Synthetic Applications of 3-(Cyanoacetyl)indoles and Related Compounds

Johnny Slätt, Tomasz Janosik, Niklas Wahlström and Jan Bergman*

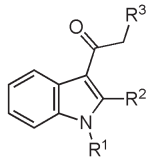
Unit for Organic Chemistry, Department of Biosciences, Karolinska Institute, Novum Research Park, SE-141 57 Huddinge, Sweden, and Södertörn University College, SE-141 04 Huddinge, Sweden
Fax +46 8 608920, E-mail: jabe@cnt.ki.se

Received June 9, 2004

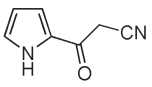
Various synthetic applications of 3-(cyanoacetyl)indoles, as well as syntheses of some related indoles, have been investigated. Diethyl 2-(1*H*-indol-3-yl)-2-oxoethylphosphonate and a methyl derivative thereof have been prepared in one step from indole. Moreover, it was demonstrated that 3-(cyanoacetyl)indoles are useful starting materials for the preparation of for example 3-(1*H*-indol-3-yl)-3-oxopropanamides, 3-heteroarylindoles or 3-heteroaroylindoles.

J. Heterocyclic Chem., **42**, 141 (2005).

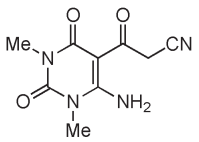
Recently, a facile procedure for the cyanoacetylation of various indoles and pyrroles leading for example to compounds **1a**–**d** and **2**–**3** has been developed in our laboratory. This one-step approach, employing cyanoacetic acid in acetic anhydride for the introduction of the cyanoacetyl functionality, provides quick and easy access to cyanoacetylated indoles, pyrroles, as well as some additional heterocycles in high yields [1]. Cyanoacetylated compounds and related ketones incorporating electron-withdrawing groups at α-position to the carbonyl are versatile precursors for the construction of more complex systems [2]. Since these readily accessible compounds may also undergo functional group transformations at the nitrile and/or ketone moieties to afford further useful indole and pyrrole derivatives which otherwise have to be prepared using multi-step procedures, we became interested in exploring the reactivity and synthetic applications of cyanoacetylated heterocycles to further extend the scope of our cyanoacetylation protocol.



1a R^1 = H, R^2 = H, R^3 = CN
1b R^1 = H, R^2 = Me, R^3 = CN
1c R^1 = Me, R^2 = H, R^3 = CN
1d R^1 = H, R^2 = H, R^3 = SO_2Me
1e R^1 = H, R^2 = H, R^3 = $P(O)(OEt)_2$
1f R^1 = H, R^2 = Me, R^3 = $P(O)(OEt)_2$

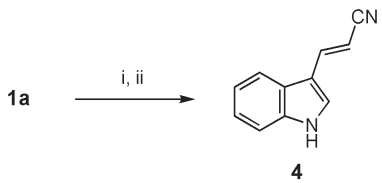


2



3

The ready preparation of the sulfone **1d** [1] by treatment of indole with (methanesulfonyl)acetic acid suggested that acetic acids having other electron withdrawing α-substituents might also prove to be useful reagents for similar applications. Therefore, the original acetylation protocol was slightly modified in order to facilitate the acetylation with diethylphosphonoacetic acid, which gave the corresponding 3-acetylated indoles **1e**–**f**. Such compounds are rather rare and do possess properties similar to indole-3-acetic acid, a well studied phytohormone [3]. Diethyl 2-(2-methyl-1*H*-indol-3-yl)-2-oxoethylphosphonate (**1f**) has previously been prepared in a multi-step sequence *via* the corresponding 3-(chloroacetyl)indole by treatment with triethyl phosphite. This ester, however, was never isolated, but hydrolysed directly to the corresponding acid [4]. Reduction of 3-(cyanoacetyl)indole (**1a**) with sodium borohydride followed by acidic workup gave selectively (*E*)-3-(1*H*-indol-3-yl)acrylonitrile (**4**) in 78% yield. A previously reported route for the preparation of **4** from 3-formylindole has been reported to afford a mixture of (*E*)- and (*Z*)-isomers [5]. In this context it is interesting to note that derivatives of **4**, for instance the corresponding 5-bromo derivative, have been shown to possess antimicrobial properties [6]. Moreover, reduction of **4** with hydrogen in the presence of Raney nickel is known to give *homo*-tryptamine [7], which belongs to a versatile class of compounds in natural product synthesis [8].



