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Microwave assisted synthesis of 3-aminoindole-2-carbonitriles from anthranilonitriles via *N*-unprotected 2-(cyanomethylamino)benzonitriles

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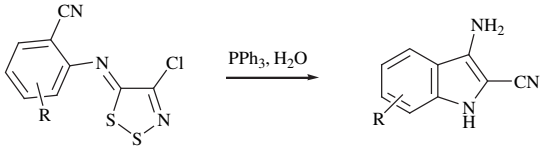
ABSTRACT

Anthranilonitrile **3a**, 4,5-dimethoxyanthranilonitrile **3b** and 5-nitroanthranilonitrile **3c**, react with paraformaldehyde, KCN and $ZnCl_2$ in acetic acid under acid catalysis (H_2SO_4) in a sealed tube at ca. 55 °C to give the corresponding 2-(cyanomethylamino)benzonitriles **4a–c** in 96, 86 and 57% yields, respectively. Thorpe–Ziegler cyclisation of the *N*-unprotected 2-(cyanomethylamino)benzonitriles **4a–c** with K_2CO_3 in EtOH at elevated temperatures and pressures using either microwave heating or conventional heating in a sealed tube gives 3-amino, 3-amino-5,6-dimethoxy, and 3-amino-5-nitroindole-2-carbonitriles **2a–c** in moderate to good yields. All new compounds are fully characterised.

1. Introduction

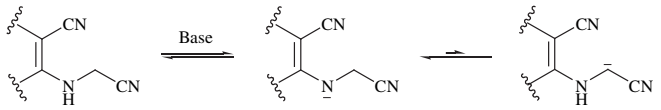
Many indoles are important in both the biological and material sciences.[1] More specifically, several substituted 2-cyanoindoles are important intermediates in the synthesis of heteroaromatic molecules and biologically active compounds.[2,3] We recently discovered a new route to 3-aminoindole-2-carbonitriles **2** starting from 2-(4-chloro-1,2,3-dithiazolylidenamino)benzonitriles **1** on reaction with triphenylphosphine.[4] This transformation however, did not tolerate methoxy substitution on the arene ring and specifically failed to provide access to 3-amino-5,6-dimethoxyindole-2-carbonitrile.



1 **2**

As such, we decided to develop a rational route to 3-aminoindole-2-carbonitriles **2** that would tolerate both electron withdrawing and donating substituents on the arene ring. To date there are only two routes to 3-aminoindole-2-carbonitriles: The first involved *N*-tosylation of the anthranilonitrile, followed by cyanomethylation to afford 2-[*N*-(cyanomethyl)-*N*-tosylamino]benzonitrile, which can then suffer base catalysed Thorpe–Ziegler cyclisation to give 3-amino-1-tosylindole-2-carbonitrile via a three-step synthesis.[5] While the second provided 3-(*N*-anilino)indole-2-carbonitriles via dehydrating or elimination steps to introduce the cyano functionality at C-2.[6] 3-Aminoindole-2-carbonitriles have been used as building blocks for pyrido[3,2-*b*]indoles (δ-carbolines),[6] and for pyrimido[5,4-*b*]indoles.[7] Interestingly, the isomeric 2-aminoindole-3-carbonitriles are more readily available,[8–11] and have found uses as scaffolds for the construction of pyrimido[1,2-*a*]indoles,[12] and pyrimido[4,5-*b*]indoles.[9,13–15]

Furthermore, it was stated that *N*-protection of the 2-(cyanomethylamino)benzonitrile was necessary for the Thorpe–Ziegler cyclisation to work.[5] Similar Thorpe–Ziegler cyclisations of (*Z*)-3-(cyanomethylamino)acrylonitriles to afford 3-aminopyrrole-2-carbonitriles also required protection of the amino group since the anion formed by the base abstraction of the NH proton would be more stable than its methylene analogue.[16,17]



Both *N*-methylation using diazomethane,[18,19] bromomethane[20] and *N*-carboalkoxylation using benzyl,[21] methyl[22] or ethyl chloroformate[17,23–28] have been used to enhance the formation of the required carbanion intermediate in the cyclisation to afford pyrroles.

