Efficient N-Aroylation of Substituted Indoles with N-Aroylbenzotriazoles

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Abstract: Stable and easily accessible N-arylbenzotriazoles react with indoles in the presence of a base to afford the corresponding N-aroylindoles in yields averaging 70%. This method is effective even when both coupling reagents possess electron-donating substituents.

Key words: N-arylbenzotriazoles, indoles, N-aroylindoles, electron-donating substituents

N-Aroylindoles are well-known nonsteroidal anti-inflammatory drugs (NSAIDs) (e.g., indomethacin, a 5-methoxyindole derivative).1 N-Aroyl-5-nitro-1H-indoles are utilized as intermediates for the synthesis of 2-aryl-5-nitro-1H-indoles effective as bacterial NorA efflux pump inhibitors.2 5-Substituted N-aroylindoles also exhibit selective cyclooxygenase-2 inhibitor activity,3 and 5-aminoo-1-(3,5-dimethylbenzoyl)-1H-indole possesses antiangiogenic activity.4 Furthermore, suitably substituted N-aroylindoles are used as precursors for the synthesis of benzannulated indolizidines.5

A variety of methods have been reported for the direct N-arylation of indoles. When neither the aroylating agent nor the indole contains an electron-donating substituent, several procedures are satisfactory.6 However, useful N-arylations of indoles to a product in which either the aryl group or indole nucleus contains a strong electron-donor substituent are rare. N-Aroylindoles have been prepared by (i) indole anion formation with sodium hydride followed by reaction with an acid chloride (36–82%),6a (ii) direct arylation of indoles with carboxylic acids using boric acid (50–82%),6c and (iii) phase-transfer-catalyzed arylation of indoles (77–94%).6d Most recently, Bremner et al.6b N-aroylated 5-substituted indoles with an electron-withdrawing substituent (NO2, CN or F) in the 5-position with carboxylic acids via DCC/DMAP coupling to give 73–95% yields of the N-aroylindoles. However, the yields for the 5-unsubstituted indoles, were 32–46% and for 5-methoxyindole only 0–15%.

N-Aroylbenzotriazoles are easily prepared activated derivatives of carboxylic acids.7 Applications of N-arylbenzotriazoles include (i) N-acylation of amines, amides,8 and sulfonamides; (ii) O-acylation of aldehydes,9 steroids,10 hydroxyterpenes, and alcohols;12 (iii) many C-acylations, viz: pyroles and indoles,13 ketones and heteroaromatics,14 alkyl sulfones,15 alkyl cyanides,16 alkyl azines,17 nitroalkanes,18 furans, and thiophenes;19 and (iv) syntheses of peptides,20 oxazolines,21 esters,22 benzodioxin-4-ones,23 ketones,24 benzodiazepin-2-ones,25 thiol esters,26 alcohols,27 hydrazides,28 and heteroaromatics.29 Earlier we13a,14b and others12 have reported regiospecific C-acylation of pyroles and indoles using N-arylbenzotriazoles. Herein, we report the efficient synthesis of electron-rich N-aroylindoles from N-arylbenzotriazoles in the presence of a base via N-arylation of indoles.

Commercially available indole (1a) and 5-methoxyindole (1b) were used as substrates for N-arylation reactions. N-Aroylbenzotriazoles (2a–d) were readily prepared from 1H-benzotriazole (BtH) and the corresponding carboxylic acid in yields of 85–95% according to a literature procedure.20 Reaction of 2,6-dimethoxybenzoic acid with BtH and thionyl chloride in dichloromethane at room temperature for one hour gave benzotriazol-1-yl-(2,6-dimethoxyphenyl)methanone (2d) (95%) (Figure 1), characterized by 1H NMR, 13C NMR, and CHN analyses.

Reaction of the sodium salt of indole (1a) with benzotriazol-1-yl-phenylmethanone (2a) in THF at 25 °C for 12 hours gave the corresponding 1-benzoyl-1H-indole (3a) in 81% yield (Table 1). Previously 3a was prepared in 32% yield from 1a and benzoyl chloride.30 We tested the generality of this method by reacting indoles 1a and 1b with electron-rich N-arylbenzotriazoles 2a–d (Figure 1). Reaction of 1a with 2b and 2c gave 1-(4-methoxyben-
zoyl)-1H-indole (3b) and 1-(2-methoxybenzoyl)-1H-indole (3e) in 91% (Lit.6b 46%) and 90% yield (Lit.6b 34%), respectively (Table 1).

