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Synthesis of a new series of ditopic proligands for metal salts: differing regiochemistry of electrophilic attack at 3{5}-amino-5{3}-(pyrid-2-yl)-1*H*-pyrazole

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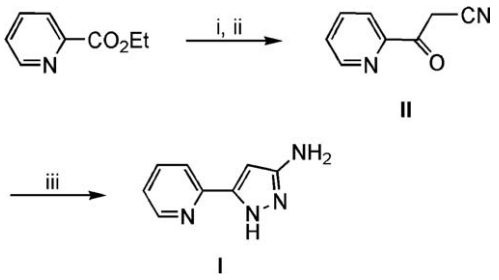
Abstract—An improved synthesis of 3{5}-amino-5{3}-(pyrid-2-yl)-1*H*-pyrazole (**I**) is described, which affords the compound on a multi-gram scale. Reaction of **I** with acid chloride and isothiocyanate electrophiles in MeCN cleanly results in attack at its amino group, yielding *N*-(3-{pyrid-2-yl}-1*H*-pyrazol-5-yl)amide and *N*-(3-{pyrid-2-yl}-1*H*-pyrazol-5-yl)thiourea products. These are good candidates as proligands for the simultaneous complexation of metal cations and anions. However, treatment of **I** with isocyanates under the same conditions instead yields attack at the pyrazole ring, giving 3-(pyridin-2-yl)-5-aminopyrazole-1-carboxylic acid amides as the only isolable products. The differing regiochemistries of these reactions were confirmed by ^{1}H NMR and X-ray crystallography.

We[1–3] and others[4] have found that metal complexes of simple *NH* pyrazoles can present a structurally defined binding pocket for halides or other anions. *tert*-Butyl and other hydrocarbon substituents at the 5-position of the metal-bound pyrazole groups appear to promote these anion-binding capabilities through hydrophobic interactions. For our own part, we have used zinc-coordinated pyrazole ligands to bind a range of inorganic anions,[1] and have found that supramolecular pyrazole···anion interactions can be used to template new metal cluster structures.[2,3] More generally, organic ligands that can bind simultaneously to a metal cation and its charge balancing anions are also of great current interest for hydrometallurgy, waste water treatment and other applications in supramolecular chemistry.[5] As an extension of our work, we proposed that 5-amino-3-(pyrid-2-yl)-1*H*-pyrazole (**I**, Scheme 1),[6] should *chelate* to both the cation and anion(s) of a coordinated metal salt. An initial study of two copper(II) complexes of **I** has proven the validity of that suggestion.[7] We reasoned that a wide range of new ditopic ligands could be accessed from **I**, by electrophilic derivitisation of its amine substituent. We were particularly keen to incorporate amide, urea and thiourea functions onto the 3{5}-(pyrid-2-yl)-1*H*-pyrazole framework, since these are particularly useful donor groups in anion receptors.[8] Towards that end, we describe here an improved synthesis of **I** and its reactions with electrophiles.



Scheme 1. Synthesis of 3{5}-(pyrid-2-yl)-5{3}-aminopyrazole (**1**). Reagents and conditions: (i) CH_3CN, NaH, toluene, 65 °C, 40 h; (ii) dil HCl; (iii) $N_2H_4{\cdot}H_2O$, EtOH, reflux, 20 h.

The preparation of **I** by the basic procedure shown in Scheme 1 has been briefly discussed, but no experimental details are given.[6] The synthesis of the intermediate 3-oxo-3-pyridin-2-yl-propionitrile (**II**, Scheme 1) under Knoevenagel conditions is better known, although very variable yields of between 7% and 60% have been reported for this reaction.[9] We have synthesised **II** in

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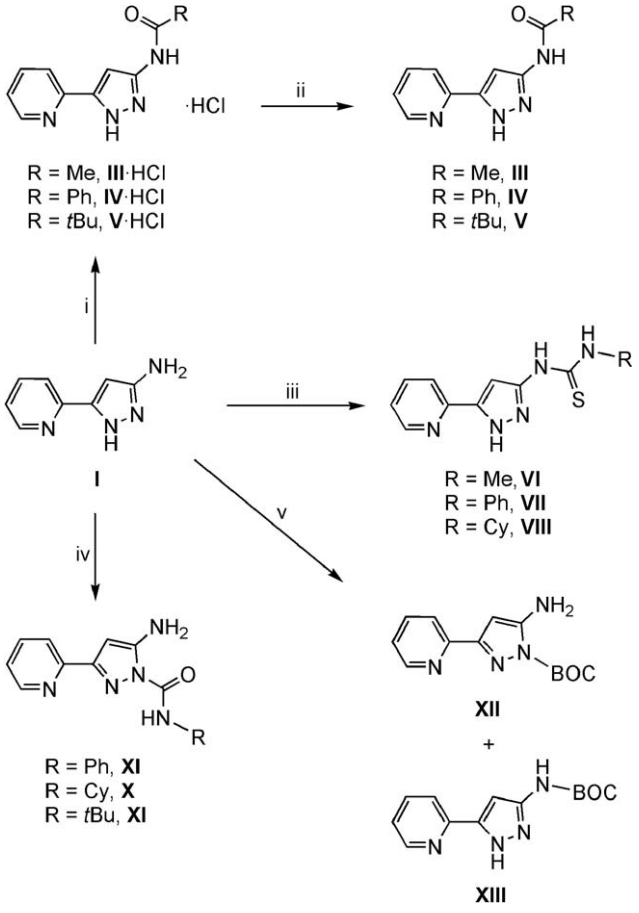
68% yield from ethyl picolinate and acetonitrile using sodium hydride as base, and modified reaction conditions and work-up. Treatment of **II** with hydrazine monohydrate affords **I** in 89% yield. Compound **I** can be prepared on a 10 g scale by this route, making it a convenient synthetic intermediate. The NMR spectra and melting point of **II** match those previously reported for this compound.[9] No characterisation data for **I** have been presented before.