Owing to difficulties encountered during the detosylation of 3-amino-1-tosylindole-2-carbonitrile,[29] we considered the alternative cyclisation of *N*-unprotected 2-(cyanomethylamino)benzonitrile **4a** rather than replace the tosyl protecting group.

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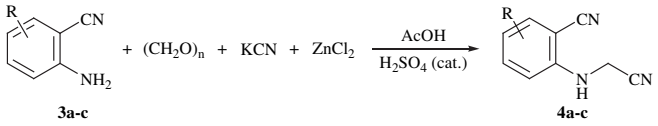
2. Results and discussion

2.1. *N*-Unprotected Thorpe–Ziegler cyclisation

Direct cyanomethylation of 2-aminobenzonitriles **3a–c** using chloroacetonitrile could not readily be achieved, however, an alternative route that made use of paraformaldehyde, KCN and zinc chloride in acetic acid catalysed by H_2SO_4 worked well.[30] A partial optimisation indicated that performing the reaction in a sealed tube allowed the use of fewer equivalents of reagents, in particular for the more electron rich aminobenzonitriles **3a** and **3b**, however 2-amino-5-nitrobenzonitrile **3c** required the use of excess reagents (Table 1).

Table 1
Reaction of 2-aminobenzonitriles **3a–c** with paraformaldehyde, KCN, $ZnCl_2$, and catalytic H_2SO_4 (cat.) in AcOH



3a-c **4a-c**

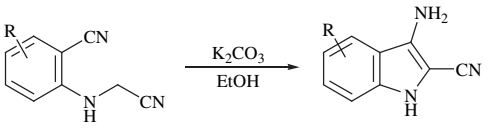
R	$(CH_2O)_n$ (equiv)	KCN (equiv)	$ZnCl_2$ (equiv)	Temp[a] (°C)	Time (h)	Yields (%)
H	3	3	8	55	3 min	**4a** (85)
H	1.5	1.5	4	25	6	**4a** (97)
H	1.1	1.1	2	55[b]	3	**4a** (96)
H	1.1	1.1	1.1	25–55[b]	48	IR[c]
4,5-$(MeO)_2$	1.5	1.5	4	25	2	**4b** (83)
4,5-$(MeO)_2$	1.1	1.1	2	55[b]	1	**4b** (86)
5-NO_2	3	3	8	55[b]	48	IR[c]
5-NO_2	5	5	10	55	48	IR[c]
5-NO_2	5	5	10	55[b]	11	**4c** (57)

[a] Preheated oil bath temperature.
[b] The reaction took place in a sealed tube.
[c] IR=Incomplete reaction.

The attempted cyclisation of 2-(cyanomethylamino)benzonitrile **4a** into 3-aminoindole-2-carbonitrile **2a** in EtOH at room temperature using a variety of bases (2 equiv) (K_2CO_3, Cs_2CO_3, NaOH, DBU) gave no reaction while at 60 °C complex mixtures were obtained. Nevertheless, repeating the reaction using K_2CO_3 (2 equiv) in EtOH, DMF or DMSO and heating in a CEM microwave reactor at ca. 120 °C at 180, 80 and 50 PSI, respectively gave the desired 3-aminoindole-2-carbonitrile **2a** in moderate yields (38–50%). Of the solvents screened, EtOH gave the highest product yields (50%) and the fastest reaction times (5 min), presumably due to the higher reaction vessel pressures. As such, EtOH was selected as the solvent for further optimisations. Indeed, in EtOH the reactions proceeded readily using only a catalytic amount of K_2CO_3 (0.5 equiv). Furthermore, by using a sealed tube and preheated Wood's metal baths the cyclisations could be achieved using conventional heating (hot plate stirrers), although product yields were somewhat lower and the reaction times longer (Table 2).

The observed differences between the microwave and the conventional heating were tentatively ascribed to the difficulty in accurately recording the internal temperature and pressure of the reactions performed in the microwave reactor using only the available external temperature and pressure probes. Nevertheless, at these elevated temperatures and pressures the formation of sufficient quantities of the required cyanomethylene carbanion allowed the desired Thorpe–Ziegler cyclisation to proceed without the need for *N*-protection. Thus allowing a rapid two-step synthesis of 3-aminoindole-2-carbonitriles **2a–c** that tolerates both electron withdrawing NO_2 and electron releasing MeO substituents on the benzo ring.

