Microwave-Promoted Synthesis of Novel N-Arylanthranilic Acids

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In this paper we report the synthesis of a series of novel N-aryl anthranilic acids, with good to excellent yields, employing microwaves as heat source to promote the Ullmann coupling between anthranilic acids and aryl bromides possessing electron donating or withdrawing groups.

Keywords: N-aryl anthranilic acids, microwaves, Ullmann coupling, green chemistry

Introduction

N-Aryl anthranilic acids are an interesting class of compounds which shows antibacterial1,2 and anti-inflammatory3 properties. It is also employed as precursor of biologically important compounds such as acridine4-6 and acridone alkaloids.7-14 The synthesis of N-aryl anthranilic acids can be usually achieved by the Ullmann condensation15 between a 2-halobenzoic acid and an aryl amine16,17 or an anthranilic acid and an aryl halide.18,19 One of the major drawbacks of these methodologies is the need of heating during long reaction time.20

One of the twelve principles of Green Chemistry is that energy requirements of chemical processes should be recognized for their environmental and economic impacts and should be minimized.21 The use of unconventional energy sources, as for example ultrasound or microwave (MW) irradiation, may greatly reduce energy consumption. Methods for carried out Ullmann reaction under ultrasonic irradiation have been reported.22,23

The use of microwaves in organic synthesis has grown in recent years and among its advantages, when compared to the reactions carried out in conventional heating, are the reduction of reaction times and, in many cases, a significant increase in yields of desired products.24-27 There are few reports in literature describing the Ullmann coupling employing microwave heating using water as solvent28,29 and solvent-free conditions.30

In this paper we report the synthesis of a series of novel N-aryl anthranilic acids, with good to excellent yields, employing microwaves as heat source to promote the Ullmann coupling between anthranilic acids and aryl bromides possessing electron donating or withdrawing groups.

Results and Discussion

In an ongoing program on the synthesis of acridone alkaloids, we firstly investigated the Ullmann reaction of 1-benzyloxy-3-bromobenzene (1a) and an anthranilic acid (2). After a series of experiments employing several literature available procedures,31-34 we observed that this reaction was best performed using the methodology described by Ma and co-workers20 (Scheme 1), employing 20 mol% of Cu and L-proline, DMSO as solvent at 90 °C for 24 h.

Our attempts to obtain the desired compounds under analogous conditions in a focused microwave oven (CEM-Discover®) were unsuccessful (Table 1, entry 1). The reason for this lack of reactivity may be due to the high dielectric loss of dimethylsulfoxide which makes the microwave effect less pronounced.26,35 Then, we performed the reaction between compound 1a and 2a with the same catalytic system but using iso-amyl alcohol as solvent and after one hour the desired compound was isolated in 78% yield (entry 2). However, reaction between aryl halide 1a and anthranilic acid 2b in analogous conditions furnished no product. The low solubility of 2b in iso-amyl alcohol

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seemed to be responsible for the unsatisfactory result, thus we performed the reaction of 1a and 2b in anhydrous DMF and compound 3b was obtained in 59% yield. The yield of 3b was improved to 82% by the use of DMF containing 10% of water (entries 6-8).

Water effect was also observed in the reaction of anthranilic acid 2b with p-bromoanisol (1b). In anhydrous DMF, compound 3c was obtained in 39% while it was isolated in 76% when performed in DMF/water (entries 9 and 10). Reaction of 1a and 2a in DMF/water resulted in the formation of a complex mixture of by-products; additionally use of iso-amyl alcohol/water resulted in the recovery of starting materials (entries 4 and 5). Formation of by-products in DMF/water system may be attributed to the higher reaction temperature. By the other hand, the lack of reactivity in iso-amyl alcohol/water system may be due to the lower solubility of the reagents, however this effect is not clear yet since the solvent dramatically affect the Ullmann reaction and inhibition of the cooper catalytic species should also be considered.36

After optimization of the Ullmann reaction we performed the coupling of different anthranilic acids and aryl halides possessing electron donating and electron withdrawing groups to evaluate the scope of this protocol (Table 2). Good to excellent isolated yields were obtained in all cases, excepting with difluor-substitute anthranilic acid 2f, which afforded relatively low yield probably due to its low reactivity once starting material was recovered.

