Cyanoacetylation of Indoles, Pyrroles and Aromatic Amines with the Combination Cyanoacetic Acid and Acetic Anhydride

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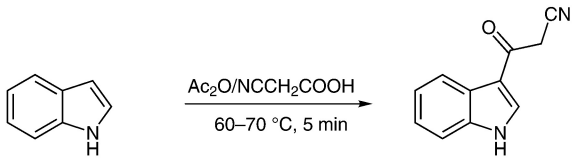
Abstract: Cyanoacetic acid was activated with acetic anhydride and when heated this reagent reacted with a variety of both activated and deactivated pyrroles, indoles and aniline derivatives.

Key words: acylations, electrophilic aromatic substitutions, heterocycles, indoles, pyrroles



Scheme 1

Introduction

Simple nitrogen containing heteroaromatic compounds have received much attention in the literature over the years. They are, among other things, pharmacophores of paramount importance,[1] which have exciting biological properties in their own right and also serve as important synthetic building blocks in drug discovery.

It is known that cyanoacetic acid can serve as a building block in various reactions like cyclizations[2] or syntheses of coumarins[3] and other heterocycles[4]. Activation of cyanoacetic acid by conversion to the mixed anhydride with acetic anhydride has been used now and then[5–8] but the generality, simplicity and usefulness has not been appreciated and the reagent has infrequently been used for N-acetylations of e.g urea and C-acylations of enamines.[9] Other activation procedures, such as conversion to cyanoacetyl chloride has also been used, albeit this reagent is notorious for its tendency to selfpolymerization (particulary when heated).[7,10]

Scope and Limitations

The present study was initiated when a large amount of 3-cyanoacetylindole was needed as starting material for various fused indoles (Scheme 1). Kreher and Wagner have described the synthesis of this molecule, but the procedure requires conversion of cyanoacetic acid to $CH_3SO_2OCOCH_2CN$.[8] In our hands this relatively tedious procedure only gave moderate yields of 3-cyanoacetylindole. However short heating (5 min) at 60–70 °C of cyanoacetic acid together with indole in acetic anhydride (Table 1, entry 1) gave the desired product in an excellent yield as a readily collectable precipitate. This procedure could subsequently be extended to pyrroles, which readily gave the expected cyanoacetylated derivatives. Only a few cyanoacetylated pyrroles have been described in the literature and they have invariably been prepared by displacements of halide in haloacetylpyrroles with e.g. potassium cyanide.[11–13] This low-yield and time-consuming approach has also been used in the indole series. Furthermore *N*-methyl-3-cyanoacetylindole (entry 4) has been recently prepared by condensation of ethyl *N*-methylindole-3-carboxylate with acetonitrile in the presence of sodamide.[14] This nitrile can likewise be conveniently prepared by our procedure (entry 4). Dissolution of *N*-methyl-3-cyanoacetylindole in hot (100 °C, 2 h) polyphosphoric acid followed by addition of water gave the corresponding amide,[15] the NMR-data of which were identical with those recently published.[14]

Despite the fact that acetic anhydride is used as solvent no acetylated products were ever isolated except for a few active anilines.[16] Several acetic acid derivatives bearing electron-withdrawing groups can form ketenes[17] and this could explain the high reactivity and selectivity. In most cases it is preferable to use two equivalents of cyanoacetic acid when the nucleophile is not very active, like 2-phenylindole. However, indole, 2,2′-biindolyl and pyrrole underwent cyanoacetylation very easily. On the other hand,

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we have not been able to efficiently cyanoacetylate thiophene, 4-nitroindole or 2,4-dinitroaniline (poor yields, 10–15%). Most likely the procedure for cyanoacetylation as developed will give considerable opportunities to use many other nucleophiles than those presented here. There should also be a possibility to use other derivatives of acetic acid, especially molecules bearing electron-withdrawing groups since methanesulfonylacetic acid was shown to react in the same fashion in excellent yields (Table 1, entry 8).