Table 2
Transformation of 2-(cyanomethylamino)benzonitriles **4a–c** into 3-aminoindole-2-carbonitriles **2a–c** in EtOH (1 mL)



4a-c **2a-c**

R (**4a–c**)	K_2CO_3 (equiv)	Temp (°C)	Time (min)	Yields (%)
H	1	120[a]	5	**2a** (60)
H	0.5	120[a]	8	**2a** (78)
H	0.1	120[a]	20	**2a** (71)
4,5-$(MeO)_2$	0.5	120[a]	45	**2b** (88)
5-NO_2	0.5	120[a]	5	**2c** (87)
H	0.5	140[b]	90	**2a** (57)
H	0.5	180[b]	25	**2a** (55)
4,5-$(MeO)_2$	0.5	140[b]	90	**2b** (88)
4,5-$(MeO)_2$	0.5	180[b]	66	**2b** (66)[c]
5-NO_2	0.5	140[b]	60	**2c** (37)
5-NO_2	0.5	180[b]	15	**2c** (56)

[a] MW 250 W, 180 PSI (max).
[b] Sealed tube in preheated Wood's metal bath.
[c] 2-Amino-5-nitrobenzonitrile **3c** was also isolated in 25% yield.

3. Conclusions

3-Aminoindole-2-carbonitriles **2a–c** supporting either NO_2 and MeO substituents on the arene were prepared from anthranilonitriles via the *N*-unprotected Thorpe–Ziegler cyclisation of the 2-(cyanomethylamino)benzonitriles **4a–c** at elevated temperatures and pressures, in two steps in best overall yields of 75, 76 and 50%, respectively.

4. Experimental

4.1. General methods and materials

Reactions were protected from atmospheric moisture by $CaCl_2$ drying tubes. Anhydrous Na_2SO_4 was used for drying organic extracts, and all volatiles were removed under reduced pressure. All reaction mixtures and column eluents were monitored by TLC using commercial glass backed thin layer chromatography (TLC) plates (Merck Kieselgel 60 F_{254}). The plates were observed under UV light at 254 and 365 nm. The technique of dry flash chromatography was used throughout for all non-TLC scale chromatographic separations using Merck Silica Gel 60 (less than 0.063 mm).[31] A CEM Discover Microwave Reactor was used for microwave experiments. Chemglass heavy wall cylindrical pressure vessels (15 mL) with a Teflon bushing as a pressure seal were used for the sealed tube studies. Melting points were determined using a PolyTherm-A, Wagner & Munz, Koefler–Hotstage Microscope apparatus. Solvents used for recrystallisation are indicated after the melting point. UV spectra were obtained using a Perkin–Elmer Lambda-25 UV/vis spectrophotometer and inflections are identified by the abbreviation 'inf'. IR spectra were recorded on a Shimadzu FTIR-NIR Prestige-21 spectrometer with a Pike *Miracle* Ge ATR accessory and strong, medium and weak peaks are represented by s, m and w, respectively. ^1H and ^{13}C NMR spectra were recorded on a Bruker Avance 300 machine (at 300 and 75 MHz, respectively). ^{13}C DEPT NMR was used to identify quaternary and tertiary carbons, which are indicated by (s) and (d) notations, respectively. Deuterated solvents were used for homonuclear lock and the signals are referenced to the deuterated solvent peaks. Low resolution (EI) mass spectra were recorded on a Shimadzu Q2010 GC–MS with direct inlet probe.

