An Economically and Environmentally Sustainable Synthesis of 1-Amidoalkyl 2-Naphthols Using Pentafluorophenylammonium Triflate (PFPAT) as a New Organocatalyst

Samad Khaksar, Roshanak Najafi, Seyed Mojtaba Ostad and Mahgol Tajbakhsh

Chemistry Department, Ayatollah Amoli Branch, Islamic Azad University, Amol, Iran
Department of Chemistry, University of Mazandaran, Babolsar, Iran

Abstract: A simple, inexpensive, environmentally friendly and efficient route for the synthesis of amidoalkyl naphthols from condensation of aldehydes with amides or urea and 2-naphthol in the presence of pentafluorophenylammonium triflate (PFPAT) as a catalyst is described. PFPAT organocatalyst is air-stable, cost-effective, easy to handle and easily removed from the reaction mixtures.

Key words: Pentafluorophenylammonium triflate • Organocatalyst • Amidoalkyl naphthols • Amide

INTRODUCTION

Amidoalkyl naphthols are of interest as structural units with wide utility for the synthesis of various biologically active natural products and potent drugs including a number of nucleoside antibiotics and HIV protease inhibitors, such as ritonavir and lipinavir [1]. 1-amidoalkyl 2-naphthols can be converted to useful and important biological building blocks and to 1-amino methyl 2-naphthols by an amide hydrolysis reaction, since compounds exhibit depressor and bradycardia effects in humans [2, 3]. Moreover, 1-aminoalkyl alcohol-type ligand has been used for asymmetric synthesis and also as a catalyst [4]. The preparation of 1-amidoalkyl-2-naphthols can be carried out in the presence of various catalysts such as p-TSA [5], montmorillonite K10 [6], Ce(SO$_4$)$_3$ [7], iodine [8], Fe(HSO$_4$)$_3$ [9], Sr(OTf)$_2$ [10], K$_2$CoW$_{12}$O$_{40}$•3H$_2$O [11], sulfamic acid [12, 13], molybdophosphoric acid [14], cation-exchange resins [15], silica sulfuric acid [16], P$_2$O$_5$ [17] and ionic liquid [18]. However, some of the reported methods suffer from disadvantages such as prolonged reaction time, use of dichloromethane like carcinogenic solvent, use of toxic, highly acidic and expensive catalysts, unsatisfactory yield, high temperature (120–125 °C) and the use of additional microwave or ultrasonic irradiation. Furthermore, the yields of the corresponding amidoalkyl naphthols are not always satisfactory. In view of these drawbacks, the synthetic protocols utilizing new catalysts devoid of metals are becoming more important due to the growing concern for sustainable chemistry. Organocatalysts have attracted extensive research interest as environmentally benign catalysts due to their specific properties such as water stability, recyclability, operational simplicity, strong tolerance to oxygen and nitrogen-containing substrates and functional groups and it can often be used in catalytic amounts [19]. In continuation of our interest in the application of organocatalysts in some common acid-catalyzed reactions [20], we report a new application of pentafluorophenylammonium triflate (PFPAT) [21] as an efficient, non-volatile and noncorrosive recyclable catalyst in an alternative method for the metal-free synthesis of amidoalkyl naphthols from condensation of aldehydes with amides or urea and 2-naphthol under mild reaction conditions (Scheme 1).

Experimental
Typical Experimental Procedure: A mixture of aldehyde (2 mmol), amides or urea (2 mmol), 2-naphthol (2 mmol) and PFPAT (0.03 g), in acetonitrile (3 mL) was prepared. The mixture was then stirred at room temperature until the reaction was completed (monitored by TLC). After completion of the reaction, the organic phase was washed with 1 M NaOH aqueous solution (1 ml). The separated organic phase was evaporated under reduced pressure to give a crude product, which was purified by recrystallization from hot ethanol to afford pure products.
Scheme 1: Synthesis of amidoaalkyl naphthols

Products were characterized by comparison of their physical and spectral data with those of authentic samples. Spectroscopic data for selected examples follow:

**N-((2-Chlorophenyl)(2-hydroxynaphthal-1-yl)methyl)-benzamide** (Table 2, entry 10): White solid, m.p 245-246 °C; FT-IR (KBr, cm⁻¹): 3394, 3067, 1633, 1573, 1538, 1346, 1075, 823; ¹H NMR (400 MHz, DMSO-d₆): δ = 7.19 (d, J = 8.8 Hz 1H), 7.25–7.30 (m, 3H), 7.35 (d, J = 5.0 Hz, 1H), 7.40–7.44 (m, 5H), 7.51 (t, J = 7.3 Hz, 1H), 7.78 (d, J = 8.8 Hz, 1H), 8.82 (d, J = 7.6 Hz, 1H), 8.78 (d, J = 7.3 Hz, 2H), 8.07 (d, J = 8.6 Hz, 1H), 9.00 (d, J = 6.2 Hz, 1H), 9.94 (br s, 1H, OH); ¹³C NMR (100 MHz, DMSO-d₆): δ = 48.6, 116.5, 118.5, 123.5, 123.8, 125.8, 126.6, 127.4, 128.2, 128.3, 128.4, 128.9, 130.1, 131.1, 132.7, 132.9, 134.5, 138.8, 153.4, 165.4.

**N-((4-Methylphenyl)(2-hydroxynaphthal-1-yl)methyl)-N-(3-nitrophenyl-acetamide** (Table 2, entry 11): mp: 222-223 °C; FT-IR (KBr, cm⁻¹): 3394, 3055, 2922, 1521, 1547, 1376, 1181, 813; ¹H NMR (400 MHz, DMSO-d₆): δ = 1.96 (s, 3H), 2.21 (s, 3H), 7.03–7.08 (m, 5H), 7.19–7.34 (m, 3H), 7.74 (d, J = 8.8 Hz, 1H), 7.82 (d, J = 7.9 Hz, 1H), 7.82 (br s, 1H, 8.36 (d, J = 8.1 Hz, 1H), 9.91 (s, 1H); ¹³C NMR (100 MHz, DMSO-d₆): 20.4, 22.6, 47.6, 118.4, 118.9, 122.2, 123.1, 125.9, 126.1, 128.4, 128.9, 133.2, 134.9, 139.4, 143.3, 152.9, 168.8.

**N-((4-Chloro-phenyl)(2-hydroxy-napthalen-1-yl)-methyl]-acetamide** (Table 2, entry 12): mp: 223-225 °C; FT-IR (KBr, cm⁻¹): 3392, 3062, 2700, 2613, 1637, 1577, 1753, 1490, 1436, 1374, 1331, 1278; ¹H NMR (400 MHz, DMSO-d₆): δ = 1.97 (s, 3H), 7.03–7.13 (m, 3H), 7.18 (d, J = 8.6 Hz, 1H), 11.7 (m, 3H), 7.31 (t, J = 7.5 Hz, 1H), 7.73–7.76 (m, 3H), 1.42 (d, J = 8.6 Hz, 1H), 10.09 (s, 1H); ¹³C NMR (100 MHz, DMSO-d₆): 20.7, 23.1, 48.1, 118.8, 119.0, 123.0, 126.8, 128.9, 129.1, 129.1, 130.0, 132.2, 132.7, 143.3, 153.7, 169.6.

**N-((4-Chloro-phenyl)(2-hydroxy-napthalen-1-yl)-methyl]-acetamide** (Table 2, entry 14): mp: 241-242 °C; FT-IR (KBr, cm⁻¹): 3373, 3088, 2598, 1645, 1524, 1322, 1158, 1063; ¹H NMR (400 MHz, DMSO-d₆): δ = 2.01 (s, 3H), 7.17 (t, J = 8.0 Hz, 1H), 7.19 (d, J = 8.6 Hz, 1H), 7.24 (t, J = 7.5 Hz, 1H), 7.38 (t, J = 7.4 Hz, 1H), 7.50–7.52 (m, 2H), 7.78 (t, J = 8.6 Hz, 2H), 7.83 (br s, 1H), 7.98 (m, 2H), 8.58 (d, J = 8.0 Hz, 1H), 10.16 (s, 1H); ¹³C NMR (100 MHz, DMSO-d₆): 23.2, 48.2, 118.4, 118.8, 120.9, 121.7, 123.3, 127.3, 127.4, 128.9, 129.2, 130.1, 130.5, 132.6, 133.4, 145.9, 148.2, 153.9, 170.4.

**RESULT AND DISCUSSION**

In order to optimize the reaction conditions, we chose condensation of 2-naphthol, 3-nitrobenzaldehyde and acetamide catalyzed by PFPAT under different conditions both in the absence and in the presence of PFPAT and results are given in Table 1.
Table 1: Effect of different PFPAT and solvent on formation of 4.

