The photochemistry of 1-alkenyl-substituted-1,2,3-benzotriazoles leading to formation of indole and fused indole derivatives

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Abstract
Under photolysis conditions involving irradiation with a 16 W low pressure mercury arc-lamp (254 nm) or sunlight, functionally substituted 1-vinylbenzotriazoles react efficiently to produce 2-acylindoles, 2-benzotriazol-1-yl-4-methylquinolin-3-ol, isatin, indolo[2,1-b]quinazoline-6,12-dione (tryptanthrin) and dihydropyrazolo[4,3-b]indole.

Keywords: Photolysis, 1-vinylbenzotriazoles, 2-acylindoles, 3-quinolinol, isatin, tryptanthrin, pyrazolo[4,3-b]indole

Introduction
It is generally known that 3-substituted indoles can be readily generated via reactions of indoles with electrophilic reagents and that 2-substituted indoles are better produced by using Nenitzescu, Madelung and Gassman ring synthesis methodologies.1 Earlier, we described a protocol for the synthesis of 3-acylindoles,2 in which difficultly obtained C-2 substituted indoles could be prepared.

Previous studies have shown that thermolytic and/or photolytic reactions of 1-substituted benzotriazole derivatives take place with elimination of N₂ followed by subsequent ring closure of the resulting biradical intermediates to form heterocyclic products (Figure 1).3-8 These efficient processes have been described by Katritzky and his coworkers.9 In a follow up to our earlier efforts in which syntheses of the benzotriazole derivatives 1a-c, 10 and 15 were developed,10a-d we gained have explored the photochemistry of these substances, postulating that the reactions would afford 2-substituted indoles in good yields. Below, we report the results of this investigations aimed at the synthesis of substances of 2-substituted indoles through photochemical reactions of benzotriazoles 1a-c, 10 and 15.
Results and Discussion

The 1-substituted benzotriazole derivatives 1a-c, 10 and 15, required in this study, were prepared following the procedures described by us earlier.10a-d These substances were fully characterized by using spectroscopic techniques. The UV spectra of these compounds display absorption maxima in the 248-296 nm wavelength regions (Table 1).

In Scheme 1 are summarized the results of reactions promoted by irradiation of acetonitrile solutions of 1a-c in quartz glass tubes with a 16 W low pressure mercury arc-lamp (254 nm) under a nitrogen atmosphere for 24 h at room temperature. Upon irradiation, benzotriazole 1a reacts to give 2-acetyl-3-dimethylaminoindole 3a (58%) and 2-benzotriazolyl-4-methylquinolin-3-ol 4 (15%). The structure of 4 is well defined by its complete 1H NMR, 13C NMR, and mass spectrometric data, as well as by x-ray crystallographic analysis (Figure 4). In a similar manner, 1b and 1c undergo photochemical reactions to form only the 2-benzoyl- and 2-cyano-3-dimethylaminoindole derivatives 3b and 3c, respectively, in respective yields of 62% and 73% (Table 1). Products 3a-c can also be generated in 10-18% yields by irradiation of acetonitrile solutions of 1a-c in Pyrex glass tubes using sunlight for 15 days (Table 1).

Scheme 1. Photolysis of 1a-c.
Table 1. Photoproducts formed by irradiation of 1a-c, 10 and 15

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate</th>
<th>( \lambda_{\text{max}} )</th>
<th>Condition</th>
<th>Product (Yield)</th>
</tr>
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<tbody>
<tr>
<td>1</td>
<td>1a</td>
<td>286</td>
<td>A</td>
<td>3a (58%) 4 (15%)</td>
</tr>
<tr>
<td>2</td>
<td>1a</td>
<td></td>
<td>B</td>
<td>3a (18%)</td>
</tr>
<tr>
<td>3</td>
<td>1b</td>
<td>296</td>
<td>A</td>
<td>3b (62%)</td>
</tr>
<tr>
<td>4</td>
<td>1b</td>
<td></td>
<td>B</td>
<td>3b (10%)</td>
</tr>
<tr>
<td>5</td>
<td>1c</td>
<td>278</td>
<td>A</td>
<td>3c (73%)</td>
</tr>
<tr>
<td>6</td>
<td>1c</td>
<td></td>
<td>B</td>
<td>3c (16%)</td>
</tr>
<tr>
<td>7</td>
<td>10</td>
<td>274</td>
<td>A</td>
<td>12 (41%) 14 (38%)</td>
</tr>
<tr>
<td>8</td>
<td>15</td>
<td>248</td>
<td>A</td>
<td>16 (68%)</td>
</tr>
</tbody>
</table>

