

# A modified reaction for the preparation of amidoalkyl naphthols

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## Abstract

An efficient synthesis of amidoalkyl naphthols using  $\text{FeCl}_3 \cdot \text{SiO}_2$  as a heterogeneous catalyst is described. This thermal solvent-free procedure offers advantages such as shorter reaction times, simple work-up, excellent yields, and recovery and reusability of the catalyst. © 2007 Elsevier Ltd. All rights reserved.

**Keywords:**  $\text{FeCl}_3 \cdot \text{SiO}_2$ ; Amidoalkyl naphthol; Multi-component reaction; Heterogeneous catalyst

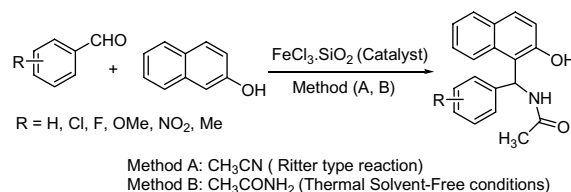
Multi-component reactions (MCRs) have proved to be remarkably successful in generating molecular complexity in a single synthetic operation.<sup>1</sup> In recent years, organic reactions on silica-supported reagents<sup>2–4</sup> have received considerable attention in organic synthesis because of their ease of handling, enhanced reaction rates, greater selectivity, simple workup, and recoverability of the catalysts. Among various heterogeneous catalysts,  $\text{FeCl}_3 \cdot \text{SiO}_2$  has advantages of low cost, ease of preparation, and catalyst recycling.<sup>3,4</sup>

The preparation of 1-amidoalkyl-2-naphthols can be carried out by condensation of aryl aldehydes, 2-naphthol, and acetonitrile or ethanamide in the presence of Lewis or Brønsted acid catalysts such as Montmorillonite K10 clay,<sup>5</sup>  $\text{Ce}(\text{SO}_4)_2$ ,<sup>6</sup> iodine,<sup>7</sup>  $\text{K}_5\text{CoW}_{12}\text{O}_{40} \cdot 3\text{H}_2\text{O}$ ,<sup>8</sup> *p*-TSA,<sup>9</sup> sulfamic acid,<sup>10</sup> cation-exchanged resins,<sup>11</sup> and silica-sulfuric acid.<sup>12</sup>

In continuation of our work<sup>13</sup> on the application of heterogeneous catalysts for the development of useful synthetic methodologies, we now show that amidoalkyl-2-naphthols can be produced using silica-supported ferric chloride<sup>14</sup> as an efficient heterogeneous catalyst (Scheme 1) via a Ritter<sup>15</sup> type reaction (Method A)<sup>16</sup> or under thermal solvent-free conditions (Method B).<sup>17</sup>

To determine the optimum quantity of  $\text{FeCl}_3 \cdot \text{SiO}_2$ ,<sup>4i-m</sup> the reaction of 2-naphthol (1 equiv), benzaldehyde (1 equiv),

and acetamide (1 equiv) was carried out under the conditions of Method B using different quantities of catalyst at 120 °C under solvent-free conditions. The use of 25 mg of catalyst resulted in the highest yield in 11 min (Fig. 1). A slight excess of the acetamide was found to be advantageous, therefore the molar ratio of 2-naphthol, aldehyde, and acetamide was kept at 1:1:1.2, respectively.



Scheme 1. Three-component synthesis of amidoalkyl naphthols.

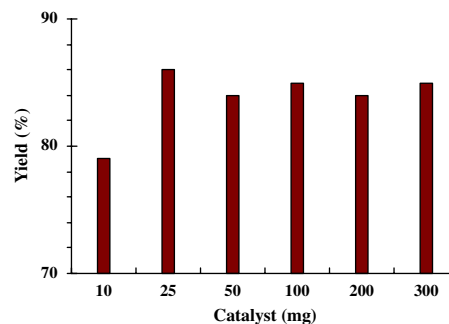


Fig. 1. Optimization quantity of  $\text{FeCl}_3 \cdot \text{SiO}_2$ .

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Table 1  
Preparation of amidoalkyl-2-naphthol derivatives<sup>a</sup> (a–r) produced via Scheme 1