Table 1 Cyanoacetylation in Acetic Anhydride

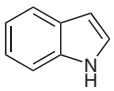
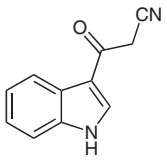
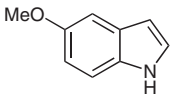
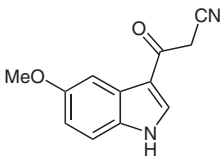
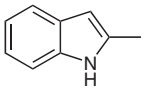
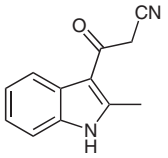
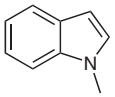
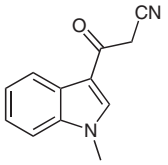
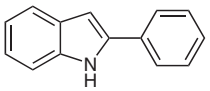
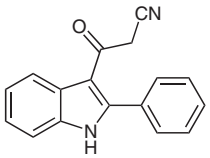
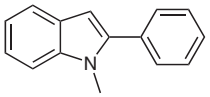
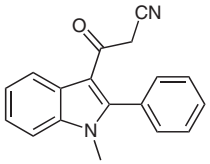
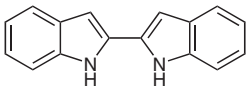
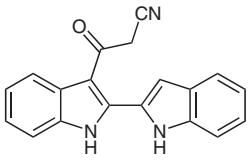
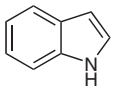
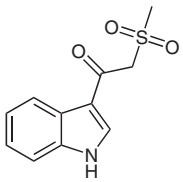
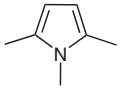
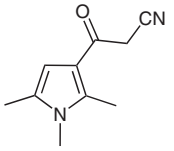
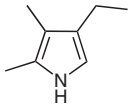
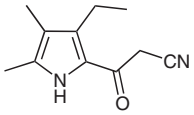
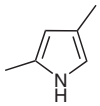
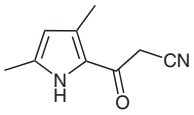
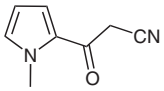
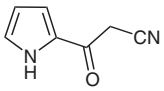
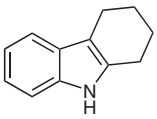
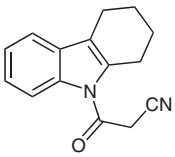
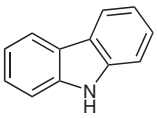
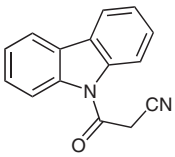
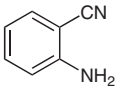
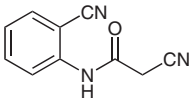
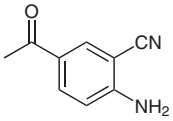
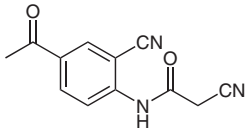
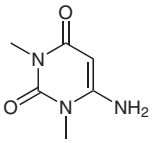
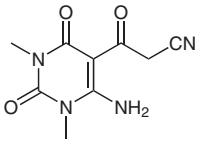
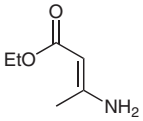
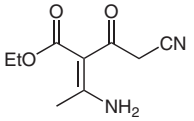
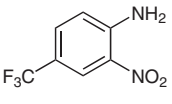
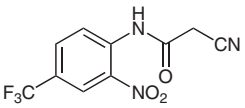
Entry	Reactant	Product	Yield (%)	Lit. Yield (%)
1			91	84[a]
2			91	–
3			90	81[a]
4			90	no yield given
5			98[a]	0[a]
6			97[a]	–
7			90	–
8			92	–

Table 1 Cyanoacetylation in Acetic Anhydride (continued)

Entry	Reactant	Product	Yield (%)	Lit. Yield (%)
9			68	75[a]
10			88	–
11			75	no yield given
12			87	no yield given
13			92	no yield given
14			91	–
15			82	–
16			51	–
17			92	–
18			99	95
19			50	13
20			63[a]	–

[a] Two equivalents of cyanoacetic acid were used.