Table 1. Ullmann coupling employing microwave irradiation

<table>
<thead>
<tr>
<th>Entry</th>
<th>Aryl bromide</th>
<th>Anthranilic acid</th>
<th>Solvent</th>
<th>Temperature / (°C)</th>
<th>Product, yield / (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1a; R1=BrO; R2=H</td>
<td>2a; R1=H</td>
<td>DMSO</td>
<td>90</td>
<td>NR</td>
</tr>
<tr>
<td>2</td>
<td>1a</td>
<td>2a</td>
<td>iso-amyl alcohol</td>
<td>140</td>
<td>3a; R1=BrO, R2=H (78%)</td>
</tr>
<tr>
<td>3</td>
<td>1a</td>
<td>2a</td>
<td>DMF</td>
<td>160</td>
<td>NR</td>
</tr>
<tr>
<td>4</td>
<td>1a</td>
<td>2a</td>
<td>iso-amyl alcohol/H2O</td>
<td>140</td>
<td>NR</td>
</tr>
<tr>
<td>5</td>
<td>1a</td>
<td>2a</td>
<td>DMF/H2O</td>
<td>160</td>
<td>NR</td>
</tr>
<tr>
<td>6</td>
<td>1a</td>
<td>2b; R1=NO2</td>
<td>iso-amyl alcohol</td>
<td>140</td>
<td>NR</td>
</tr>
<tr>
<td>7</td>
<td>1a</td>
<td>2b</td>
<td>DMF</td>
<td>160</td>
<td>3b; R1=BrO; R2=H, R3=NO2 (59%)</td>
</tr>
<tr>
<td>8</td>
<td>1a</td>
<td>2b</td>
<td>DMF/H2O</td>
<td>160</td>
<td>3b; R1=BrO; R2=H, R3=NO2 (59%)</td>
</tr>
<tr>
<td>9</td>
<td>1b; R1=H; R2=MeO</td>
<td>2b</td>
<td>DMF</td>
<td>160</td>
<td>3c; R1=H; R2=MeO; R3=NO2 (39%)</td>
</tr>
<tr>
<td>10</td>
<td>1b</td>
<td>2b</td>
<td>DMF/H2O</td>
<td>160</td>
<td>3c (76%)</td>
</tr>
</tbody>
</table>

aIsolated yield after purification.
Microwave-Promoted Synthesis of Novel N-Arylanthranilic Acids


spectrometer. Mass Spectra were recorded on a Shimadzu GCMS-QP5000 or Mass Spectrometer QuatroLC-Micromass. Elemental analyses were performed on a Fisons EA 1108 CHNS-O. Analytical thin-layer chromatography was performed on a 0.25 µm film of silica gel containing fluorescent indicator UV254 supported on an aluminum sheet (Sigma-Aldrich). Flash column chromatography was performed using silica gel (Kieselgel 60, 230-400 mesh, E. Merck). Gas chromatography was performed in a Shimadzu GC-17A with H2 as carrier and using a DB-5 column. Melting points were performed in Microquimica MQAPF-301.

General procedure

Aryl bromide (0.84 mmol), anthranilic acid (0.42 mmol), CuI (0.084 mmol), L-proline (0.084 mmol), K 2CO3 (0.42 mmol) and solvent (1 mL) (Tables 1 and 2) were placed in a glass tube, purged with oxygen-free nitrogen during 10 min sealed and irradiated during 1h in a focused microwave oven (CEM Discover®).

Table 2. Ullmann reaction of different anthranilic acids and aryl halides

<table>
<thead>
<tr>
<th>Entry</th>
<th>Aryl bromide</th>
<th>Anthranilic acid</th>
<th>Product, yield / (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1c: R1=NO2; R2=BnO</td>
<td>2a: R'=R''=R'''=H</td>
<td>3d, 83</td>
</tr>
<tr>
<td>2</td>
<td>1d: R'=MeO; R''=BnO</td>
<td>2a</td>
<td>3e, 85</td>
</tr>
<tr>
<td>3</td>
<td>1e: R''=H; R'''=BnO</td>
<td>2b: R'=R''=H; R'''=NO2</td>
<td>3f, 69</td>
</tr>
<tr>
<td>4</td>
<td>1f: R'; R''=H</td>
<td>2b</td>
<td>3g, 82</td>
</tr>
<tr>
<td>5</td>
<td>1c</td>
<td>2c: R'=MeO; R''=R'''=H</td>
<td>3h, 54</td>
</tr>
<tr>
<td>6</td>
<td>1d</td>
<td>2d</td>
<td>3i, 70</td>
</tr>
<tr>
<td>7</td>
<td>1c</td>
<td>2e: R'=R''=R'''=MeO</td>
<td>3j, 83</td>
</tr>
<tr>
<td>8</td>
<td>1d</td>
<td>2f: R'=H; R''=R'''=F</td>
<td>3k, 38</td>
</tr>
<tr>
<td>9</td>
<td>1c</td>
<td>2f</td>
<td>3l, 54</td>
</tr>
</tbody>
</table>