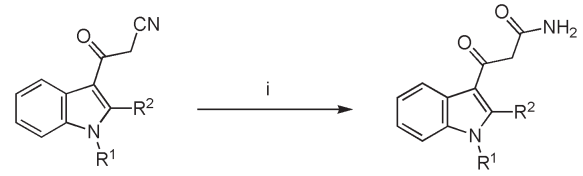
4

i. $NaBH_4$; ii. HCl

It is well established that photocyclization reactions of 3-cyanovinyl-2-aryl- or 3-cyanovinyl-2-heteroarylindoles can be used to synthesize carbazoles [9–12]. However, all attempts to react **4** with dimethyl

acetylenedicarboxylate or various maleimides under thermal conditions in refluxing toluene or xylenes failed. The limited solubility of the substrate **4** in these solvents may account for the low reactivity.

Previous hydrolyses of 3-cyanoindole derivatives have been shown, depending on the reaction conditions, to give the corresponding amides [13] or the carboxylic acids [14]. Thus heating of 3-(cyanoacetyl)indoles **1a–c** at 100 °C for 2 h in polyphosphoric acid (PPA) [15], followed by addition of water produced the desired amides **5a–c** in good yields. Since the previous synthesis of the amide **5c** was not practical due to the limited scale (0.25 mmol), and required a rather long reaction time (14 h) [13a], our approach constitutes a considerable improvement. Interestingly, certain diketo indoles having structures related to **5a–c** have been shown to exhibit HIV-inhibiting properties [16].

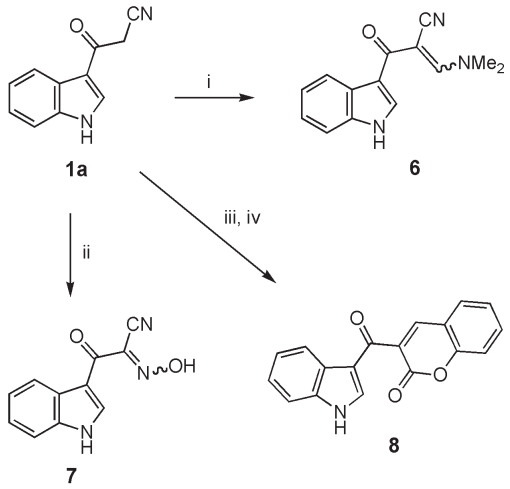


1a $R^1 = R^2 = H$
1b $R^1 = H$, $R^2 = Me$
1c $R^1 = Me$, $R^2 = H$

5a $R^1 = R^2 = H$
5b $R^1 = H$, $R^2 = Me$
5c $R^1 = Me$, $R^2 = H$

i. PPA, 100 °C, 2 h

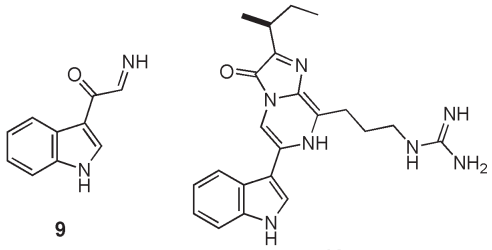
The activated methylene group in **1a** readily takes part in numerous reactions providing access to more complex molecules. Thus for example, condensation of **1a** with *N*,*N*-dimethylformamide dimethyl acetal (DMFDMA) proceeded smoothly to give the previously known compound **6** [17] in good yield. Likewise, nitrosation of **1a** with sodium nitrite in acetic acid gave as expected the interesting oxime **7**. The reactivity of the methylene moiety of **1a** was further demonstrated by its facile condensation with salicylaldehyde, followed by a subsequent attack of the *o*-hydroxyl group on the cyano group to generate an intermediate iminocoumarine (not isolated), which was directly hydrolyzed with dilute hydrochloric acid to the final coumarine derivative **8**.