4.1.1. 2-(Cyanomethylamino)benzonitrile ***4a****: (Typical procedure, see Table 1).* To a stirred solution of 2-aminobenzonitrile **3a** (200 mg, 1.69 mmol) in acetic acid (5 mL), in a sealed tube at room temperature, were added paraformaldehyde (55.8 mg, 1.86 mmol, 1.1 equiv), potassium cyanide (121.1 mg, 1.86 mmol, 1.1 equiv), zinc chloride (461 mg, 3.38 mmol, 2 equiv) and sulfuric acid (1 drop, ca. 16 mg). The mixture was then warmed to ca. 55 °C for 3 h until no starting material remained (TLC). The reaction mixture was allowed to cool to rt, poured onto ice and made pH neutral (Na_2CO_3). Filtration of the precipitate gave the *title compound* **4a** (255 mg, 96%) white cotton, mp 95–96 °C (from cyclohexane/EtOH); (Found: C, 68.7; H, 4.4; N, 26.7. $C_9H_7N_3$ requires C, 68.8; H, 4.5; N, 26.7%); λ_{max}(DCM)/nm 228 inf (log ε 3.84), 244 (4.06), 318 (3.79); ν_{max}/cm^{-1} 3379m (NH), 2218m (C≡N), 1603s, 1582m, 1522s, 1460m, 1427w, 1317m, 1273m, 1256w, 1165m, 1134w, 1076m, 986w, 880w, 845w, 818w, 752s; δ_H(300 MHz; DMSO-d_6) 7.55–7.51 (2H, m, Ph *H*-4 and 6), 6.91 (1H, d, *J* 8.7, Ph *H*-3), 6.83 (1H, dd, *J* 7.7, 7.7, Ph *H*-5), 6.78 (1H, br m, CH_2NH), 4.36 (2H, d, *J* 6.0, CH_2NH); δ_C(75 MHz; DMSO-d_6) 148.5 (s), 134.6 (d), 133.4 (d), 118.1 (d), 117.8 (*C*≡N), 117.4 (*C*≡N), 111.7 (d), 96.2 (*CC*≡N), 31.2 (CH_2); *m*/*z* (EI) 157 (M$^+$, 90%), 130 (M$^+$−HCN, 49), 117 (13), 103 (100), 90 (39), 76 (17), 63 (17), 51 (13).

4.1.2. 2-(Cyanomethylamino)-4,5-dimethoxybenzonitrile ***4b****.* Yield 209 mg, 86%, white cotton, mp 143–144 °C (from cyclohexane/EtOH); (Found: C, 60.8; H, 5.0; N, 19.25. $C_{11}H_{11}N_3O_2$ requires C, 60.8; H, 5.1; N, 19.3%); λ_{max}(DCM)/nm 232 (log ε 4.53), 260 (4.10), 324 (3.88); ν_{max}/cm^{-1} 3370m and 3358w (NH), 2986w, 2963w, 2934w and 2833w (CH_2, CH_3), 2205s (C≡N), 1618s, 1587m, 1531s, 1520s, 1477m, 1462w, 1450w, 1437w, 1414m, 1360w, 1341m, 1294w, 1283s, 1261m, 1250w, 1231s, 1215s, 1146m, 1078s, 1045w, 1011s, 966w, 872s, 839w, 833m, 822m; δ_H(300 MHz; CD_2Cl_2) 6.94 (1H, s, Ph *H*-3 or 6), 6.32 (1H, s, Ph *H*-6 or 3), 4.78 (1H, br t, *J* 6.15, CH_2NH), 4.22 (2H, d, *J* 6.6, CH_2NH), 3.92 (3H, s, CH_3O), 3.78 (3H, s, CH_3O); δ_C(75 MHz; CD_2Cl_2) 155.5 (s), 144.6 (s), 143.0 (s), 117.8 (*C*≡N), 116.6 (*C*≡N), 115.4 (d), 96.6 (d), 88.3 (*CC*≡N), 56.9 (CH_3O), 56.4 (CH_3O), 32.9 (CH_2); *m*/*z* (EI) 217 (M$^+$, 95%), 202 (100), 190 (5), 177 (22), 175 (16), 174 (15), 150 (12), 147 (83), 132 (15), 117 (12), 104 (18), 90 (7), 77 (20), 76 (18), 68 (15), 64 (12), 53 (13).

