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Unexpected product distributions in the synthesis of 2,6-bis-(indazolyl)pyridine and 2-(pyrazol-1-yl)-6-(indazolyl)pyridine

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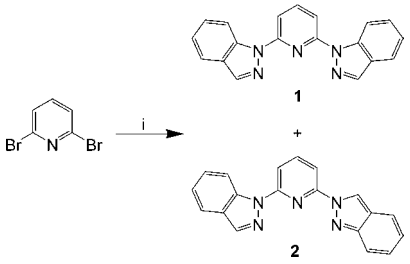
ABSTRACT

Reaction of 2-bromopyridine with 2 equiv of sodium indazolide in diglyme at 140 °C affords 2,6-bis-(indazol-1-yl)pyridine and 2-(indazol-1-yl)-6-(indazol-2-yl)pyridine in purified yields of 24% and 68% respectively. A similar reaction, using 1 equiv of sodium indazolide at 70 °C, gives a low-yield mixture of 2-(indazol-1-yl)-6-bromopyridine and 2-(indazol-2-yl)-6-bromopyridine. Both these intermediates are transformed into 2-(pyrazol-1-yl)-6-(indazol-1-yl)pyridine and 2,6-di(pyrazol-1-yl)pyridine upon treatment with 1 equiv of sodium pyrazolide in diglyme at 140 °C. These observations imply that the indazolyl group is a leaving group comparable to a bromo substituent under nucleophilic attack by pyrazolide or indazolide ions under these conditions. No reaction was observed between 2-(pyrazol-1-yl)-6-bromopyridine and 1 equiv of sodium indazolide under the same conditions. A single crystal structure of its iron(II) complex confirmed the regiochemistry of 2,6-bis-(indazol-1-yl)pyridine, and revealed significant conformational flexibility in the distal ligand indazolyl groups.

2,6-Di(pyrazol-1-yl)pyridine (1-bpp) derivatives are finding increasing use as ligands for d- and f-block metal ions.[1] Their homoleptic iron(II) complexes have been of particular interest, since these often undergo thermal spin-crossover[2,3] at accessible temperatures. We[1,4–6] and others[7–9] have exploited the relative ease of incorporating substituents onto the 1-bpp backbone, to yield materials showing a wide variety of different spin-transition regimes, based around the same metal:ligand core. In our work, we have noted that several $[FeL_2]X_2$ salts (L = 1-bpp, 2,6-di(pyrazol-1-yl)pyrazine or a derivative thereof; X^- = a monovalent anion) exhibit extremely consistent abrupt thermal spin-transitions, despite adopting different crystallographic space groups.[5] This cooperativity appears to be mediated by π–π stacking between the pyrazolyl groups of neighbouring molecules. To extend these ideas, we were keen to gain access to related tridentate ligands incorporating indazolyl functionality. We reasoned that replacement of pyrazolyl by indazolyl groups in a terpyridine embrace structure should lead to stronger intermolecular π–π stacking within the fourfold layers, which could afford increased spin-crossover cooperativity.[10] No bis-(azolyl)pyridines incorporating indazolyl groups have been reported to date, although a small number of comparable mono-(indazol-1-yl)pyridines have been made before.[11] We report here that the usual method used to make 1-bpp derivatives yields unexpected product distributions when applied to indazolylpyridines.

Reaction of 2,6-dibromopyridine with 2 equiv of Na[Ind] (IndH = indazole) in hot diglyme, under the normal conditions for the synthesis of 1-bpp and its derivatives,[6,12,13] affords a mixture of products. Flash silica chromatography of the crude mixture in $CHCl_3$ allowed the isolation of pure 2,6-bis-(indazol-1-yl)pyridine (**1**) and 2-(indazol-1-yl)-6-(indazol-2-yl)pyridine (**2**) in 24% and 68% yields, respectively (Scheme 1). A small amount of the third potential regioisomer, 2,6-bis-(indazol-2-yl)pyridine, also appeared to be present in the crude reaction mixture by ^{1}H NMR but was not isolated in pure form. The regiochemistry of **1** was confirmed by the crystal structure determination of its iron(II) complex described below, and by ^{13}C NMR spectroscopy (the chemical shifts of the C3, C7 and C7a resonances all differ by ca. 10 ppm in 1-substituted and 2-substituted indazole regioisomers[14]). Two ^{1}H NMR resonances from the 2-(indazolyl)pyridine res-



Scheme 1. Synthesis of 2,6-bis-(indazolyl)pyridine derivatives. Reagents and conditions: (i) 2 equiv Na[Ind], diglyme, 140 °C, 4 d.