1a **6** **7** **8**

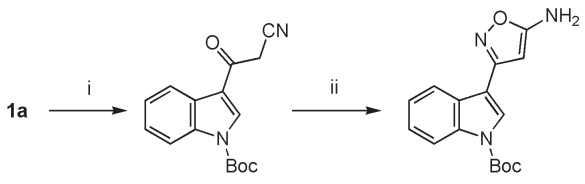
i. DMFDMA; ii. $NaNO_2$, AcOH; iii. salicylaldehyde; iv. aq. HCl

In connection with the easy preparation of the oxime **7**, it is worth mentioning that the closely related imine **9** has been employed as a key intermediate in the synthesis of cypridinaluciferin (**10**) [18].



9 **10**

During all experiments outlined so far, we noticed that the carbonyl group of **1a** displayed rather low reactivity due to the electron-releasing properties of the indole nitrogen atom. The prospect of accessing further interesting derivatives by reactions at the carbonyl part of the cyanoacetyl group prompted us to activate the carbonyl group by attaching an electron-withdrawing group to the indole nitrogen. Thus, Boc-protection of **1a** under standard conditions (Boc_2O, DMAP) produced **11** in good yield. As anticipated, treatment of compound **11** with hydroxylamine hydrochloride in the presence of base gave the interesting isoxazole **12**. Similar transformations of cyanoacetyl moieties to 5-aminoisoxazoles have been reported previously [19].



11 **12**

i. Boc_2O, DMAP, THF, rt; ii. $HONH_2 \cdot HCl$, NaOAc, CH_2Cl_2, MeOH

In conclusion, we have developed a convenient one-step procedure for the synthesis of 2-(1*H*-indol-3-yl)-2-oxoethylphosphonates. Several transformations of 3-(cyanoacetyl)indoles have also been investigated, leading to easy access to (*E*)-3-(1*H*-indol-3-yl)acrylonitrile

and 3-(1*H*-indol-3-yl)-3-oxopropanamides. Moreover, 3-(cyanoacetyl)indoles also proved to be useful starting materials for the synthesis of various 3-heteroarylindoles and 3-heteroaroylindoles.

EXPERIMENTAL

General.

^{1}H nmr and ^{13}C nmr spectra were recorded on a Bruker DPX 300 spectrometer operating at 300 MHz and 75.5 MHz, respectively. The ^{31}P nmr data were acquired using a JEOL Eclipse 500 spectrometer operating at 202.5 MHz employing 85% H_3PO_4 as external standard. The ir spectra were recorded on a Thermo Nicolet Avatar 330 FT-IR. Mass spectra (ESI) were obtained using a Perkin Elmer API 150 EX spectrometer or a Waters Micromass ZQ system. Elemental analyses were performed by H. Kolbe Mikroanalytisches Laboratorium, Mülheim an der Ruhr, Germany. Melting points were taken on a Büchi B-545 apparatus in open capillary tubes and are uncorrected. Chromatography was performed on Merck Silica Gel 60. All solvents and reagents were of analytical grade and were used as received, except THF, which was distilled from sodium and benzophenone.

Diethyl 2-(1*H*-Indol-3-yl)-2-oxoethylphosphonate (**1e**).