Procedures

All starting materials and solvents (p.a. grade) are commercially available and were used without any further purification. All temperatures were measured in the reaction mixture unless stated otherwise. NMR spectra were recorded in DMSO-d_6 solutions, unless stated otherwise, on a Bruker DPX 300 spectrometer, operating at 300 MHz for ^{1}H and 75 MHz for ^{13}C; δ values are reported in ppm and *J* values are in Hertz. IR spectra were recorded on a Perkin-Elmer 1600 FTIR instrument using KBr pellets. Elemental analyses were preformed by H. Kolbe Mikroanalytisches Laboratorium, Mülheim an der Ruhr, Germany. Melting points were determined using a Büchi melting point B-545 apparatus and are uncorrected.

3-Cyanoacetylindole (entry 1)

Indole (5.85g, 50 mmol) was added to a solution prepared by dissolution of cyanoacetic acid (5.0 g, 50 mmol) in Ac_2O (50 mL) at 50 °C. The solution was heated at 85 °C for 5 min. During that period 3-cyanoacetylindole started to crystallize. After 5 more min, the mixture was allowed to cool and the solid was collected, washed with MeOH, and dried; yield: 8.38 g (91%); mp 241 °C (Lit.[8] mp 240 °C).

IR: 3214, 3120, 2251, 1633, 1580, 1523, 1489, 1457, 1433, 1397, 1377, 1336, 1318, 1279, 1236, 1202, 1139, 1095, 1007, 980, 922, 900, 876, 784, 744 cm^{-1}.

^{1}H NMR: δ = 4.50 (s, 2 H), 7.20–7.28 (m, 2 H), 7.50–7.55 (m, 1 H), 8.13–8.17 (m, 1 H), 8.38–8.39 (m, 1 H), 12.19 (br s, NH).

^{13}C NMR: δ = 29.4 (t), 112.4 (d), 114.4 (s), 116.4 (s), 121.0 (d), 122.3 (d), 123.3 (d), 125.1 (s), 135.4 (d), 136.6 (s), 182.8 (s).

For entries 2–4 and 7 the procedure as given for entry 1 was used.

3-Cyanoacetyl-5-methoxyindole (entry 2)

Yield: 89%; mp 270 °C.

IR: 3223, 2258, 1631, 1589, 1522, 1484, 1466, 1434, 1298, 1287, 1263, 1235, 1209, 1158, 1091, 1023, 902, 849, 807, 745 cm^{-1}.

^{1}H NMR: δ = 3.79 (s, 3 H), 4.46 (s, 2 H), 6.88 (dd, *J* = 2.7, 8.7, 1 H), 7.40 (d, *J* = 8.7 Hz, 1 H), 7.63 (d, *J* = 2.7 Hz, 1 H), 8.30 (d, *J* = 3.2 Hz, 1 H), 12.08 (br s, HN).

^{13}C NMR: δ = 29.3 (t), 55.3 (d), 102.7 (d), 113.1 (d), 113.2 (d), 114.3 (d), 116.4 (s), 126.0 (s), 131.4 (s), 135.5 (d), 155.8 (s), 182.7 (s).

Anal. Calcd for $C_{12}H_{10}N_2O_2$ (214.22): C, 67.28; H, 4.71; N, 13.08. Found: C, 67.34; H, 4.79; N, 13.12

3-Cyanoacetyl-2-methylindole (entry 3)

Yield: 90%; mp 230 °C (Lit.[8] mp 237 °C).

IR: 3272, 2952, 2258, 1627, 1581, 1530, 1459, 1387, 1317, 1283, 1247, 1172, 1104, 1046, 964, 923, 888, 751, 713, 629, 583 cm^{-1}.

^{1}H NMR: δ = 2.68 (s, 3 H), 4.51 (s, 2 H), 7.15–7.20 (m, 2 H), 7.37–7.43 (m, 1 H), 7.94–8.00 (m, 1 H), 12.08 (br s, NH).

^{13}C NMR: δ = 14.9 (q), 32.5 (t), 111.0 (d), 111.4 (s), 116.2 (s), 120.4 (d), 121.8 (d), 122.2 (d), 126.4 (s), 134.7 (s), 145.8 (s), 183.3 (s).