4.1.3. 2-(Cyanomethylamino)-5-nitrobenzonitrile ***4c****.* Yield 141.6 mg, 57%, yellow cotton, mp 138–139 °C (from cyclohexane/EtOH); (Found: C, 53.45; H, 2.9; N, 27.7. $C_9H_6N_4O_2$ requires C, 53.5; H, 3.0; N, 27.7%); λ_{max}(DCM)/nm 228 (log ε 4.11), 243 inf (3.93), 327 (4.31); ν_{max}/cm^{-1} 3345m (NH), 3096w (Ar CH), 2978w (CH_2), 2226m (C≡N), 1611m, 1587s, 1537m, 1510s, 1449w, 1339s, 1312s, 1271w, 1256w, 1179m, 1159m, 1099s, 1070w, 989w, 924w, 914m, 903w, 833m, 808m, 748s, 725w; δ_H(300 MHz; DMSO-d_6) 8.55 (1H, d, *J* 2.7, Ph *H*-6), 8.39 (1H, dd, *J* 2.7, 9.3, Ph *H*-4), 7.94 (1H, br s, N*H*), 7.11 (1H, d, *J* 9.3, Ph *H*-3), 4.53 (2H, s, CH_2); δ_C(75 MHz; DMSO-d_6) 152.8 (s), 137.6 (s), 130.4 (d), 130.0 (d), 116.9 (*C*≡N), 115.4 (*C*≡N), 111.5 (d), 95.7 (*CC*≡N), 31.3 (CH_2); *m*/*z* (EI) 202 (M$^+$, 100%), 185 (10), 175 (M$^+$−HCN, 49), 172 (12), 158 (12), 156 (14), 148 (26), 145 (80), 129 (56), 116 (58), 102 (46), 89 (31), 75 (27), 62 (24).

4.2. 3-Aminoindole-2-carbonitrile 2a: (Typical microwave procedure, see Table 2)

To a stirred solution of 2-(cyanomethylamino)benzonitrile **4a** (50 mg, 0.32 mmol) in EtOH (1 mL) was added K_2CO_3 (22 mg, 0.16 mmol, 0.5 equiv) and the mixture was sealed and heated to ca. 120 °C in a microwave reactor (250 W, 180–160 PSI), for 8 min until no starting material remained (TLC). The reaction mixture was then allowed to cool to rt, added to water (50 mL) and extracted with DCM (3×10 mL). The combined organic extracts were dried (Na_2CO_3) and the volatiles removed under reduced pressure to give the title compound **2a** (39.2 mg, 78%) as light yellow cotton fibres, mp 172–173 °C (lit.,[4] 172–173 °C) (from cyclohexane/EtOH); ν_{max}/cm^{-1} 3356m (NH), 3309 (NH_2), 3231w, 3059 (Ar CH), 2924w, 2212s (C≡N), 1628m, 1597w, 1584w, 1557m, 1493w, 1450w, 1344s, 1310s, 1292w, 1248w, 1182m, 1159s, 1105w, 1090w, 1042w, 1016w, 1009w, 932w, 891w, 814m, 746s, 739s, 727s; δ_H(300 MHz; DMSO-d_6) 10.67 (1H, br s, N*H*), 7.73 (1H, d, *J* 8.1, indole *H*-4), 7.24 (1H, ddd, 1.1, 7.5, 7.5, indole *H*-5), 7.18 (1H, d, *J* 7.8, indole *H*-7), 6.94 (1H, ddd, 1.2, 7.5, 7.5, indole *H*-6), 5.71 (2H, br s, NH_2); δ_C(75 MHz; DMSO-d_6) 139.0 (s), 136.8 (s), 126.1 (d), 120.2 (d), 118.2 (s), 118.0 (d), 116.2 (s), 111.6 (d), 86.6 (*CC*≡N); *m*/*z* (EI) 157 (M$^+$, 100%), identical to an authentic sample.