Indole (1.17 g, 10 mmol) dissolved in acetic acid (5 mL) was added slowly to a hot (100 °C) mixture of diethylphosphonoacetic acid (1.96 g, 10 mmol) and acetic anhydride (20 mL). After complete addition, the reaction mixture was heated for 4 h and was then allowed to cool. The solvent was evaporated. Addition of diisopropyl ether to the residue gave a precipitate, which was collected by filtration and dried to afford **1e** as a colourless solid (0.8 g, 29%), mp 170–171 °C; ir (neat): 3114, 2981, 2922, 1634, 1522, 1437, 1215, 1183, 1018, 945, 749, 719, 658 cm^{-1}; ^{1}H nmr (DMSO-d$_6$): δ 1.20 (t, J = 7.0 Hz, 6H), 3.62 (d, J = 22.2 Hz, 2H), 4.03 (q, J = 7.2, 4H), 7.17–7.25 (m, 2H), 7.45–7.50 (m, 1H), 8.16–8.20 (m, 1H), 8.42–8.43 (m, 1H), 12.05 (br s, 1H); ^{13}C nmr (DMSO-d$_6$): δ 16.1 (d, J_{C-P} = 6.1 Hz), 38.6 (d, J_{C-P} = 126.1 Hz), 61.6 (d, J_{C-P} = 6.2 Hz), 112.1, 116.7 (d, J_{C-P} = 2.9 Hz) 121.3, 121.9, 123.0, 125.4, 136.1, 136.6, 185.9 (d, J_{C-P} = 6.2 Hz); ^{31}P nmr (DMSO-d_6): δ 22.7 ppm; ms: (ESI+) m/z 296 [M + H]$^+$.

Anal. Calcd. for $C_{14}H_{18}NO_4P$: C, 56.95; H, 6.14; N, 4.74. Found: C, 57.07; H, 6.22; N, 4.65.

Diethyl 2-(2-Methyl-1*H*-indol-3-yl)-2-oxoethylphosphonate (**1f**).

2-Methylindole (1.31 g, 10 mmol) dissolved in acetic acid (10 mL) was added slowly to a hot (100 °C) mixture of diethylphosphonoacetic acid (1.96 g, 10 mmol) and acetic anhydride (15 mL). After complete addition the reaction mixture was heated at 100 °C for 2 h and was then allowed to cool. The solvent was evaporated. Trituration of the residue with diisopropylether gave a precipitate, which was collected by filtration and dried to afford **1f** (1.05 g, 35%) as a colourless solid, mp 132–133 °C; ir (neat): 3165, 3131, 3097, 3040, 2975, 2913, 1616, 1582, 1488, 1457, 1435, 1406, 1389, 1235, 1190, 1018, 990, 959, 916, 755 cm^{-1}; ^{1}H nmr (DMSO-d$_6$): δ 1.20 (t, J = 7.0 Hz, 6H), 2.73 (s, 3H), 3.61 (d, J = 21.4 Hz, 2H), 4.04 (q, J = 7.3, 4.4 Hz, 4H), 7.12–7.17 (m, 2H), 7.34–7.39 (m, 1H), 8.05–8.08 (m, 1H), 11.94 (br s, 1H); ^{13}C nmr (DMSO-d$_6$): δ 15.0, 16.2 (d, J_{C-P} = 5.9 Hz), 40.5 (d, J_{C-P} = 129.8 Hz) 61.6 (d, J_{C-P} = 6.3 Hz), 111.3, 113.7 (d, J_{C-P} = 4.1 Hz), 120.7, 121.6, 122.1, 126.9, 134.7, 145.1, 186.5 (d, J_{C-P} = 7.8 Hz); ^{31}P nmr (DMSO-d_6): δ 22.4 ppm; ms: (ESI+) m/z 310 [M + H]$^+$.

Anal. Calcd. for $C_{15}H_{20}NO_4P$: C, 58.25; H, 6.52; N, 4.53. Found: C, 58.08; H, 6.16; N, 4.63.

(*E*)-3-(1*H*-Indol-3-yl)acrylonitrile (**4**).

To a suspension of 3-(cyanoacetyl)-1*H*-indole (**1a**) (2.34 g, 12.7 mmol) in methanol (60 mL) was added sodium borohydride (1.44 g, 38.1 mmol) in small portions to give a clear solution. The mixture was allowed to cool (30 minutes) and was thereafter acidified with concentrated hydrochloric acid to pH < 2. The resulting mixture was stirred for 1 h and was then diluted with water to give a precipitate, which was collected by filtration and dried to give **4** (1.68 g, 78%) as a beige solid, mp 143–144 °C (Lit. [5] 143–144 °C).