3-Cyanoacetyl-*N*-methylindole (entry 4)

Yield: 90%; mp 154 °C.

IR: 3100, 3043, 2256, 1639, 1603, 1577, 1448, 1421, 1402, 1375, 1336, 1299, 1235, 1197, 1147, 1129, 1085, 1048, 1009, 977, 890, 869, 796, 766, 750, 734 cm^{-1}.

^{1}H NMR: δ = 3.85 (s, 3 H), 4.47 (s, 2 H), 7.27–7.35 (m, 2 H), 7.53–7.56 (m, 1 H), 8.15–8.18 (m, 1 H), 8.35 (s, 1 H).

^{13}C NMR: δ = 29.5 (t), 33.4 (q), 110.9 (d), 113.3 (s), 116.3 (s), 121.1 (d), 122.7 (d), 123.4 (d), 125.6 (s), 137.3 (s), 138.7 (d), 182.3 (s).

3-Cyanoacetyl-2,2′-biindolyl (entry 7)

Yield: 90%; mp 256 °C (Lit.[18] mp 246–254 °C).

IR: 3305, 2944, 2264, 1639, 1614, 1547, 1469, 1446, 1392, 1338, 1236, 1182, 1160, 1088, 965, 925, 794, 762, 747, 727 cm^{-1}.

^{1}H NMR: δ = 4.52 (s, 2 H), 7.09–7.14 (m, 1 H), 7.22–734 (m, 4 H), 7.52–7.55 (m, 1 H), 7.60–7.63 (m, 1 H), 7.68–7.70 (m, 1 H), 8.01–8.03 (m, 1 H), 12.13 (br s, NH), 12.62 (br s, NH).

^{13}C NMR: δ = 32.6, (t), 104.7 (d), 111.5 (s), 112.1 (d), 112.2 (d), 116.1 (s), 120.1 (d), 120.7 (d), 121.2 (d), 122.5 (d), 123.2 (d), 123.7 (d), 126.3 (s), 127.6 (s), 128.1 (s), 136.0 (s), 136.5 (s), 137.7 (s), 184.8 (s).

3-Methanesulfonylacetylindole (entry 8)

Indole (1.17 g 10 mmol) was added to a solution prepared by dissolution of methanesulfonylacetic acid (1.38 g 10 mmol) in Ac_2O (15 mL) at 85 °C. The solution was heated to 90 °C during 15 min, whereupon the mixture was allowed to cool and the precipitate formed was collected, washed with EtOH and dried.

Yield: 2.18 g (92%); mp 241 °C.

IR: 3214, 1615, 1516, 1435, 1380, 1286, 1237, 1178, 1126, 1093, 953, 903, 805, 742, 698, 648, 612, 516, 482 cm^{-1}.

^{1}H NMR: δ = 3.18 (s, 3 H), 4.87 (s, 2 H), 7.25–7.27 (m, 2 H), 7.51–7.52 (m, 1 H), 8.20–8.22 (m, 1 H), 8.58–8.58 (m, 1 H).

^{13}C NMR: δ = 42.6 (q), 62.4 (t), 113.0 (d), 117.4 (s), 121.8 (d), 123.0 (d), 124.0 (d), 125.9 (s), 137.4 (s), 137.7 (d), 183.7 (s).

Anal. Calcd for $C_{11}H_{11}NO_3$ (237.3): C, 55.68; H, 4.67; N, 5.90. Found: C, 55.76; H, 4.46; N, 5.87.

2-Cyanoacetylpyrrole (entry 13)

Pyrrole (10.7 g 0.16 mol) was added to a mixture of cyanoacetic acid (13.7 g 0.16 mol) and Ac_2O (80 mL) and heated at 75 °C for 35 min. The mixture was allowed to cool and poured on ice. The precipitate formed was collected and dried.

Yield: 15.0 g (70%); mp 78 °C (Lit.[19] mp 79–81 °C).

IR: 3301, 2258, 1653, 1544, 1408, 1274, 1108, 1050, 906, 846, 758, 603, 534 cm^{-1}.