Entry	R	Method A time (h)/yield (%)	Method B time (min)/yield (%)	Mp [lit.] <sup>Ref.</sup> (°C)
a	H	20/80	11/86	245–246 [241–243] <sup>6</sup>
b	4-Me	20/78	35/81	222–223
c	4-NO <sub>2</sub>	20/88	8/93	248–250
d	4-NMe <sub>2</sub>	20/65	40/78	123–125 [78–79] <sup>6</sup>
e	4-Cl	20/79	7/87	223–225 [224–227] <sup>6</sup>
f	4-Br	20/77	7/89	227–229 [228–230] <sup>5</sup>
g	4-OMe	20/75	24/80	183–185 [184–186] <sup>6</sup>
h	3-NO <sub>2</sub>	20/84	8/94	241–242 [182–184] <sup>6</sup>
i	3-F	20/75	8/89	248–249
j	4-F	20/72	10/86	230–232 [209–210] <sup>6</sup>
k	2,4-Cl <sub>2</sub>	20/79	8/90	201–203 [198–199] <sup>6</sup>
l	2,5-(OMe) <sub>2</sub>	20/81	9/86	251–253
m	2-Cl	20/75	20/84	213–215 [194–196] <sup>12</sup>
n	3-OMe	20/71	17/81	201–204 [203–205] <sup>5</sup>
o	2-NO <sub>2</sub>	20/80	25/87	179–182 [180–182] <sup>6</sup>
p	2-Me	20/72	30/77	199–202 [200–202] <sup>12</sup>
q	3,4-(OMe) <sub>2</sub>	20/77	12/85	235–237 [235–236] <sup>6</sup>
r	<i>n</i> -Heptanal	20/Trace	60/Trace	—

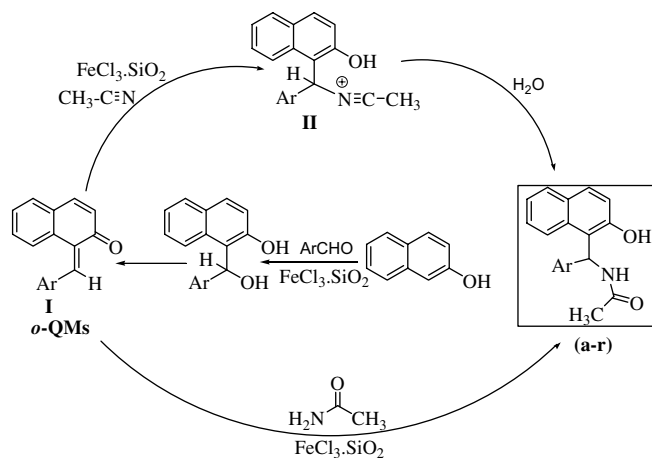
<sup>a</sup> Yields refer to the pure isolated products. All known products have been reported previously in the literature and were characterized by comparison of IR and NMR spectra and melting points with authentic samples.<sup>5–12</sup>

Thus, we prepared a range of amidoalkyl naphthols under the optimized reaction conditions (Table 1).

Table 2

Comparison of FeCl<sub>3</sub>·SiO<sub>2</sub> with Montmorillonite K10 clay,<sup>5</sup> Ce(SO<sub>4</sub>)<sub>2</sub>,<sup>6</sup> iodine,<sup>7</sup> and K<sub>5</sub>CoW<sub>12</sub>O<sub>40</sub>·3H<sub>2</sub>O<sup>8</sup> in the synthesis of 1-amidoalkyl-2-naphthols (entries a, h, and k from Table 1)

Entry	Catalyst	Aldehyde/2-naphthol/(catalyst mol %); conditions	Time	Yield (%)
(a)	Ce(SO <sub>4</sub> ) <sub>2</sub>	1/1/(100 mol %); under reflux	36 h	72
	I <sub>2</sub>	1/1/(5 mol %); solvent-free, 125 °C	4.5 h	87
	K-10 clay	1/1/(0.1 g); solvent-free, 125 °C	1.5 h	89
	K <sub>5</sub> CoW <sub>12</sub> O <sub>40</sub> ·3H <sub>2</sub> O	1/1/(1 mol %); solvent-free, 125 °C	2 h	90
	FeCl <sub>3</sub> ·SiO <sub>2</sub>	1/1/(0.025 g); Method B	11 min	86
(h)	Ce(SO <sub>4</sub> ) <sub>2</sub>	1/1/(100 mol %); under reflux	16 h	65
	I <sub>2</sub>	1/1/(5 mol %); solvent-free, 125 °C	5 h	76
	K-10 clay	1/1/(0.1 g); solvent-free, 125 °C	0.5 h	96
	K <sub>5</sub> CoW <sub>12</sub> O <sub>40</sub> ·3H <sub>2</sub> O	1/1/(1 mol %); solvent-free, 125 °C	3 h	78
	FeCl <sub>3</sub> ·SiO <sub>2</sub>	1/1/(0.025 g); Method B	8 min	94
(k)	Ce(SO <sub>4</sub> ) <sub>2</sub>	1/1/(100 mol %); under reflux	36 h	56
	I <sub>2</sub>	1/1/(5 mol %); solvent-free, 125 °C	6.5 h	82
	K-10 clay	1/1/(0.1 g); solvent-free, 125 °C	1 h	84
	K <sub>5</sub> CoW <sub>12</sub> O <sub>40</sub> ·3H <sub>2</sub> O	1/1/(1 mol %); solvent-free, 125 °C	3 h	82
	FeCl <sub>3</sub> ·SiO <sub>2</sub>	1/1/(0.025 g); Method B	8 min	90



Scheme 2. Suggested mechanism for the preparation of amidoalkyl naphthols via a Ritter type reaction (Method A) and conjugated addition (Method B).