3-(1*H*-Indol-3-yl)-3-oxopropanamide (**5a**).

3-(Cyanoacetyl)-1*H*-indole (**1a**) (2.5 g, 13.6 mmol) was added to PPA (20 mL), and the resulting mixture was heated at 100 °C for 2 h, whereupon the mixture was poured on ice. The precipitate formed was collected by filtration and washed with water to afford **5a** (2.5 g, 82%) as a beige solid, mp 208 °C (dec); ir (neat): 3408, 3189, 1641, 1597, 1579, 1519, 1430, 1377, 1237, 1144, 962, 742 cm^{-1}; ^{1}H nmr (DMSO-d$_6$): δ 3.70 (s, 2H), 7.05 (br s, 1H), 7.16–7.24 (m, 2H), 7.46–7.49 (m, 1H), 7.54 (br s, 1H), 8.16–8.20 (m, 1H), 8.34–8.35 (m, 1H), 12.00 (br s, 1H); ^{13}C nmr (DMSO-d$_6$): δ 47.8, 112.2, 117.5, 121.3, 121.9, 122.9, 125.4, 135.1, 136.7, 169.0, 189.1; ms: (ESI+) m/z 203 [M + H]$^+$.

Anal. Calcd. for $C_{11}H_{10}N_2O_2$: C, 65.34; H, 4.98; N, 13.85. Found: C, 65.24; H, 5.10; N, 13.76.

3-(2-Methyl-1*H*-indol-3-yl)-3-oxopropanamide (**5b**).

3-(Cyanoacetyl)-2-methyl-1*H*-indole (**1b**) (2.25 g, 11.3. mmol) was added to PPA (18 mL) and the resulting mixture was heated at 100 °C for 2 h, and thereafter poured on ice. The precipitate formed was collected by filtration and washed with water to give **5b** (2.14 g, 87%) as a beige solid, mp 196–197 °C (Lit. [13b] 197 °C); ir (neat): 3408, 1667, 1595, 1577, 1435, 1382, 1239, 1154, 1056, 988, 743 cm^{-1}; ^{1}H nmr (DMSO-d$_6$): δ 2.69 (s, 3H), 3.73 (s, 2H), 7.04 (br s, 1H), 7.08–7.16 (m, 2H), 7.32–7.40 (m, 1H), 7.47 (br s, 1H), 7.98–8.02 (m, 1H), 11.89 (br s, 1H); ^{13}C nmr (DMSO-d$_6$): δ 14.9, 49.8, 111.2, 113.3, 120.5, 121.4, 121.9, 126.8, 134.7, 144.7, 169.0, 189.6.

3-(1-Methyl-1*H*-indol-3-yl)-3-oxopropanamide (**5c**).

3-(Cyanoacetyl)-1-methyl-1*H*-indole (**1c**) (3.5 g, 17.7 mmol) was added to PPA (20 mL) and the resulting mixture was heated at 100 °C for 2 h, and was thereafter poured on ice. The precipitate formed was collected by filtration and washed with water to afford **5c** (3.56 g, 93%) as a beige solid, mp 181 °C (Lit. [13a] 179.5–181.5 °C); ir (neat): 3554, 3326, 1672, 1614, 1530, 1376, 1234, 1126, 1087, 902, 731 cm^{-1}; ^{1}H nmr (DMSO-d$_6$): δ 3.66 (s, 2H), 3.87 (s, 3H), 7.02 (br s, 1H), 7.21–7.32 (m, 2H), 7.50 (br s, 1H), 7.53–7.56 (m, 1H), 8.17–8.20 (m, 1H), 8.36 (s, 1H); ^{13}C nmr (DMSO-d$_6$): δ 33.5, 47.8, 111.0, 115.6, 121.7, 122.6, 123.4, 126.0, 137.6, 138.9, 169.5, 189.0; ms: (ESI+) m/z 217 [M + H]$^+$.