A: Irradiation using a low pressure mercury arc-lamp (254 nm); B: Irradiation using sunlight

The structures of all new compounds were assigned by using spectroscopic and analytical methods. The structure of 3a is readily assigned based on 2D NMR results. The \(^1\)H and \(^{13}\)C signal assignments and the H-C correlations from the HMBC 2-D experiments are displayed in Figure 2. The important HMBC results include the observations that H-4 at 7.83 ppm correlates with C-2a, C-6 at 135.2 ppm, 126.1 ppm; H-7 at 7.25 ppm correlates with C-3a, C-5 at 124.3 ppm, 119.6 ppm; H-6 at 7.21 ppm correlates with C-2a, C-4 at 135.2 ppm, 122.9 ppm; H-5 at 6.99 ppm correlates with C-3a, C-7 at 124.3 ppm, 112.6 ppm; H-9 at 2.66 ppm correlates with C-8, C-2 at 190.5 ppm, 128.7 ppm; H-10 at 2.98 ppm correlates with C-3 at 137.8 ppm. Finally, single crystal X-ray structure analysis (Figures 3 and 4) confirmed the structures of the new compounds 3c and 4.

2-Acetyl-3-dimethylamino-1H-indole

Figure 2. Important HMBC, H-C correlation of compound 3a.
The formation of 3a-c in these processes can be readily explained by a mechanism involving initial photo-extrusion of N$_2$ to form the corresponding diradical intermediates 2, which then cyclize followed by a 1,3-H shift to yield the indole derivatives. On the other hand, formation of 2-benzotriazolyl-4-methylquinolin-3-ol 4 from 1a is likely a result of initial excited state N1-C bond cleavage to give radical 5, which then reacts with another molecule of 1a to form 6. The latter intermediate then loses N$_2$ and rearranges to give radicals 7, 8 and 9 sequentially and finally 4 (Scheme 2).
Scheme 2. Possible mechanism for the formation of 4.

Photochemical reaction of ethyl 2-benzotriazol-1-yl-3-dimethylaminoacrylate 10 gives isatin 12 (41%) and indolo[2,1-b]quinazoline-6,12-dione (tryptanthrin) 14 (39%) (Scheme 3, Table 1). A plausible route for formation of isatin involves the intermediacy of biradical 11. A similar pathway has been previously described. On the other hand, the tetracyclic product 14 is most likely formed by secondary photochemical reaction of 12 giving isatoic anhydride 13 that relies on the presence of traces of water in the reaction mixture. This assumption was probed by carrying out photoreaction of 12, which after a 24 h irradiation period gave 13 in quantitative yield. It has been previously reported that under basic conditions anhydride 13 reacts with 12 to produce 14. It should be noted that the present method serves as a direct route for the preparation of tryptanthrin 14, a well known and biologically interesting natural product.

Scheme 3. Photolysis products of compound 10.
The current studies were extended to include the exploration of the photochemistry of 1-(5-phenyl-1H-pyrazol-4-yl)-1H-benzotriazole 15, which was observed to undergo irradiation promoted N₂ elimination to generate a biradical intermediate that cyclizes to yield the corresponding 3-phenyl-1,4-dihydropyrazolo[4,3-b]indole 16 in 68% yield (Scheme 4).

Scheme 4. Photolysis of 15.