*aAll reactions were performed in anhydrous iso-amyl alcohol as solvent at 140 °C; except for anthranilic acid 2b which was performed in DMF/H2O 90% at 160 °C. *Isolated yield after purification.

2-(3-Benzylxy-phenylamino)-5-nitrobenzoic acid (3b)

Purified by flash chromatography employing hexanes: ethyl acetate:acetic acid (70:30:0.3) as eluent; yellow solid; mp 194.3 °C (dec.); 'H NMR (200 MHz, CDCl3): δ 5.07 (s, 2H), 6.94-6.77 (m, 1H), 7.06 (d, J=9.4 Hz, 1H), 7.38-7.21 (m, 7H), 8.06 (dd, J=9.4, 2.7 Hz, 1H), 8.93 (d, J=2.7 Hz, 1H), 10.42 (s, 1H). 13C NMR (50 MHz, CDCl3): δ 69.8, 76.3, 77.0, 77.6, 110.4, 110.8, 112.1, 112.7, 127.1 (2C), 127.8, 128.4 (2C), 128.8, 129.2, 130.2, 136.3, 137.0, 139.5, 152.5, 159.5, 169.3. Anal. Calc. for C20H16N2O5: C 65.93; H 4.43; N 7.69. Found: C 65.13; H 4.50; N 7.03.

2-(3-Methoxy-phenylamino)-5-nitrobenzoic acid (3c)

Purified by flash chromatography employing hexanes: ethyl acetate:acetic acid (70:30:0.3) as eluent; yellow solid; mp 230.8 °C; 'H NMR (200 MHz, DMSO-d6): δ 3.77 (s, 3H), 6.84-7.27 (m, 6H), 8.08 (dd, J=9.0, 4.0 Hz, 1H), 8.66 (d, J=4.0 Hz, 2H), 10.71 (s, 1H). 13C NMR (50 MHz, DMSO-d6): δ 55.2, 110.1, 112.7, 114.9 (2C), 126.4 (2C), 128.4, 129.1, 130.6, 136.0, 137.0, 153.4, 157.5, 168.6. Anal. Calc. for C14H12N2O5: C 58.33; H 4.20; N 9.72. Found: C 58.09; H 4.33; N 9.72.

2-(4-Methoxy-phenylamino)-5-nitrobenzoic acid (3d)

Purified by flash chromatography employing hexanes: ethyl acetate:acetic acid (70:30:0.3) as eluent; yellow solid; mp 197.2 °C; 'H NMR (200 MHz, DMSO-d6): δ
5.28 (s, 2H), 6.80 (t, J 8.0 Hz, 1H), 7.09 (d, J 8.0 Hz, 1H), 7.63-7.56 (m, 9H), 7.77 (d, J 2.0 Hz, 1H), 7.90 (d, J 8.0 Hz, 1H), 9.55 (s, 1H). 13C NMR (50 MHz, DMSO-d6): δ 70.7, 104.7, 112.9, 113.6, 116.8, 117.8, 118.2, 127.3 (2C), 128.0, 128.1, 128.4 (2C), 131.8, 133.8, 134.2, 136.0, 139.9, 146.8, 168.6. Anal. Calc. for C20H16N2O5: C 65.93; H 4.43; N 7.69. Found: C 66.22; H 4.75; N 7.94.