2-Cyano-3-(dimethylamino)-1-(1*H*-Indol-3-yl)propen-1-one (**6**).

To a solution of 3-(cyanoacetyl)-1*H*-indole (**1a**) (4.63 g, 25.0 mmol) in DMF (30 mL) was added DMFDMA (3.0 g, 25.2

mmol) and the mixture was heated at 60 °C for 4 h. After cooling, the mixture was left overnight. The crystals which separated from the solution were collected by filtration and washed with ethanol to give **6** (5.34 g, 89%) as a yellow solid, mp 187–188 °C. (Lit. [17] 187–188 °C); ir (neat): 3299, 2191, 1625, 1558, 1512, 1436, 1422, 1346, 1298, 1240, 1132, 748 cm^{-1}; ^1H nmr (DMSO-d_6): δ 3.25 (s, 3H), 3.35 (s, 3H), 7.12–7.22 (m, 2H), 7.48–7.50 (m, 1H), 8.00 (s, 1H), 8.17–8.20 (m, 1H), 8.32 (s, 1H), 11.78 (br s, 1H); ^{13}C nmr (DMSO-d_6): δ 38.5, 47.4, 77.7, 111.9, 114.7, 121.2, 121.8, 121.8, 122.6, 126.8, 131.2, 135.9, 158.7, 181.8; ms: (ESI+) m/z 239 $[M + H]^+$.

2-(Hydroxyimino)-3-(1*H*-indol-3-yl)-3-oxopropanenitrile (**7**).

To a warm (60 °C) mixture of 3-(cyanoacetyl)-1*H*-indole (**1a**) (1.0 g, 5.34 mmol) in acetic acid (15 mL) sodium nitrite (3.5 g, 52.2 mmol) was added slowly over 30 minutes. After complete addition, the mixture was heated to 120 °C to give a clear solution and was then allowed to cool. The mixture was thereafter poured into water to give a precipitate, which was collected by filtration and washed with water to afford **7** (0.72 g, 62%) as a yellow solid, mp 216 °C (dec); ir (neat): 3226, 2243, 1591, 1580, 1434, 1226 1144, 1119, 1085, 1038, 937, 879, 837, 741, cm^{-1}; ^1H nmr (DMSO-d_6): δ 7.22–7.30 (m, 2H), 7.51–7.56 (m, 1H), 8.19–8.24 (m, 1H), 8.35–8.36 (m, 1H), 12.44 (br s, 1H), 14.7 (br s, 1H); ^{13}C nmr (DMSO-d_6): δ 109.6, 112.3, 112.6, 121.2, 122.6, 123.5, 126.2, 133.6, 136.2, 137.0, 177.6; ms: (ESI+) m/z 214 $[M + H]^+$.

Anal. Calcd. for $C_{11}H_7N_3O_2$: C, 61.97; H, 3.31; N, 19.71. Found: C, 62.02; H, 3.26; N, 19.63.

1-(Chromene-2-one-3-yl)-1-(1*H*-indol-3-yl)methanone (**8**).

To a mixture of 3-(cyanoacetyl)-1*H*-indole (**1a**) (0.74 g, 4.0 mmol) and *o*-salicylaldehyde (0.49 g, 4 mmol) in ethanol (60 mL), piperidine (5 drops) was added. The reaction mixture turned yellowish immediately. The reaction was monitored with TLC and after about 2.5 h no starting material could be detected. The solvent was evaporated to give a residue which was treated with ethanol (30 mL) and concentrated hydrochloric acid (1 mL). This mixture was heated at reflux for 30 minutes. After cooling, a precipitate formed and was collected by filtration to give **8** (0.8 g, 73%) as a white solid, mp 294–295 °C; ir (neat): 3304, 1719, 1709, 1596, 1513, 1432, 1243, 1141, 1130, 1118, 957, 886, 873, 773 cm^{-1}; ^1H nmr (DMSO-d_6): δ 7.23–7.30 (m, 2H), 7.38–7.43 (m, 1H), 7.46–7.53 (m, 2H), 7.67–7.72 (m, 1H), 7.80–7.83 (m, 1H), 8.21–8.24 (m, 2H), 8.29 (s, 1H), 12.18 (br s, 1H); ^{13}C nmr (DMSO-d_6): δ 112.4, 115.8, 116.2, 118.6, 121.3, 122.3, 123.4, 124.7, 125.6, 128.4, 129.3, 132.7, 137.0, 137.7, 142.2, 153.8, 158.3, 184.8; ms: (ESI+) m/z 290 $[M + H]^+$.