Conclusion

The investigation described above has resulted in an efficient direct photochemical methodology for the preparation of new indole derivatives, some of which are difficult to obtain using other procedures. Also, a new interesting photochemical route for synthesis of the biologically active natural product tryptanthrin as well as other biologically and pharmaceutically interesting indole and condensed indole derivatives have been developed.13-15

Experimental Section

General. Melting points were recorded on a Gallenkamp apparatus. IR spectra were recorded using KBr pellets on a Perkin-Elmer 2000 FT-IR spectrophotometer. ¹H- and ¹³C- NMR spectra were recorded on a Bruker DPX 400 MHz, AvanceII 600 MHz super-conducting NMR spectrometer with proton spectra measured at 400 MHz and carbon spectra at 100 and 150 MHz. All chemical shifts are reported in ppm relative to tetramethylsilane (TMS) for ¹H or CHCl₃ for ¹³C. IR data are reported in cm⁻¹. Mass spectra were measured on a VG Auto-spec-Q (high resolution, high performance, tri-sector GC/MS/MS) and with LCMS using Agilent 1100 series LC/MSD with an API-ES/APCI ionization mode. Microanalysis were performed on a LECO CH NS-932 Elemental Analyzer. The UV/VIS absorption spectra were recorded using a Varian Cary 5 instrument. X-Ray analysis were performed using a Rigaku Rapid II diffractometer.

Starting materials. Starting compounds 1a-c, 10 and 15 were prepared using previously reported procedures.¹⁰a-d
Preparation of (15). A mixture of 1b (2.92 g, 10 mmol) and hydrazine hydrate (99%, 3 mL) in ethanol (25 mL) was stirred at reflux for 3-4 h. Concentration of the mixture in vacuo gave a residue which was subjected to crystallization from ethanol.

1-(5-Phenyl-1H-pyrazol-4-yl)-1H-benzotriazole (15). Yield 2.0 g (76%) from ethanol, mp 168-170 °C. UV/VIS (CHCl3); λ_max = 248 nm. 1H NMR (400 MHz, DMSO-d6): 13.58 (br, 1H, NH), 8.36 (s, 1H), 8.17 (d, 1H, J 8.4 Hz), 7.53 (t, 1H, J 8.4 Hz), 7.47 (t, 1H, J 8.4 Hz), 7.40 (d, 1H, J 8.4 Hz), 7.27 (m, 3H), 7.16 (m, 2H). 13C NMR (100 MHz, DMSO-d6): 145.3, 144.9, 134.3, 131.3, 129.2, 128.7, 128.5, 128.2, 124.5, 119.5, 114.8, 110.4. MS: m/z (%) 261 (M+, 40), 233 (100), 205 (50). Anal. Calc. for C13H11N5 (261.3): C 68.95; H 4.24; N 26.80. Found: C 68.90; H 4.19; N 26.77%.

Photochemistry

Method A. Irradiation using a low pressure mercury arc-lamp. Each of the substrates 1a-c, 10 and 15 (1.0 mmol) was dissolved in acetonitrile (25 mL) in a quartz tube and purged with nitrogen while being irradiated for 24 h at room temperature (RT). The progress of each reaction was monitored by using TLC. The solvent was removed in vacuo and the resulting residue was subjected to column chromatography on silica gel using ethyl acetate/petroleum (b.p. 60-80 °C) as the eluent to give the corresponding products (Table 1).

Method B. Irradiation using sunlight. Each of the substrates 1a-c (0.5 g) was dissolved in acetonitrile (150 mL) in a Pyrex tube, purged with nitrogen, and exposed to direct sunlight for 15 days (July 1-15) at RT. The progress of each reaction was monitored by using TLC and LCMS. The solvent was removed in vacuo and the resulting residue was subjected to column chromatography on silica gel using ethyl acetate/petroleum (b.p. 60-80 °C) as eluent to give the products 3a-c in 10-18% yields (Table 1).

2-Acetyl-3-dimethylamino-1H-indole (3a). Yellow crystals from ethanol, mp 145-146 °C, yield 58% (method A), 18% (method B). (Rf 0.48, EtOAc: petroleum b.p. 40-60 °C: 1:8 v/v). IR: 3337, 3064, 2974, 1639, 1571, 1527, 1452, 1332, 1249, 1192, 975, 927, 744, 712. 1H NMR (400 MHz, CDCl3): 8.58 (br, 1H, NH), 7.83 (d, 1H, J 8.0 Hz), 7.25 (d, 1H, J 8.0 Hz), 7.21 (t, 1H, J 7.8 Hz), 6.99 (t, 1H, J 7.8 Hz), 2.98 (s, 6H, 2CH3), 2.66 (s, 3H, CH3). 13C NMR (100 MHz, CDCl3): 190.5, 137.8, 135.2, 128.7, 126.1, 124.3, 122.9, 119.6, 112.6, 45.9 (2C), 27.1. LCMS: m/z = 203 (M + 1). MS: m/z (%) 202 (M+, 100), 158 (75), 105 (100). Anal. Calc. for C12H14N2O (202.3): C 71.26; H 6.98; N 13.85. Found: C 71.20; H 6.90; N 13.79%.