Reaction of 1b with 2a, 2b, and 2c gave 1-benzoyl-5-methoxy-1H-indole (3d) (87%, Lit.6b 15%), 5-methoxy-1-(4-methoxybenzoyl)-1H-indole (3e) (77%, Lit.6b 9%), and the novel 5-methoxy-1-(2-methoxybenzoyl)-1H-indole (3f) (42%, Lit.6b 0%) (Table 1). A previous attempt to prepare 3f from the corresponding acid chloride was unsuccessful.6c In order to confirm unambiguously the structures of these products the X-ray crystal structure of a representative example, 3f, was determined.30 Figure 2 shows a perspective view of the structure which is in accord with that proposed and confirms the N-arylation.

Reactions of 1a and 1b with more electron-rich (thus less reactive) N-arylbenzotriazole 2d gave novel 1-(2,6-

### Table 1 Preparation of N-Aroylindoles 3a–h

<table>
<thead>
<tr>
<th>Entry</th>
<th>Indole</th>
<th>RCOBt</th>
<th>Product</th>
<th>Yield (%) (^{a–c})</th>
<th>Lit.(^b) yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1a</td>
<td>2a</td>
<td>3a(^a)</td>
<td>81</td>
<td>32</td>
</tr>
<tr>
<td>2</td>
<td>1a</td>
<td>2b</td>
<td>3b(^a)</td>
<td>91</td>
<td>46</td>
</tr>
<tr>
<td>3</td>
<td>1a</td>
<td>2c</td>
<td>3c</td>
<td>90</td>
<td>34</td>
</tr>
<tr>
<td>4</td>
<td>1b</td>
<td>2a</td>
<td>3d</td>
<td>87</td>
<td>15</td>
</tr>
<tr>
<td>5</td>
<td>1b</td>
<td>2b</td>
<td>3e</td>
<td>77</td>
<td>9</td>
</tr>
<tr>
<td>6</td>
<td>1b</td>
<td>2c</td>
<td>3f</td>
<td>42</td>
<td>0</td>
</tr>
<tr>
<td>7</td>
<td>1a</td>
<td>2d</td>
<td>3g</td>
<td>60</td>
<td>this work</td>
</tr>
<tr>
<td>8</td>
<td>1b</td>
<td>2d</td>
<td>3h</td>
<td>36</td>
<td>this work</td>
</tr>
</tbody>
</table>

\(^{a}\) Isolated yield after column purification and determined from a single experiment.

\(^{b}\) TLC profile (EtOAc–hexanes, 1:4).

\(^{c}\) Silica gel column chromatography (5–20% EtOAc in hexanes).

\(^{d}\) H-3' proton appears as a singlet because the coupling constants between H-3' and H-2' are 2–4 Hz (low resolution).
dimethoxybenzoyl)-1H-indole (3g) and 1-(2,6-dimethoxybenzoyl)-5-methoxy-1H-indole (3h) in 60% and 36% yield, respectively (Table 1). These results demonstrate that the present method of synthesis is compatible with up to a total of three electron-donating substituents in both the indole and phenyl rings. Readily available electronic N-arylbenzotriazoles under basic conditions efficiently N-arylate indoles, including those with an electron-donor substituent at the 5-position.

Melting points are uncorrected. 1H NMR and 13C NMR spectra were recorded on a FT-Bruker AT-300 instrument using TMS as an internal standard and CDCl3 as solvent. Compounds were characterized by elemental analysis using a Carlo-Erba EA1112 instrument.

Benzotriazol-1-yl-(2,6-dimethoxyphenyl)methane (2d)
2.6-Dimethoxybenzoic acid (1.82 g, 10 mmol) was placed in a 100 mL Schlenk flask and anhyd CH2Cl2 (20 mL) was added. Then, benzotriazole (3.63 g, 30.5 mmol) and CH2Cl2 (20 mL) were added followed by SOCl2 (0.77 mL, 10.5 mmol). The solid precipitate was difficult to stir and hence it was shaken in a New Brunswick Scientific apparatus at a speed of 40 rpm for 1 h at r.t. The white precipitate was filtered and the filtrate was evaporated under reduced pressure to give the crude product, which was then washed with anhyd Et2O (2 × 10 mL) to obtain the pure 2d (2.62 g, 95%); white crystals; mp 154–155 °C.

