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

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Anthranilonitrile 3a, 4,5-dimethoxyanthranilonitrile 3b and 5-nitroanthranilonitrile 3c, react with paraformaldehyde, KCN and ZnCl₂ in acetic acid under acid catalysis (H₂SO₄) 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 K₂CO₃ 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. More specifically, several substituted 2-cyanoindoles are important intermediates in the synthesis of heteroaromatic molecules and biologically active compounds. We recently discovered a new route to 3-aminoindole-2-carbonitriles starting from 2-(4-chloro-1,2,3-dithiazolylidenamino)benzonitriles on reaction with triphenylphosphine. 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.

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. While the second provided 3-(N-anilino)indole-2-carbonitriles via dehydrating or elimination steps to introduce the cyano functionality at C-2. Aminoindole-2-carbonitriles have been used as building blocks for pyrido[3,2-b]indoles (5-carbolines), and for pyrimido[5,4-b]indoles. Interestingly, the isomeric 2-aminoindole-3-carbonitriles are more readily available, and have found uses as scaffolds for the construction of pyrimido[1,2-a]indoles, and pyrimido[4,5-b]indoles.

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

Both N-methylation using diazomethane and N-carboxaloxoylation using benzyl, methyl or ethyl chloroformate have been used to enhance the formation of the required carbanion intermediate in the cyclisation to afford pyroles. Owing to difficulties encountered during the detosylation of 3-amino-1-tosylindole-2-carbonitrile, 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-Protected 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, KCl and zinc chloride in acetic acid catalysed by H2SO4 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).

The attempted cyclisation of 2-(cyanomethylamino)benzonitriles 4a–c into 3-aminoindole-2-carbonitriles 2a–c in EtOH (1 mL)

Table 1. Reaction of 2-aminobenzonitriles 3a–c with paraformaldehyde, K2CO3, and catalytic H2SO4 (cat.) in AcOH

<table>
<thead>
<tr>
<th>R</th>
<th>(CH2O)n (equiv)</th>
<th>K2CO3 (equiv)</th>
<th>Temp° (C)</th>
<th>Time (h)</th>
<th>Yields (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>H</td>
<td>3.0</td>
<td>1.5</td>
<td>25</td>
<td>6</td>
<td>4a (85)</td>
</tr>
<tr>
<td>H</td>
<td>3.0</td>
<td>1.1</td>
<td>55b</td>
<td>3</td>
<td>4a (96)</td>
</tr>
<tr>
<td>H</td>
<td>1.1</td>
<td>1.1</td>
<td>25–55b</td>
<td>48</td>
<td>IRc</td>
</tr>
<tr>
<td>4,5-(MeO)2</td>
<td>1.5</td>
<td>1.5</td>
<td>25</td>
<td>2</td>
<td>4b (83)</td>
</tr>
<tr>
<td>4,5-(MeO)2</td>
<td>1.1</td>
<td>1.1</td>
<td>55b</td>
<td>1</td>
<td>4b (86)</td>
</tr>
<tr>
<td>5-NO2</td>
<td>3.0</td>
<td>3.0</td>
<td>55b</td>
<td>48</td>
<td>IRc</td>
</tr>
<tr>
<td>5-NO2</td>
<td>5.0</td>
<td>5.0</td>
<td>10</td>
<td>55b</td>
<td>IRc</td>
</tr>
<tr>
<td>5-NO2</td>
<td>5.0</td>
<td>5.0</td>
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<tr>
<td>5-NO2</td>
<td>5.0</td>
<td>5.0</td>
<td>10</td>
<td>55b</td>
<td>IRc</td>
</tr>
</tbody>
</table>

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

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 cyanoethylene carbonanion allowed the desired Thorpe–Ziegler cyclisation to proceed without the need for N-protaction. Thus allowing a rapid two-step synthesis of 3-aminoindole-2-carbonitriles 2a–c that tolerates both electron withdrawing NO2 and electron releasing MeO substituents on the benzo ring.

3. Conclusions

3-Aminooindole-2-carbonitriles 2a–c supporting either NO2 and MeO substituents on the arenne were prepared from anthranilonitriles via the N-protected 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 CaCl2 drying tubes. Anhydrous Na2SO4 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 F254). 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, Koehler–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 infrared absorption 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 13C NMR spectra were recorded on a Bruker Avance 300 machine (at 300 and 75 MHz, respectively). 13C 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 QP2010 GC–MS with direct inlet probe.

4.2. Materials

2-Amino-5-nitrobenzonitrile 3c was also isolated in 25% yield.
4.1.1. 2-(Cyanomethylamino)benzotriazole 4a: (Typical procedure, see Table 1). To a stirred solution of 2-aminobenzotriazole 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 with no starting material remaining (TLC). The reaction mixture was allowed to cool to rt, poured onto ice and washed with Na2CO3 (aq.). 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, 26.8%).

4.1.2. 2-(Cyanomethylamino)-4,5-dimethoxybenzotriazole 4b. Yield 209 mg, 86% white cotton, mp 143–144 °C from cyclohexane/EtOH; (Found: C, 60.8; H, 5.0; N, 19.25. C16H15N3O2 requires C, 60.8; H, 4.4; N, 26.7%; C in a microwave reactor (250 W, 180–160 PSI), for 8 min until 137.6 (s), 130.4 (d), 130.0 (d), 116.9 (s), 103.6 (s), 76.4 (s), 52.8 (s); m/z (EI) 337.9 (M+1), 217 (M+2), 191 (M+3), 165 (M+4), 139 (M+5), 113 (M+6) (EI) 217 (M+1), 202 (M+2), 197 (M+3), 182 (M+4), 112 (M+5), 91 (M+6), 79 (M+7), 70 (M+8) (EI) 202 (M+1, 100%), identical to an authentic sample.

4.2. 3-Aminooindole-2-carbonitrile 2a: (Typical conventional heating procedure, see Table 2). To a stirred solution of 2-(cyanomethylamino)benzotriazole 4a (50 mg, 0.32 mmol) in EtOH (1 ml) was added K2CO3 (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 x 10 ml). The combined organic extracts were dried (Na2CO3) 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 (from cyclohexane/EtOH); identical to that described above.

4.3. 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.

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References and notes