<table>
<thead>
<tr>
<th>Entry</th>
<th>PFPAT amount (mol %)</th>
<th>Condition/solvent</th>
<th>Time (h)/yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0</td>
<td>r.t./CH3CN</td>
<td>24/0</td>
</tr>
<tr>
<td>2</td>
<td>5</td>
<td>r.t./CH3CN</td>
<td>10/80</td>
</tr>
<tr>
<td>3</td>
<td>10</td>
<td>r.t./CH3CN</td>
<td>5/95</td>
</tr>
<tr>
<td>4</td>
<td>10</td>
<td>r.t./CH2Cl2</td>
<td>24/45</td>
</tr>
<tr>
<td>5</td>
<td>10</td>
<td>r.t./THF</td>
<td>24/40</td>
</tr>
<tr>
<td>6</td>
<td>10</td>
<td>r.t./ethanol</td>
<td>10/60</td>
</tr>
<tr>
<td>7</td>
<td>10</td>
<td>r.t./H2O</td>
<td>24/10</td>
</tr>
<tr>
<td>8</td>
<td>10</td>
<td>r.t./toluene</td>
<td>10/50</td>
</tr>
<tr>
<td>9</td>
<td>15</td>
<td>r.t./CH3CN</td>
<td>8/95</td>
</tr>
</tbody>
</table>

It is noteworthy that in the absence of catalyst, the reaction failed to give the desired product, even after long reaction time (24 h, Table 1, entry 1).

Then, the effect of temperature, the amount of catalyst and the reaction time on the yield of the product were examined. Increasing either the amount of catalyst and/or prolonging the reaction time did not improve the yield (Table 1, entry 9), while reducing these factors led to a reduction in product yield (Table 1, entry 2). Building upon this result further studies were conducted and it was found that 10 mol% of PFPAT was optimum for this reaction and gave a product of 95% yield in just 5 h (Table 1, entry 3). The reaction was also examined in solvents such as H2O, THF, CH2Cl2, ethanol and toluene. In the presence of solvents reaction was sluggish and formation of byproducts was observed (Table 1, entries 4-8).

Using these optimized reaction conditions, the scope and efficiency of this approach was explored for the synthesis of a wide variety of substituted amidoalkyl naphthols and results are summarized in Table 2.

A wide range of structurally varied aldehyde reacted smoothly and quickly to give the corresponding amidoalkyl naphthole in high yield and purity as listed in Table 2. In all cases, aromatic aldehydes substituted with either electron-donating or electron-withdrawing groups underwent the reaction smoothly and gave the products in good yields. It could also be concluded that the aldehydes bearing electron-withdrawing groups required shorter time and gave higher yields (Table 2, entry 1-5).

Acetamide, benzamide and urea all underwent smooth transformations under the reaction conditions. In particular, n-butyraldehyde, as a typical aliphatic aldehyde, was tested under the reaction conditions and the corresponding desired products were isolated in good yields (Table 2, entry 9). In all cases, amidoalkyl naphthols were the sole products and no by-product was observed.

A possible mechanism for this transformation is proposed in Scheme 2. We supposed that the reaction of 2-naphthol with aromatic aldehydes in the presence of acid catalyst is known to provide ortho-quinone methides (o-QMs) [17]. The o-QMs were reacted with amides or urea to produce 1-amidoalkyl-2-naphthol derivatives (Scheme 2).
Scheme 2: Tentative mechanism showing the formation of amidoalkyl naphthol

The highly hydrophobic wall of pentafluorophenyl moiety effectively repels H$_2$O produced by the dehydration steps [21].

In addition, the PFPAT catalyst was easily separated from the reaction mixture after work-up; washing with NaOH aqueous solution removed CF$_3$SO$_2$H, followed by distillation under reduced pressure (C$_6$F$_5$NH$_2$: bp 153 °C at 760 mmHg).

In conclusion, we have developed a facile, convenient and solvent-free method for the one-pot synthesis of amidoalkyl naphthols derivatives by coupling various aromatic aldehydes with amides or urea and 2-naphthol using PFPAT as an efficient catalyst. In contrast to the existing methods using potentially hazardous catalysts/additives, the present method offers the following competitive advantages: (i) PFPAT is easy-toPrepare from commercially available pentafluoroaniline and triflic acid, (ii) ease of product isolation/purification by non-aqueous work-up, (iii) no side reaction, (iv) low costs and simplicity in process and handling and (v) amidoalkyl naphthols are produced by an environmentally benign process.

ACKNOWLEDGMENT

This research is supported by the Islamic Azad University, Ayatollah Amoli Branch.

REFERENCE