Anal. Calcd. for $C_{18}H_{11}NO_3$: C, 74.73; H, 3.83; N, 4.84. Found: C, 74.50; H, 3.61; N, 4.97.

[1-(*tert*-Butoxycarbonyl)-1*H*-indol-3-yl]-1-oxopropanenitrile (**11**).

To a suspension of 3-(cyanoacetyl)-1*H*-indole (**1a**) (11.04 g, 60.0 mmol) in anhydrous THF (200 mL) was added di-*tert*-butyl dicarbonate (16.38 g, 75.0 mmol), followed by DMAP (70 mg, 0.57 mmol). The mixture was stirred at room temperature under N_2 for 42 h, and was thereafter concentrated *in vacuo*. Trituration of the residue with Et_2O (~200 mL) gave a precipitate, which was collected by filtration and dried to afford **11** (12.4 g) as a colourless solid. Two additional crops (2.2 g and 0.52 g) were obtained after slow concentration of the mother liquors. Total yield: 15.12 g (89%). Colourless solid, mp 241 °C (dec); ir (neat): 1756, 1735, 1672, 1449, 1375, 1364, 1310, 1236, 1138, 1107, 898, 836, 764, 750 cm^{-1}; ^1H nmr ($CDCl_3$): δ 1.72 (s, 9H), 3.97 (s, 2H), 7.35–7.45 (m, 2H), 8.10–8.13 (m, 1H), 8.26 (s, 1H), 8.28–8.31 (m, 1H); ^{13}C nmr ($CDCl_3$): δ 28.3, 30.2, 86.5, 114.2, 115.3, 118.2, 122.6, 125.1, 126.4, 127.0, 133.0, 135.6, 148.8, 182.2; ms: (ESI–) m/z 283 $[M - H]^-$.

Anal. Calcd. for $C_{16}H_{16}N_2O_3$: C, 67.59; H, 5.67; N, 9.85. Found: C, 67.68; H, 5.73; N, 9.81.

1-(*tert*-Butoxycarbonyl)-3-(5-aminoisoxazol-3-yl)-1*H*-indole (**12**).

A mixture of **11** (1.12 g, 3.9 mmol), hydroxylamine hydrochloride (0.84 g, 12.1 mmol), and sodium acetate (1.32 g, 16.1 mmol) in anhydrous CH_2Cl_2 (20 mL) and methanol (20 mL) was stirred at 40–50 °C under N_2 for 24 h, and thereafter at room temperature for an additional period of 18 h. After concentration, the residue was partitioned between ethyl acetate (100 mL) and water (100 mL). The organic layer was washed with water (50 mL), brine (50 mL) and dried over $MgSO_4$. Removal of the solvent at reduced pressure gave a yellow foam, which was subjected to column chromatography on silca gel [hexane–ethyl acetate (3:2)] to afford **12** (1.07 g, 92%) as a cream-coloured solid, mp 165–166 °C; ir (neat): 3457, 3421, 3333, 3132, 1713, 1637, 1447, 1371, 1308, 1254, 1145, 748 cm^{-1}; ^1H nmr ($CDCl_3$): δ 1.69 (s, 9H), 4.65 (br s, 2H), 5.44 (s, 1H), 7.29–7.40 (m, 2H), 7.92 (s, 1H), 8.12–8.18 (m, 2H); ^{13}C nmr ($CDCl_3$): δ 28.3, 78.7, 84.6, 111.3, 115.3, 122.1, 123.6, 125.2, 125.7, 127.8, 135.8, 149.6, 159.0, 168.5; ms: (ESI+) m/z 300 $[M + H]^+$.