4.2.1. 3-Amino-5,6-dimethoxyindole-2-carbonitrile ***2b****.* Yield 25.1 mg, 89%, yellow needles, mp 194–195 °C (from cyclohexane/EtOH); (Found: C, 60.8; H, 5.0; N, 19.3. $C_{11}H_{11}N_3O_2$ requires C, 60.8; H, 5.1; N, 19.3%); λ_{max}(DCM)/nm 232 (log ε 4.24), 248 (4.24), 311 (4.33); ν_{max}/cm^{-1} 3426w (NH), 3347m (NH_2), 3007w (Ar CH), 2949w, 2907w, 2839w, 2185s (C≡N), 1636m, 1591w, 1557s, 1485s, 1462m, 1439m, 1385w, 1331s, 1319s, 1240m, 1225s, 1204s, 1190s, 1169s, 1105m, 1032w, 1001m, 910w, 853m, 822w, 806m, 754m; δ_H(300 MHz; CD_2Cl_2) 7.46 (1H, br s, N*H*), 6.86 (1H, s, indole *H*-4 or 7), 6.73 (1H, s, indole *H*-4 or 7), 3.99 (2H, br s, NH_2), 3.86 (6H, s, 2×CH_3O); δ_C(75 MHz; CD_2Cl_2) 151.8 (s), 146.0 (s), 138.0 (s), 132.6 (s), 115.3 (s), 111.6 (s), 99.7 (d), 94.5 (d), 89.0 (s), 56.5 (OCH_3), 56.2 (OCH_3), *m*/*z* (EI) 217 (M$^+$, 100%), 202 (M$^+$−CH_3, 28), 189 (5), 174 (12), 159 (23), 147 (23), 131 (7), 120 (6), 117 (6), 109 (6), 104 (10), 90 (4), 77 (11), 63 (4), 52 (7).

4.2.2. 3-Amino-5-nitroindole-2-carbonitrile ***2c****.* Yield 56 mg, 87%, red cotton fibres, mp 310–311 °C (lit.,[4] 310–311 °C) (from PhH); ν_{max}/cm^{-1} 3463w (NH_2), 3376m and 3279m (NH), 3065w, 2204s (C≡N), 1635m, 1614m, 1588m, 1533m, 1521w, 1476s, 1398w, 1327s, 1244w, 1190m, 1132w, 1064m, 942w, 914w, 846w, 814m, 778w, 755m; δ_H(300 MHz; DMSO-d_6) 11.62 (1H, br s, N*H*), 8.95 (1H, d, *J* 2.4, indole *H*-4), 8.07 (1H, dd, *J* 2.3, 9.2, indole *H*-6), 7.33 (1H, d, *J* 9.3, indole *H*-7), 6.29 (2H, br s, NH_2); δ_C(75 MHz; DMSO-d_6) 141.0 (s), 139.4 (s), 138.5 (s), 120.8 (d), 118.9 (d), 117.2 (s), 115.0 (s), 112.1 (d), 87.4 (*CC*≡N); *m*/*z* (EI) 202 (M$^+$, 100%), identical to an authentic sample.

4.3. 3-Aminoindole-2-carbonitrile 2a: (Typical conventional heating procedure, see Table 2)

To a stirred solution of 2-(cyanomethylamino)benzonitrile **4a** (50 mg, 0.32 mmol) in EtOH (1 mL) was added K_2CO_3 (22 mg, 0.16 mmol, 0.5 equiv) and the mixture was sealed in a thick glass walled tube and heated at ca. 140 °C in a preheated Wood's metal bath, for 90 min until no starting material remained (TLC). The reaction mixture was then allowed to cool to ca. 20 °C, added to water (50 mL) and extracted with DCM (3×10 mL). The combined organic extracts were dried (Na_2CO_3) and the volatiles removed under reduced pressure to give the title compound **2a** (28.6 mg, 57%) as light yellow cotton fibres, mp 172–173 °C (lit.,[4] 172–173 °C) (from cyclohexane/EtOH); identical to an authentic sample.

4.3.1. 3-Amino-5,6-dimethoxyindole-2-carbonitrile ***2b****.* Yield 61 mg, 88%, as yellow needles, mp 194–195 °C (from cyclohexane/EtOH), identical to that described above.

4.3.2. 3-Amino-5-nitroindole-2-carbonitrile ***2c****.* Yield 23.9 mg, 37%, red cotton fibres, mp 310–311 °C (lit.,[4] 310–311 °C) (from PhH); identical to an authentic sample.

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