1H NMR (300 MHz, CDCl3): δ = 8.45 (d, J = 8.2 Hz, 1 H), 8.13 (d, J = 8.2 Hz, 1 H), 7.70 (t, J = 7.3 Hz, 1 H), 7.53 (t, J = 7.3 Hz, 1 H), 7.45 (t, J = 8.4 Hz, 1 H), 6.67 (d, J = 8.4 Hz, 2 H), 3.76 (s, 6 H).

13C NMR (75 MHz, CDCl3): δ = 165.6, 158.2, 146.4, 132.9, 131.4, 130.3, 126.3, 120.2, 112.4, 117.2, 104.1, 56.2.

Anal. Calcd for C18H17NO2: C, 76.48; H, 5.21; N, 5.57. Found: C, 76.43; H, 4.83; N, 5.67.

1-Benzoyl-5-methoxy-1H-indole (3d)
Yield: 0.218 g (87%); white crystals; mp 106–107 °C (Lit.6b mp 106–107 °C).

1H NMR (300 MHz, CDCl3): δ = 8.25 (d, J = 9.1 Hz, 1 H), 7.65 (dd, J = 6.9, 1.5 Hz, 2 H), 7.55–7.41 (m, 3 H), 7.18 (dd, J = 3.0, 0.5 Hz, 1 H), 6.99 (d, J = 2.5 Hz, 1 H), 6.92 (dd, J = 8.9, 2.5 Hz, 1 H), 6.47 (d, J = 3.7 Hz, 1 H), 3.80 (s, 3 H).

13C NMR (75 MHz, CDCl3): δ = 168.4, 156.6, 134.5, 131.7, 130.6, 129.1, 128.5, 128.2, 117.2, 113.3, 108.5, 103.5, 55.6.

Anal. Calcd for C18H16NO2: C, 76.48; H, 5.21; N, 5.57. Found: C, 76.36; H, 5.15; N, 5.50.

5-Methoxy-1-(4-methoxybenzoyl)-1H-indole (3e)
Yield: 0.218 g (77%); white crystals; mp 106–108 °C (Lit.6b mp 105–106 °C).

1H NMR (300 MHz, CDCl3): δ = 8.33 (d, J = 9.1 Hz, 1 H), 7.78 (tt, J = 9.7, 2.7, 2.0 Hz, 2 H), 7.38 (d, J = 3.7 Hz, 1 H), 7.12 (d, J = 2.5 Hz, 1 H), 7.07–7.02 (m, 3 H), 6.56 (d, J = 3.7 Hz, 1 H), 3.94 (s, 3 H), 3.92 (s, 3 H).

13C NMR (75 MHz, CDCl3): δ = 167.8, 162.5, 156.4, 131.6, 131.5, 130.7, 128.3, 126.4, 116.9, 113.7, 113.2, 107.9, 103.3, 55.6, 55.4.

Anal. Calcd for C18H16NO2: C, 72.58; H, 5.37; N, 4.98. Found: C, 72.84; H, 5.32; N, 4.85.

5-Methoxy-1-(2-methoxybenzoyl)-1H-indole (3f)
Yield: 0.119 g (42%); white crystals; mp 93–95 °C.

1H NMR (300 MHz, CDCl3): δ = 8.35 (br d, J = 7.3 Hz, 1 H, H-2), 7.50 (td, J = 9.0, 1.6 Hz, 1 H, H-6), 7.43 (dd, J = 7.5, 1.6 Hz, 1 H, H-4), 7.08 (d, J = 7.4 Hz, 1 H, H-7), 7.05–7.00 (m, 3 H, H-3,5), 6.97 (dd, J = 8.9, 2.4 Hz, 1 H, H-3), 6.47 (d, J = 3.7 Hz, 1 H, H-6), 3.87 (s, 3 H, OCH3), 3.79 (s, 3 H, OCH3).

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References


Crystal data for 3f: C17H15NO3, MW 281.30, monoclinic, space group Cc, a = 15.1850 (14), b = 4.3143 (4), c = 21.398 (2) Å, β = 103.703 (3)°. V = 1362.0(2) Å³, F(000) = 592, Z = 4, T = −170 °C, μ (MoKα) = 0.095 mm⁻¹, Dcalcd = 1.372 g.cm⁻³, 2θmax 50° APEX II CCD area detector, MoKα radiation, SHELXS and SHELXL, GOF = 1.08, wR(F²) = 0.074 (all 2244 data), R = 0.029 (2039 data with I > 2σI). CCDC # 639667. Copies of the crystal data can be obtained free of charge from CCDC, 12, Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336 033; e-mail: deposit@ccdc.cam.ac.uk.