^{1}H NMR: δ = 4.40 (s, 2 H), 6.23–6.24 (m, 1 H), 7.07–7.08 (m, 1 H), 7.19–7.20 (m, 1 H), 12.11 (br s, NH).

^{13}C NMR: δ = 28.8 (t), 111.0 (d), 116.7 (s), 119.2 (d), 127.8 (d), 130.0 (s), 178.2 (s).

For entries 9–12 the procedure as given for entry 13 was used.

2-Cyanoacetyl-1,2,5-trimethylpyrrole (entry 9)

Yield: 68%; mp 110 °C (Lit.[8] mp 108 °C).

2-Cyanoacetyl-3-ethyl-4,5-dimethylpyrrole (entry 10)

Yield: 88%: mp 215 °C.

IR: 3306, 2959, 2266, 1643, 1580, 1497, 1442, 1372, 1317, 1252, 1198, 1110, 1060, 972, 924, 822 cm^{-1}.

^{1}H NMR: δ = 0.93–0.98 (m, 3 H), 2.16–2.19 (m, 6 H), 2.27–2.35 (m, 2 H), 4.22 (s, 2 H), 11.29 (br s NH).

^{13}C NMR: δ = 10.8 (q), 10.9 (q), 15.2 (q), 16.4 (t), 29.6 (t), 116.2 (s), 124.3 (s), 124.8 (s), 127.5 (s), 133.4 (s), 175.7 (s).

Anal. Calcd for $C_{11}H_{14}N_2O$ (190.24): C, 75.82; H, 8.10; N, 16.09. Found: C, 75.55; H, 8.22; N, 15.95

2-Cyanoacetyl-3,5-dimethylpyrrole (entry 11)

Yield: 75%; mp 109 °C (Lit.[16] mp 108 °C).

3-Cyanoacetyl-*N*-methylpyrrole (entry 12)

Yield: 87%; mp 110 °C (Lit.[20] mp 107–109 °C).

IR: 3141, 2259, 1639, 1530, 1467, 1438, 1410, 1396, 1384, 1294, 1250, 1212, 1105, 1074, 923, 907, 880, 762 cm^{-1}.

^1H NMR: δ = 3.85 (s, 3 H), 4.42 (s, 2 H), 6.16–6.17 (m, 1 H), 7.12–7.13 (m, 1 H), 7.24–7.25 (m, 1 H).

^{13}C NMR: δ = 29.3 (t), 37.0 (q), 108.5 (d), 116.1 (s), 121.3 (d), 128.0 (s), 133.3 (d), 178.2 (s).

_N_-Cyanoacetylcarbazole (entry 15)
Carbazole (2.0 g 12.0 mmol) was added to a mixture of cyanoacetic acid (1.3 g 15.3 mmol) and Ac_2O (15 mL) and then heated slowly to 95 °C for 1.5 h. The reaction mixture was allowed to cool and left overnight. The precipitate formed was collected by filtration and dried; yield: 2.3 g (82%); mp 150 °C.

IR: 2956, 2263, 1691, 1596, 1490, 1477, 1444, 1406, 1395, 1334, 1304, 1272, 1238, 1195, 1105, 1155, 1125, 1102, 1038, 966, 943, 931, 870, 858 787, 775, 753, 720, 675 cm^{-1}.

^1H NMR: δ = 5.00 (s, 2 H), 7.42–7.57 (m, 4 H), 8.14–8.25 (m, 4 H).

^{13}C NMR: δ = 30.8 (t), 115.1 (s), 116.4 (d), 120.3 (d), 124.2 (d), 125.9 (s), 127.7 (d), 164.0 (s).

Anal. Calcd for $C_{15}H_{10}N_2O$ (234.25): C, 76.91; H, 4.30; N, 11.96. Found: C, 77.08; H, 4.35; N, 11.83.

For entry 14 the same procedure as for entry 15 was used.

3-Cyanoacetyl-5,6,7,8-tetrahydrocarbazole (entry 14)
Yield: 91%; mp 181 °C.

IR: 2946, 2860, 2259, 1699, 1618, 1453, 1374, 1331, 1282, 1215, 1181, 1097, 1020, 949, 779 cm^{-1}.