2-Benzotriazol-1-yl-4-methylquinolin-3-ol (4). Yield 15%, (method A). Yellow crystals from ethanol: mp 174-176 °C. (Rf 0.68, EtOAc: petroleum b.p. 40-60 °C, 1:5). IR: 3181, 3065, 2955, 2860, 1728, 1451, 1379, 1272, 1122, 1072, 747 cm−1. 1H NMR (600 MHz, CDCl3): 10.69 (s, 1H, OH), 9.13 (d, 1H, J 8.4 Hz), 8.25 (d, 1H, J 8.4 Hz), 8.12 (dd, 1H, J 8.0, 1.4 Hz), 8.00 (dd, 1H, J 8.0, 1.4 Hz), 7.79 (t, 1H, J 8.0 Hz), 7.68-7.59 (m, 3H), 2.78 (s, 3H, CH3). 13C NMR (150 MHz, CDCl3): 145.1, 140.6, 140.5, 139.0, 132.0, 130.4, 129.8, 128.9, 128.4, 127.2, 126.9, 126.1, 123.2, 120.1, 116.4, 11.0. LCMS: m/z = 277 (M + 1). MS: m/z (%) 276 (M+, 20), 248 (45), 219
(100). Anal. Calc. for C_{16}H_{2}N_{4}O (276.3): C 69.55; H 4.38; N 20.28. Found: C 69.49; H 4.34; N 20.27%. HRMS = 276.1005, requires C_{16}H_{12}N_{4}O 276.1005.

2-Benzoyl-3-dimethylamino-1H-indole (3b). Yellow crystals from ethanol: mp 197-198 °C, yield 62% (method A), 10% (method B), (R_{f} 0.47, EtOAc: petroleum b.p. 40-60 °C: 3:7). IR: 3337, 3064, 2974, 1639, 1571, 1527, 1452, 1332, 1249, 1193, 975, 927, 744, 712 cm\(^{-1}\). \(^1\)H NMR (400 MHz, CDCl\(_3\)): 8.08 (d, 1H, J 8.4 Hz), 7.68 (d, 1H, J 8.0 Hz), 7.55 (d, 2H, J 8.0 Hz), 7.40-7.33 (m, 3H), 7.26 (t, 2H, J 7.8 Hz), 7.03 (t, 1H, J 8.0 Hz), 3.28 (s, 6H, 2 CH\(_3\)). \(^{13}\)C NMR (100 MHz, CDCl\(_3\)): 190.6, 151.7, 138.5, 134.4, 130.0, 128.1, 127.9, 127.7, 127.3, 125.9, 123.6, 119.2, 108.4, 43.0 (2C). LCMS: m/z = 265 (M+1). MS: m/z (%) 264 (M\(^+\), 20), 208 (65), 105 (50), 77 (100). (HRMS = 264.1258, requires C\(_{17}\)H\(_{16}\)N\(_2\)O 264.1257).