Anal. Calcd. for $C_{16}H_{17}N_3O_3$: C, 64.20; H, 5.72; N, 14.04. Found: C, 64.11; H, 5.64; N, 13.96.

REFERENCES AND NOTES

[1] J. Slätt, I. Romero and J. Bergman, *Synthesis*, in press (2004).

[2a] P. B. Russel and G. H. Hitchings, *J. Am. Chem. Soc*., **73**, 3763 (1951); [b] J. R. Ross and J. W. Sowell, Sr., *J. Heterocyclic Chem*., **24**, 757 (1987); [c] T. S. Mansour, *Tetrahedron Lett*., **29**, 3437 (1988); [d] G. Purrello and A. L. Vullo, *J. Heterocyclic Chem*., **11**, 481 (1974).

[3] B. Bartel, *Annu. Rev. Physiol. Plant Mol. Biol*., **48**, 51 (1997).

[4] P. Crandiadès, *J. Recherches Centre Natl. Recherche Sci*., **35**, 119 (1956).

[5] S. Mahboobi and G. Grothus, *Arch. Pharm. (Weinheim)*, **327**, 349 (1994).

[6] C. W. Whitehead and C. A. Whitesitt, *J. Med. Chem*., **17**, 1298 (1974).

[7] J. Schoepfer, H. Fretz, B. Gay, P. Furet, C. García-Echeverría, N. End and G. Caravatti, *Bioorg. Med. Chem. Lett*., **9**, 221 (1999).

[8] M. E. Kuehne, S. D. Cowen, F. Xu and L. S. Borman, *J. Org. Chem*., **66**, 5303 (2001).

[9] W. E. Noland, W. C. Kuryla, R. F. Lange, *J. Am. Chem. Soc*., **81**, 6010 (1959).

[10] S. Brooks, M. Sainsbury and D. K Weerasinge, *Tetrahedron*, **38**, 3019 (1982).

[11] C. Galvez, I. Fernandez, R. Segura and J. Vasquez, *J. Chem. Res (S)*, 16 (1987).

[12] J. Claret, I. Fernandez, C. Galvez and R. Lapouyade, *J. Photochem. Photobiol. A*, **55**, 347 (1991).

[13a] V.Gotor, R. Liz and A. Tetera, *Tetrahedron*, **60**, 607 (2004); [b] A. Albanese, *Gazz. Chim. Ital*. **60**, 23 (1930).

[14] Q. Mingoia, *Gazz. Chim. Ital*., **59**, 113 (1929).

[15a] C. R. Hauser and C. J. Eby, C. *J. Am. Chem. Soc*., **79**, 725

(1957); [b] K. Takayama, M. Iwata, H. Hisamischi, Y. Okamoto, M. Aoki and A. Niwa, *Chem. Pharm. Bull*., **50**, 1050 (2002).

[16] W. Pluymers, G. Pais, B. Van Maele, C. Pannecouque, V. Fikkert, T. R. Burke, Jr., E. De Clerq, M. Witvrouw, N. Neamati and Z. Debyser, *Antimicrob. Agents Chemother*., **46**, 3292 (2002).

[17] US Patent 6579983, Celltech R & D Ltd. (2000); *Chem. Abstr*., **134**, 71598 (2000).

[18] T. P. Karpetsky and E. H. White, *J. Am. Chem. Soc*., **93**, 2333 (1971).

[19a] E. Wahlberg, *Ber*., **65**, 1857 (1932); [b] T. Nishiwaki, T. Saito, *J. Chem. Soc. (C)*, 3021 (1971); [c] A. Takase, A. Murabayashi, S. Sumimoto, S. Ueda, Y. Makisumi, *Heterocycles*, **32**, 1153 (1991).