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idue are also diagnostic in these compounds, and those described below. First is the singlet for the indazole H3 atoms. This appears near 8.3 ppm for (indazol-1-yl)pyridine groups and at 9.1 ppm for the (indazol-2-yl)pyridines, the latter being >0.5 ppm downfield of the usual range for 2-substituted indazoles.[15] Second is the doublet for the pyridine H3 or H5 atom, adjacent to the indazole substituent. This appears at 8.8 ppm in the (indazol-1-yl)pyridine compounds (around 1 ppm higher compared to most 1-bpp derivatives[6,12]), and near 8.3 ppm in the (indazol-2-yl)pyridines.

We also investigated the synthesis of unsymmetric 2-(indazol-yl)-6-(pyrazol-1-yl)pyridine derivatives (Scheme 2). Reaction of 2,6-dibromopyridine with 1 equiv of Na[Ind] in diglyme at 70 °C,[12] gives the expected mixture of 2-(indazol-1-yl)-6-bromopyridine (**3**) and 2-(indazol-2-yl)-6-bromopyridine (**4**), in purified yields of 33% and 18%, respectively.

Unexpectedly, however, treatment of both these intermediates with a twofold excess of Na[Pz] (PzH = pyrazole) in diglyme at 130 °C yielded the same two isolable products: 2-(pyrazol-1-yl)-6-(indazol-1-yl)pyridine (**5**), and 1-bpp (Scheme 2). The yield of each product was broadly similar, whether **3** or **4** was used as starting material. The alternative approach, of reacting pre-formed 2-(pyrazol-1-yl)-6-bromopyridine (**6**)[12] with 2 equiv of Na[Ind] under the same conditions as before, produced no reaction (Scheme 2). The bromo substituent in 2-(azolyl)-6-bromopyridines is deactivated towards substitution compared to 2,6-dibromopyridine itself,[12] and Ind^- (a weaker nucleophile than Pz^-) is apparently insufficiently reactive to undergo this reaction.

Given that indazolide anions undergo electrophilic attack preferentially at the 1- rather than at the 2-position,[15,16] all the abovementioned results can be explained if the indazolyl ring is a leaving group comparable to a bromo substituent under these conditions. This would allow an incoming Pz^- or Ind^- nucleophile to displace an indazolyl group rather than a bromo group from the pyridine ring. The liberated Ind^- anion is then free to re-attack a second equivalent of bromopyridyl reagent or intermediate, resulting in enrichment of the preferred indazol-1-yl regioisomer in the product mixture. This suggestion accounts for the higher-than-expected yield of **2** (68%, when the maximum possible theoretical yield without nucleophilic exchange of Ind^- groups would be 50% on statistical grounds); and, for the isomerisation of **4** during its reaction with Na[Pz].

Since **1** did not form single crystals, to confirm its regiochemistry a structure determination was achieved from a solvated crystal of its iron(II) complex $[Fe(\mathbf{1})_2][BF_4]_2$.[17] The crystal contained three formula units per asymmetric unit, with several disordered anions and solvent molecules. The three unique complex cations have similar bond lengths and angles at their iron centres, all of which