^1H NMR: δ = 1.74–184 (m, 4 H), 2.49–2.61 (m, 2 H), 2.89–2.91 (m, 2 H), 4.70 (s, 2 H), 7.23& ndash;7.31 (m, 2 H), 7.41–7.44 (m, 1 H), 8.13–8.17 (m, 1 H).

^{13}C NMR: δ = 20.6 (t), 21.2 (t), 23.1 (t), 26.7 (t), 30.0 (t), 115.1 (s), 115.7 (d), 117.7 (d), 118.3 (s), 123.5 (d), 124.2 (d), 129.7 (s), 134.4 (s), 135.4 (s), 163.4 (s).

Anal. Calcd for $C_{15}H_{14}N_2O$ (238.28): C, 75.61; H, 5.92; N, 11.76. Found: C, 75.54; H, 6.07; N, 11.68.

4-Amino-3-cyano-_N_-cyanoacetylacetophenone (entry 17)
3-Cyano-4-amino-acetophenone (1.6 g, 10 mmol) was added to a solution prepared by dissolving cyanoacetic acid (0.9 g, 11 mmol) in Ac_2O (10 mL) at 85 °C. The solution was heated at 90 °C for 5 min and allowed to cool. The precipitate formed was collected by filtration and dried; yield: 2.09 g (92%); mp 211 °C.

IR: 3292, 2234, 1727, 1683, 1587, 1536, 1401, 1339, 1281, 1167, 1116, 922, 850, 607 cm^{-1}.

^1H NMR: δ = 2.6 (s, 3 H), 4.09 (s, 2 H), 7.88 (d, *J* = 8.7 Hz, 1 H), 8.21 (dd, *J* = 2.3, 8.7 Hz, 1 H), 8.39 (d, *J* = 2.3 Hz, 1 H).

^{13}C NMR: δ = 27.2 (t), 27.2 (q), 106.3 (s), 116.0 (s), 116.5 (s), 124.8 (d), 133.9 (d), 134.2 (d), 134.6 (d), 143.6 (s), 163.0 (s), 196.2 (s).

Anal. Calcd for $C_{12}H_9N_3O_2$ (227.2): C, 63.43; H, 3.99; N, 18.49. Found: C, 63.49; H, 3.94; N, 18.46.

For entries 16, 18, 19 the same procedure given for entry 17 was used.

2-Cyano-_N_-(2-cyanophenyl)acetamide (entry 16)
Yield: 51%; mp 171 °C.

IR: 3263, 2972, 2922, 2262, 2229, 1672, 1607, 1581, 1539, 1447, 1388, 1349, 1296, 1253, 1191, 953, 767, 683 cm^{-1}.

^1H NMR: δ = 4.01 (s, 2 H), 7.36–7.41 (m, 1 H), 7.61–7.64 (m, 1 H), 7.69–7.74 (m, 1 H), 7.82–7.85 (m, 1 H), 10.56 (br s, 1 H, NH).

^{13}C NMR: δ = 26.2 (t), 107.0 (s), 115.6 (s), 116.5 (s), 125.4 (d), 126.3 (d), 133.4 (d), 134.0 (d), 139.3 (d), 162.1 (s).

Anal. Calcd for $C_{10}H_7N_3O$ (185.2): C, 64.86; H, 3.81; N, 22.69. Found: C, 64.94; H, 3.77; N, 22.65.

3-(6-Amino-1,3-dimethyl-2,4-dioxo-1,2,3,4-tetrahydro-5-pyrimidinyl)-3-oxopropanenitrile (entry 18)
Yield: 99%; mp 260 °C (Lit.[5] mp 250–251 °C).

Ethyl (_E_)-3-Amino-2-(2-cyanoacetyl)but-2-enoate (entry 19)
Yield: 50%; mp 110 °C (Lit.[9] mp 112–114 °C).