3-Dimethylamino-1H-indole 2-carbonitrlle (3c). Colorless crystals, mp 91-92 °C, yield 73% (method A), 16% (method B), (R_{f} 0.57, EtOAc: petroleum bp 40-60 °C: 1:9). IR: 3305, 3067, 2924, 2202, 1571, 1549, 1455, 1339, 1219, 1137, 915, 744. \(^1\)H NMR (600 MHz, CDCl\(_3\)): 7.73 (d, 1H, J 8.4 Hz), 7.71 (br, 1H, NH), 7.33 (dt, 1H, J 8.4, 1.2 Hz), 7.26 (d, 1H, J 8.4 Hz), 7.10 (dt, 1H, J 8.0, 1.2 Hz), 3.18 (s, 6H, 2 CH\(_3\)). \(^{13}\)C NMR (100 MHz, CDCl\(_3\)): 142.6, 137.2, 126.6, 121.6, 120.7, 120.0, 116.8, 111.9, 91.9, 43.8 (2C). MS: m/z (%) 185 (M\(^+\), 100), 170 (60), 142 (50). Anal. Calc. for C\(_{11}\)H\(_{11}\)N\(_3\) (185.2): C 71.33; H 5.99; N 22.69. Found: C 71.23; H 5.90; N 22.63%. (HRMS = 185.0948, requires C\(_{11}\)H\(_{11}\)N\(_3\) 185.0947).

1H-Indol-2,3-dione (Isatin) (12). Red brown crystals, mp 196-197 °C (lit.\(^{16}\) 195-197 °C).

Isatoic anhydride (13). Colorless crystals from ethanol, mp 243-45 °C (lit.\(^{12a}\) 243-47 °C).

Indolo[2,1-b]quinazoline-6,12-dione (Tryptanthrin) (14). Greenish yellow needles, mp 265-267 °C (lit.\(^{12b}\) mp 266-267 °C). IR: 3020, 2938, 1732, 1691, 1585, 1462, 1314, 1194, 1110, 1036, 916, 751. \(^1\)H NMR (600 MHz, CDCl\(_3\)): 8.65 (d, 1H, J 8.0 Hz), 8.47 (dd, 1H, J 8.0, 1.2 Hz), 8.06 (dd, 1H, J 8.0, 1.2 Hz), 7.94 (dd, 1H, J 7.8, 1.0 Hz), 7.88 (dt, 1H, J 7.8, 1.2 Hz), 7.80 (dt, 1H, J 7.8, 1.2 Hz), 7.71 (t, 1H, J 8.0 Hz), 7.46 (t, 1H, J 7.8 Hz). \(^{13}\)C NMR (150 MHz, CDCl\(_3\)): 182.6, 158.1, 146.7, 146.4, 144.4, 138.3, 135.1, 130.8, 130.3, 127.6, 127.2, 125.4, 123.8, 121.9, 118.0. MS: m/z (%) 248 (M\(^+\), 100), 220 (30), 192 (15). Anal. Calc. for C\(_{15}\)H\(_{8}\)N\(_2\)O\(_2\) (248.28): C 72.58; H 3.25; N 11.28. Found: C 72.50; H 3.24; N 11.19%.

3-phenyl-1,4-dihydropyrazolo[4,3-b]indole (16). Colorless crystal from ethanol, mp 195-197 °C, yield 68% (method A), (R_{f} 0.47, EtOAc: petroleum, bp 40-60°: 1 : 5). IR: 3020, 2938, 1732, 1691, 1595, 1462, 1314, 1194, 1110, 1036, 916, 751. \(^1\)H NMR (400 MHz, DMSO-d\(_6\)): 12.98 (br, 1H, NH), 10.97 (br, 1H, NH), 7.98 (d, 2H, J 7.8 Hz), 7.77 (d, 1H, J 7.8 Hz), 7.50 (d, 1H, J 7.8 Hz), 7.46 (t, 2H, J 7.8 Hz), 2.79 (m, 2H), 7.09 (t, 1H, J 7.8 Hz). \(^{13}\)C NMR (100 MHz, CDCl\(_3\)): 145.3, 131.7, 130.9, 129.1, 128.7, 127.9, 127.7, 125.5, 125.4, 119.9, 119.7, 114.7, 112.5. MS: m/z (%) 233 (M\(^+\) 100), 205 (10), 103 (25). Anal. Calc. for C\(_{15}\)H\(_{11}\)N\(_3\) (233.3): C 77.23; H 4.75; N 18.01. Found: C 77.20; H 4.68; N 18.07.
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References and Notes


17. Crystallographic data of for the structures (excluding structure factors) in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication numbers CCDC 836134 3c and CCDC 836135 4. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK, (fax: +44-(0)1223-336033 or e-mail: deposit@ccdc.cam.ac.UK).