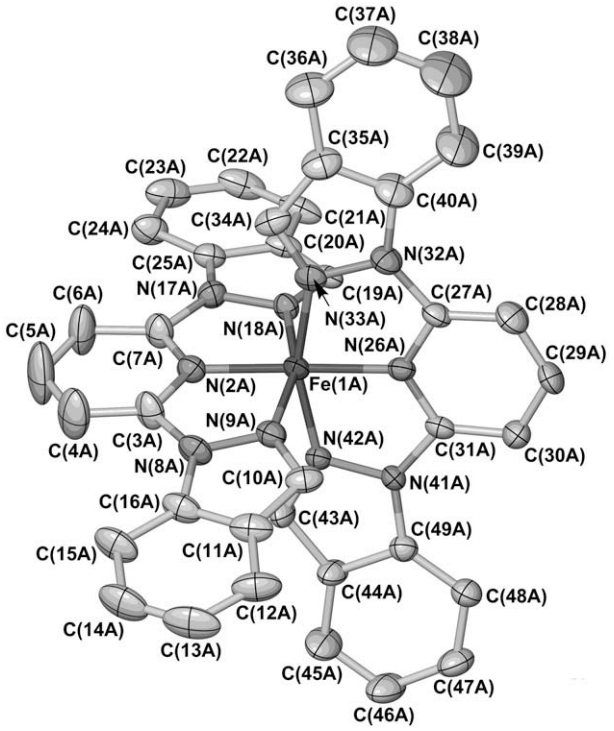
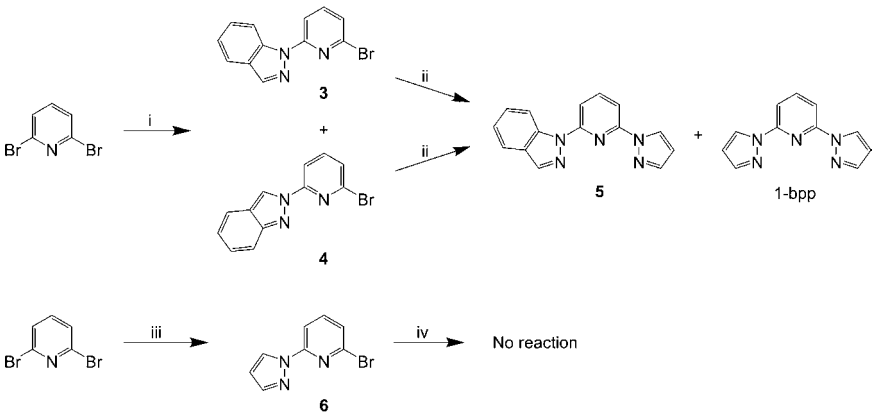


Figure 1. One of the three unique molecules (molecule A) in the crystal solvate of $[Fe(\mathbf{1})_2][BF_4]_2$.[17] All H atoms have been omitted for clarity, and thermal ellipsoids are at the 50% probability level. Molecules B and C use the same atom numbering scheme as shown here (see Supplementary data).

imply that they are low-spin at the temperature of measurement 150 K (Fig. 1 and Supplementary data). However, the molecules differ significantly in the conformations of the ligands **1**, some of which are significantly distorted from planarity. This is exemplified by the dihedral angles between the least squares planes of the pyridyl groups, and the annelated benzo groups, which span a range of 2.8(2)–17.5(3)°. These distortions give rise to either a bowl-shaped or S-shaped ligand conformation; three of the six unique ligands in the model adopt each type of conformation, to differing degrees (Fig. 2). We attribute these distortions from planarity to intramolecular steric repulsion between the pyridyl H3 and H5 atoms, and the H7 atoms on the neighbouring indazolyl rings, all of which lie 2.0–2.1 Å apart. These distances should be treated with caution as the H atoms in the structure were placed in calculated positions



Scheme 2. Synthesis of 2-(indazol-1-yl)-6-(pyrazol-1-yl)pyridine. Reagents and conditions: (i) 1 equiv Na[Ind], diglyme, 70 °C, 2 d; (ii) 2 equiv Na[Pz], diglyme, 140 °C, 4 d; (iii) 1 equiv Na[Pz], diglyme, 70 °C, 2 d; (iv) 2 equiv Na[Ind], diglyme, 140 °C, 4 d.

Figure 2. Alternative views of molecules A (top), B (centre) and C (bottom) in the crystal solvate of $[Fe(\mathbf{1})_2][BF_4]_2$,[17] showing the flexibility of the ligands **1**. All atoms have arbitrary radii.

rather than being directly refined. However, they are clearly shorter than the sum of the van der Waals radii of two H atoms, 2.4 Å.[18]

In conclusion, the 2,6-di(indazolyl)pyridines **1** and **2** can be accessed from 2,6-dibromopyridine by nucleophilic substitution with 2 equiv of Na[Ind]. Similar reactions using 1 equiv of Na[Ind] afforded the 2-(indazolyl)-6-bromopyridines **3** and **4**, both of which gave 2-(pyrazol-1-yl)-6-(indazolyl)pyridine **5** upon reaction with Na[Pz]. The synthetic yield of **2** is higher than expected on statistical grounds, while the isolation of 1-bpp as a byproduct in the synthesis of **5** shows that indazolyl groups can be displaced from the pyridine ring by pyrazolyl groups during the reaction. These observations imply that indazolyl substituents can serve as leaving groups from the pyridine ring during the reaction, resulting in enrichment of the preferred indazol-1-yl products.

Acknowledgements

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Supplementary data

Supplementary data (Experimental procedures and characterisation data for the compounds in this study, and further details on the crystal structure, its data collection and refinement) associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2009.03.035.

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