2-Cyano-_N_-[4-(trifluoromethyl)-2-nitrophenyl]acetamide (entry 20)
4-Amino-3-nitrobenzotrifluoride (2.0 g 10 mmol) was added to a solution prepared by dissolving cyanoacetic acid (1.7 g 20 mmol) in Ac_2O (12 mL). The reaction mixture was heated at 90 °C for 1 h and then allowed to cool. The precipitate formed was collected by filtration after dilution with EtOH and dried; yield: 1.67 g (63%); mp 156 °C.

IR: 3317, 3128, 2955, 2261, 1715, 1637, 1593, 1525, 1467, 1402, 1355, 1324, 1275, 1233, 1173, 1130, 1086, 946, 898, 859, 765, 697, 620 cm^{-1}.

^1H NMR: δ = 4.07 (s, 2 H), 7.92 (d, *J* = 8.7 Hz, 1 H), 8.10 (d, *J* = 8.7 Hz, 1 H), 8.32 (s, 1 H), 10.90 (br s, 1 H, NH).

^{13}C NMR: δ = 26.5, 115.2, 122.5 (q, $^3J_{C,F}$ = 3.9 Hz), 122.9 (q, $^1J_{C,F}$ = 272.0 Hz), 125.5 (q, $^2J_{C,F}$ = 33.8 Hz), 126.1, 130.6 (q, $^3J_{C,F}$ = 3.9 Hz) 133.8, 141.7, 162.2.

Anal. Calcd for $C_{10}H_6F_3N_3O_3$ (273.2): C, 43.97; H, 2.21; N, 15.38. Found: C, 43.91; H, 1.87; N, 15.33.

For entries 5 and 6 the same procedure as given for entry 20 was used.

3-Cyanoacetyl-2-phenylindole (entry 5)
Yield: 98%; mp 187 °C.

IR: 3254, 2259, 1627, 1585, 1450, 1434, 1386, 1374, 1319, 1242, 1187, 1122, 1102, 938, 918, 890, 751, 697, 644 cm^{-1}.

^1H NMR: δ = 3.93 (s, 2 H), 7.23–7.31 (m, 2 H), 7.44–7.48 (m, 1 H), 7.56–7.60 (m, 3 H), 7.64–7.68 (m, 2 H), 8.14–8.17 (1 H), 12.39 (br s, NH).

^{13}C NMR: δ = 31.8 (t), 111.9 (s), 112.0 (d), 115.9 (s), 121.3 (d), 122.4 (d), 123.4 (d), 126.7 (s), 128.7 (d), 129.9 (d), 130.0 (d), 131.7 (s), 135.5 (s), 146.1 (s), 183.6 (s).

Anal. Calcd for $C_{17}H_{12}N_2O$ (260.29): C, 78.44; H, 4.65; N, 10.76. Found: C, 78.56; H, 4.71; N, 10.69.

3-Cyanoacetyl-_N_-methyl-2-phenylindole (entry 6)
Yield: 97%; mp 161 °C.

IR: 2251, 1637, 1577, 1527, 1464, 1437, 1402, 1377, 1252, 1129, 1081, 1049, 903, 852, 760, 704 cm^{-1}.

^1H NMR: δ = 3.57 (s, 3 H), 3.60 (s, 2 H), 7.30–7.39 (m, 2 H), 7.56–7.65 (m, 6 H), 8.26–8.29 (m, 1 H).

^{13}C NMR: δ = 31.0 (q), 31.5 (t), 111.0 (d), 112.6 (s), 121.4 (d), 123.0 (d), 123.3 (d), 123.6 (d), 125.9 (s), 129.1 (d), 130.2 (d), 130.3 (d), 130.4 (s), 136.5 (s), 147.4 (s), 183.0 (s).

Anal. Calcd for $C_{18}H_{14}N_2O$ (274.31): C, 78.81; H, 5.14; N, 10.21. Found: C, 78.82; H, 5.10; N, 10.14.

3-Amidoacetyl-_N_-methylindole
N-Methyl-3-cyanoacetylindole (3.5 g 17.6 mmol) was added to PPA (10 mL) and heated at 100 °C for 2 h, whereupon the mixture was poured into ice. The precipitate formed was collected by filtra-

tion and carefully washed with H_2O and dried; yield 93%; mp 181 °C (Lit.[14] mp 179.5–181.5 °C).