As shown in Table 1, Method A, the three-component reaction of 2-naphthol, aryl aldehyde, and acetonitrile (reactant as well as solvent) was performed in the presence of FeCl<sub>3</sub>·SiO<sub>2</sub>. In all cases, aromatic aldehydes with either electron-donating or electron-withdrawing groups gave the desired products via a Ritter type reaction in 65–88% yields after 20 h. A mechanistic rationale for Method A is shown in Scheme 2. It is suggested that the benzaldehyde first reacted with 2-naphthol to give *ortho*-quinone methides (*o*-QMs) I, which then reacted with acetonitrile to produce intermediate II in a Ritter type reaction. Hydrolysis of II then gave the desired 1-amidoalkyl-2-naphthol.

We also performed the reaction in the presence of acetamide under solvent-free conditions. In all cases, aromatic aldehydes reacted successfully and gave the products in high yields. It was shown that aromatic aldehydes with electron-withdrawing groups reacted faster than those with electron-releasing groups as expected (Table 1, Method B). Sterically hindered aromatic aldehydes required longer reaction times. The rate of reaction of these aldehydes

decreased compared to aldehydes with electron-donating groups, but the yield of the corresponding products was higher than benzaldehydes with electron-donating groups. Aliphatic aldehydes reacted sluggishly and gave side products (Table 1, entry r). A possible mechanism for Method B has been proposed in Scheme 2. As reported in the literature,<sup>7–9</sup> reaction of 2-naphthol with aromatic aldehydes in the presence of an acid catalyst is known to give *ortho*-quinone methides (*o*-QMs). The same *o*-QMs, generated in situ, have been reacted with acetamide via conjugate addition to form 1-amidoalkyl-2-naphthol derivatives. Electron-withdrawing groups on the benzaldehyde in the *o*-QMs intermediates increase the rate of the 1,4-nucleophilic addition reaction because the alkene LUMO is at lower energy in the presence of electron-withdrawing groups compared with electron-donating groups.<sup>18</sup>

To show the merit of the present work in comparison with reported results in the literature, we compared the reactions of FeCl<sub>3</sub>·SiO<sub>2</sub> with Ce(SO<sub>4</sub>)<sub>2</sub>,<sup>6</sup> iodine,<sup>7</sup> and K<sub>5</sub>CoW<sub>12</sub>O<sub>40</sub>·3H<sub>2</sub>O<sup>8</sup> in the synthesis of 1-amidomethyl-2-naphthol derivatives. As shown in Table 2, FeCl<sub>3</sub>·SiO<sub>2</sub> is a better catalyst with respect to reaction times and yields of the products.

FeCl<sub>3</sub>·SiO<sub>2</sub> as an inexpensive and non-hazardous solid acid catalyst which can be handled easily and removed from the reaction mixtures by simple filtration. The recovered catalyst was reused five times without any loss of activity.

In conclusion, a reliable, rapid, and environmentally benign method for synthesizing 1-amidoalkyl-2-naphthols has been developed, which involves the use of recyclable silica-supported ferric chloride. In addition to the purity of the products, the short reaction times and ease of work-up make the method advantageous.