2-(4-Benzyloxy-3-methoxy-phenylamino)-2-naphthoic acid

(3e)

Purified by flash chromatography employing hexanes: ethyl acetate:acetic acid (80:20:0.3) as eluent; yellowish solid; mp 187.6 °C; 1H NMR (200 MHz, DMSO-d6): δ 3.57 (s, 3H), 3.68 (s, 3H), 4.95 (s, 2H), 6.15 (dd, J 8.0, 2.0 Hz, 1H), 6.43 (d, J 2.0 Hz, 1H), 6.80 (d, J 8.0 Hz, 1H), 7.01 (t, J 8.0 Hz, 1H), 7.19-7.46 (m, 8H). 13C NMR (50 MHz, DMSO-d6): δ 55.4 (2C), 70.8, 103.1, 108.6, 114.8, 116.0, 120.6, 121.0, 122.7, 127.6 (2C), 127.8, 128.2 (2C), 134.5, 137.5, 138.8, 141.8, 144.9, 151.8, 169.4. Anal. Calc. for C20H16N2O5: C 69.64; H 5.58; N 3.69. Found: C 69.26; H 6.09; N 3.85.

3-(4-Benzylx-3-nitro-phenylamino)-2-naphthoic acid

(3i)

Purified by flash chromatography employing hexanes: ethyl acetate:acetic acid (70:30:0.3) as eluent; yellow solid; mp 187.7 °C; 1H NMR (200 MHz, DMSO-d6): δ 3.57 (s, 3H), 3.84 (s, 3H), 3.86 (s, 3H), 5.21 (s, 2H), 7.04-7.44 (m, 10H). 13C NMR (50 MHz, DMSO-d6): δ 55.9, 59.2, 60.7, 70.9, 109.3, 111.7, 116.5, 117.2, 121.1, 127.3 (2C), 127.9, 128.4 (2C), 131.5, 136.4, 138.9, 139.6, 144.3, 146.5, 146.9, 150.0, 169.7. Anal. Calc. for C22H18N2O5: C 70.36; H 4.67; N 7.69. Found: C 70.60; H 4.69; N 7.69.
2-(4-Benzyloxy-3-methoxy-phenylamino)-4,5-difluorobenzoic acid (3m)

Purified by flash chromatography employing hexanes: ethyl acetate:acetic acid (80:20:0.3) as eluent; white solid; mp 192.7 °C; 1H NMR (200 MHz, DMSO-d6): δ 3.76 (s, 3H), 5.06 (2H), 6.75-7.05 (m, 5H), 7.29-7.48 (m, 5H), 7.78 (dd, J 11.0, 8.0 Hz, 1H), 9.45 (s, 1H). 13C NMR (50 MHz, DMSO-d6): δ 55.6, 70.2, 101.2 (d, J 13.5 Hz), 140.5 (dd, J 234.0, J 13.5 Hz), 145.1, 146.7 (dd, J 10.0, 1.0 Hz), 150.0, 153.3 (dd, J 249.2, 13.5 Hz), 168.3 (dd, J 2.2, 0.5 Hz). Anal. Calc. for C21H17F2NO4: C 65.45; H 4.45; N 7.16. Found: C 65.63; H 5.55; N 3.72.

2-(4-Benzylthio-3-nitro-phenylamino)-4,5-difluorobenzoic acid (3n)

Purified by flash chromatography employing hexanes: ethyl acetate:acetic acid (80:20:0.3) as eluent; yellow solid; mp 216.8 °C; 1H NMR (200 MHz, DMSO-d6): δ 5.06 (s, 2H), 6.97 (dd, J 4.5, 2.2, 1H), 7.30-7.59 (m, 8H), 7.76-7.86 (m, 2H), 9.55 (s, 1H). 13C NMR (50 MHz, DMSO-d6): δ 70.2, 102.1 (d, J 20.0 Hz), 108.8 (dd, J 4.5, 2.5 Hz), 119.8, 119.1, 119.7 (d, J 15.5 Hz), 127.7 (2C), 128.0, 128.4 (2C), 128.7, 133.0, 136.0, 139.9, 141.3 (dd, J 235.7, 13.5 Hz), 145.2 (dd, J 9.5, 1.0 Hz), 147.4, 153.3 (dd, J 262.0, 13.5 Hz), 168.1 (d, J 1.5 Hz). Anal. Calc. for C20H14F2N2O5: C 60.00; H 3.52; N 9.49; found: C 59.66; H 3.87; N 7.16.

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References


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