12</sub> O <sub>40</sub>	2 mol%	80	94
			Cu <sub>1.5</sub> PMo <sub>12</sub> O <sub>40</sub>	5 mol%	90	92
2	NH <sub>2</sub> CONH <sub>2</sub>		K10	0.1 g	90	86
			I <sub>2</sub>	5 mol%	270	87
			K <sub>5</sub> CoW <sub>12</sub> O <sub>40</sub> ·3H <sub>2</sub> O	1 mol%	180	80
			Cu <sub>1.5</sub> PW <sub>12</sub> O <sub>40</sub>	2 mol%	80	95
			Cu <sub>1.5</sub> PMo <sub>12</sub> O <sub>40</sub>	5 mol%	90	93

**Scheme 2.**

of acid catalyst is known to give ortho-quinone methides (O-QMs). The same O-QMs, generated in-situ, have been reacted with acetamide to form 1-amidoalkyl-2-naphthol derivatives. A reasonable explanation for this result can be given by considering the nucleophilic addition to O-QM intermediate favourable via conjugate addition on the  $\alpha,\beta$ -unsaturated carbonyl group and finally this intermediate will aromatize to produce the final aromatic compound. A plausible way of formation of **4** is shown in scheme 2.

#### 4. Conclusion

In conclusion, we have developed a very simple and efficient method for the high-yielding synthesis of amidoalkyl naphthols by one-pot three-component coupling of  $\beta$ -naphthol, various aromatic aldehydes

and urea or amides using Cu<sub>1.5</sub>PMo<sub>12</sub>O<sub>40</sub> and Cu<sub>1.5</sub>PW<sub>12</sub>O<sub>40</sub> as heterogeneous acid catalysts which can be reused without significant loss of activity. The reaction was conducted in molten tetrabutylammonium bromide as a cost effective ionic liquid.

#### Acknowledgements

We gratefully acknowledge the financial support from the Research Council of Shahid Bahonar University of Kerman, Iran.

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