## Acknowledgement

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- Preparation of the FeCl<sub>3</sub>·SiO<sub>2</sub> reagent*:<sup>4i</sup> In a 250 ml flask, chromatographic grade silica gel (50 g) (70–230 mesh) and anhydrous ferric chloride (4 g) (8% of the weight of SiO<sub>2</sub>) were vigorously stirred under solvent-free conditions at room temperature for 24 h to achieve a homogeneous adsorption. A pale yellowish-green powder (2.0 g, equiv to 2 mmol of FeCl<sub>3</sub>)<sup>4i–m</sup> was obtained.
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- Typical experimental procedure for the synthesis of amidoalkyl-2-naphthols (Method A)*: To a solution of 2-naphthol (1 mmol) and benzaldehyde (1 mmol) in acetonitrile (5 mL, reactant as well as solvent), FeCl<sub>3</sub>·SiO<sub>2</sub> (25 mg) was added, then the reaction mixture was stirred for 20 h at 85 °C under reflux. The reaction progress was monitored by TLC. After completion of the reaction, the reaction mixture was filtered and the heterogeneous catalyst was recovered. The solution was then concentrated to afford a solid product, which was purified by recrystallization from aqueous EtOH (15%).
- Typical experimental procedure for synthesis of amidoalkyl-2-naphthols (Method B)*: To a mixture of 2-naphthol (1 mmol), aldehyde (1 mmol), and acetamide (1.2 mmol), FeCl<sub>3</sub>·SiO<sub>2</sub> (25 mg) was added. The mixture was stirred at 120 °C in an oil bath and the reaction was followed by TLC. After completion of the reaction the mixture was cooled to 25 °C and the solid residue was dissolved in EtOAc and the mixture stirred for 5 min. The catalyst was recovered and the solvent was evaporated to afford a solid, which was recrystallized from aqueous EtOH (15%). The desired pure product(s) were characterized by comparison of their physical data with those of known compounds.<sup>5–12</sup> The spectral data of some representative amidoalkyl naphthols are given: *N*-[(3-Fluorophenyl)-(2-hydroxynaphthalen-1-yl)-methyl]-acetamide (i): [mp: 248–249 °C]; <sup>1</sup>H NMR (500 MHz, DMSO-*d*<sub>6</sub>): δ = 1.98 (s, 3H), 6.98–6.92 (m, 3H), 7.12 (d, *J* = 8.3 Hz, 1H), 7.27–7.19 (m, 3H), 7.37 (t, *J* = 7.3 Hz, 1H), 7.76 (d, *J* = 8.6 Hz, 1H), 7.80 (d, *J* = 8.0 Hz, 1H), 7.84 (br d, 1H), 8.44 (d, *J* = 8.2 Hz, 1H), 10.01 (s, 1H) ppm; <sup>13</sup>C NMR (125 MHz, DMSO-*d*<sub>6</sub>): 22.5, 47.5, 112.5 (d, <sup>2</sup>*J*<sub>C–F</sub> = 22.1 Hz), 112.7 (d, <sup>2</sup>*J*<sub>C–F</sub> = 20.9 Hz), 118.3, 118.4, 122.1 (d, <sup>4</sup>*J*<sub>C–F</sub> = 2.5 Hz), 122.4, 122.9, 126.4, 128.3, 128.5, 129.4,

129.8 (d,  $^3J_{C-F} = 8.1$  Hz), 132.1, 145.9 (d,  $^3J_{C-F} = 6.6$  Hz), 153.1, 162.0 (d,  $^1J_{C-F} = 241.2$  Hz), 169.3 ppm; IR (KBr,  $\text{cm}^{-1}$ ): 3410, 3160, 1640, 1589, 1545, 1484, 1439, 1335, 1280, 1064, 989, 814, 760, 743. MS (EI, 70 eV)  $m/z = 310$  ( $M+1$ , 5%), 309 ( $M^+$ , 21%), 266 (5%), 251 (9%), 250 (52%), 249 (100%), 231 (14%), 220 (16%), 202 (3%), 170 (3%), 145 (4%), 127 (4%), 122 (7%), 115 (9%), 95 (3%), 75 (2%). Anal. Calcd for  $C_{19}H_{16}FNO_2$ : C, 73.77; H, 5.21; N, 4.53%. Found: C, 73.74; H, 5.25; N, 4.48%. *N*-[(2,5-Dimethoxyphenyl)-(2-hydroxynaphthalen-1-yl)-methyl]-acetamide (I): [mp: 251–253 °C];  $^1H$  NMR (500 MHz,  $DMSO-d_6$ ):  $\delta = 1.88$  (s, 3H), 3.48 (s, 3H), 3.64 (s, 3H), 6.77–6.72 (m, 2H), 7.23–7.10 (m, 4H), 7.39 (s, 1H), 7.73–7.66 (m, 2H), 8.27–8.15 (m, 2H), 9.75

(s, 1H) ppm;  $^{13}C$  NMR (125 MHz,  $DMSO-d_6$ ): 22.5, 44.4, 55.2, 55.9, 111.1, 111.9, 115.7, 118.5, 118.9, 122.0, 123.2, 125.7, 128.1, 128.6, 131.7, 132.4, 150.7, 152.7, 153.1, 168.1 ppm; IR (KBr,  $\text{cm}^{-1}$ ): 3365, 3174, 3002, 2939, 1614, 1577, 1497, 1436, 1370, 1317, 1277, 1218, 1084, 1052, 819, 797, 727; MS (EI, 70 eV)  $m/z = 351$  ( $M^+$ , 18%), 308 (6%), 276 (6%), 262 (36%), 261 (100%), 218 (17%), 205 (3%), 189 (5%), 164 (4%), 144 (7%), 115 (8%), 95 (2%), 77 (2%). Anal. Calcd for  $C_{21}H_{21}NO_4$ : C, 71.78; H, 6.02; N, 3.99%. Found: C, 71.73; H, 5.93; N, 4.08%.

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