IR: 3553, 3326, 3167, 3102, 1672, 1614, 1576, 1529, 1490, 1464, 1444, 1427, 1376, 1338, 1293, 1261, 1234, 1192, 1143, 1127, 1087, 1050, 1008, 969, 954, 902, 882, 770, 748, 731 cm^{-1}.

^1H NMR: δ = 3.66 (s, 2 H), 3.87 (s, 3 H), 7.03 (br s, 1 H, NH), 7.21–7.32 (m, 2 H), 7.50 (br s, 1 H, NH), 7.53–7.56 (m, 1 H), 7.17–8.20 (m, 1 H), 8.35 (s, 1 H).

^{13}C NMR: δ = 33.5 (q), 47.8 (t), 111.0 (d), 115.6 (s), 121.7 (d), 122.6 (d), 123.4 (d), 126.1 (s), 137.6 (s), 138.9 (d), 169.6 (s), 189.0 (s).

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References

(1) Güner, I.; Osman, F. *Pharmacophore Perception, Development, and Use in Drug Design*; International University Line: La Jolla, California, **2000**.
(2) Batchelor, M. J.; Moffat, J.; David, F. C.; Davis, J. M.; Hutchings, M. C. Celltech R & D Limited., PCT Int appl. WO 2000078731, **2000**; *Chem. Abstr.* **2000**, *134*, 71598.
(3) Schroeder, C.; Link, K. P. *J. Am. Chem. Soc.* **1953**, *75*, 1886.
(4) Baraldi, P. G.; Romagnoli, R.; Pavani, M. G.; Nuñez, M. C.; Tabrizi, M. A.; Shryock, J. C.; Leung, E.; Moorman, A. R.; Uluoglu, C.; Iannotta, V.; Merighi, S.; Borea, P. A. *J. Med. Chem.* **2003**, *46*, 794.
(5) Smirnova, N. M.; Cherdantseva, N. M.; Burova, O. A.; Nesterov, V. M.; Safonova, T. S. *Chem. Heterocycl. Compd.* **1990**, 811.
(6) Farbenfabriken Bayer, DE 175415, **1906**; *Chem. Abstr.* **1907**, *1*, 6240.
(7) Schroeter, G.; Seidler, C.; Sulzbacher, M.; Kanitz, R. *Ber. Dtsch. Chem. Ges.* **1932**, *65*, 432.
(8) Kreher, R.; Wagner, P. H. *Chem. Ber.* **1980**, *113*, 3675.
(9) Kappe, T.; Stelze, H. P.; Ziegler, E. *Monatsh. Chem.* **1983**, *114*, 953.
(10) Schroeter, G.; Finck, E. *Ber. Dtsch. Chem. Ges.* **1938**, *71*, 671.
(11) Ingraffia, F. *Gazz. Chim. Ital.* **1934**, *64*, 778.
(12) Ingraffia, F. *Gazz Chim. Ital.* **1934**, *64*, 784.
(13) Fischer, H.; Schneller, K.; Zerweck, W. *Ber. Dtsch. Chem. Ges.* **1922**, *55*, 2390.
(14) Gotor, V.; Liz, R.; Testera, A. M. *Tetrahedron* **2004**, *60*, 607.
(15) Takayama, K.; Iwata, M.; Hisamichi, H.; Okamoto, Y.; Aoki, M.; Niwa, A. *Chem. Pharm. Bull.* **2002**, *50*, 1050.
(16) Slätt, J.; Bergman, J., unpublished results.
(17) Shelkov, R.; Nahmany, M.; Melman, A. *J. Org. Chem.* **2002**, *67*, 8975.
(18) Hayashi, H.; Ohmoto, S.; Somei, M. *Heterocycles* **1997**, *45*, 1647.
(19) Walker, G. N. Ciba-Geigy, European Patent 156091, **1984**; *Chem. Abstr.* **1987**, *106*, 156268.
(20) Walker, G. N. Ciba-Geigy, US Patent 4256759, **1981**; *Chem. Abstr.* **1981**, *95*, 7046.