Reaction of **I** with acid chlorides RC{O}Cl (R = Me, Ph or *t*-Bu) in refluxing MeCN yields white precipitates of the appropriate *N*-(3-{pyrid-2-yl}-1*H*-pyrazol-5-yl)-amide as its hydrochloride salt, **III**·HCl–**V**·HCl (Scheme 2), in ca. 70% yield. The free bases of these compounds can be obtained in low yield by treating the hydrochloride salts with aqueous Na_2CO_3 under biphasic conditions. Acid-free **III**–**V** were also obtained directly in 10–25% yield by performing the acetylations using pyridine instead of MeCN as solvent, although these reactions required more extended purifications. Our difficulties in obtaining the free bases **III**–**V** reflect the fact that they strongly retain solvent in the solid state, being obtained as analytically impure solids from many of the common organic solvents. A structure determination of crystals of formula **III**·*n*-CH_2Cl_2 ($n \approx 0.25$) provided some insight into this problem, showing that its crystal lattice contains channels that are occupied by the (disordered) solvent.[10] After many attempts we found that **III**·H_2O and solvent-free **V** can be obtained cleanly, but with substantial solubility losses, by recrystallisation from MeOH, while small amounts of **IV** can be obtained in pure form from ethyl acetate. Given the difficulties in handling **III**–**V**, it is probably more convenient to use their hydrochloride salts as reagents in further chemical transformations or metal salt complexation reactions, deprotonating them in situ if required.



Scheme 2. Reactions of **1** with electrophiles. Reagents and conditions: (i) RCOCl, MeCN, reflux, 16 h; (ii) Na_2CO_3, $CHCl_3/H_2O$, reflux, 16 h; (iii) RNCS, MeCN, reflux, 16 h; (iv) RNCO, MeCN, reflux, 16 h; (v) $[t\text{-BuOC(O)}]_2O$, MeCN, reflux, 16 h.

Treatment of **I** with the isothiocyanates RNCS (R = Me, Ph or Cy) in refluxing MeCN affords the *N*-(3-{pyrid-2-yl}-1*H*-pyrazol-5-yl)thioureas **VI**–**VIII** as analytically pure white precipitates in 44–81% yield (Scheme 2). However, an analogous reaction using *t*-BuNCS gave only unreacted starting material following the usual work-up, for reasons that are unclear. In contrast, reaction of **I** with isocyanates RNCO (R = Ph, Cy or *t*-Bu) under the same conditions instead gave the 3-(pyridin-2-yl)-5-aminopyrazole-1-carboxylic acid amides **IX**–**XI** as the only isolable products, in 48–71% isolated yield (Scheme 2). The different regiochemistry of these reactions has some literature precedent in the chemistry of 3{5}-aminopyrazole itself. It is known that *N*-(pyrazol-1*H*-3-yl)thioureas are obtained cleanly by treatment of 3{5}-aminopyrazole with isothiocyanates.[11] However, reaction of 3{5}-aminopyrazole with acid chlorides[12,13] or isocyanates[14] can result in functionalisation of the amino group or either of the pyrazole N atoms, yielding up to three different products.[13,14] Our isolation of regioisomerically pure products **III**–**V** (as their HCl adducts) and **IX**–**XI** in good yields contrasts with these earlier studies, where mixtures of products were commonly observed.[12–14] Treatment of **I** with $(Boc)_2O$ under the same conditions did lead to a crude mixture of **XII** [δ\{N–H\} = 6.35 (2H) ppm] and **XIII** [δ\{N–H\} = 9.51 (1H) and 12.83 (1H) ppm] according to the ^1H NMR criteria in $\{CD_3\}_2SO$ described below, however, in an approximate yield ratio of 3:1. Unfortunately, we were unable to separate these two products by crystallisation or flash chromatography.

The different regiochemistry of the reactions in Scheme 2 was confirmed by crystal structure determinations of **III** (as its CH_2Cl_2 solvate), **VI**, **X** and **XI** (Fig. 1).[10,15–17] Although **III** and **VI** crystallise as their 5-pyridyl-1*H* tautomers, the rapid tautomeric interconversion undergone by many pyrazoles in solution[18] (including **III**–**V**, see below) means that the 3-pyridyl-1*H* tautomer required for chelation to a metal ion through N(1) and N(8) (Fig. 1) should be readily accessible under suitable conditions. The amide N–H group in **III** is *syn* to the pyrazole N atoms, which is the conformation required for **III** to chelate to an anion by hydrogen-bonding through N(9) and N(12) (in the alternative 3-pyridyl-1*H* form; Fig. 1). The amide and pyrazole groups are not coplanar, however, the torsion C(11)–C(10)–N(12)–C(13) angle being 16.5(5)°. This reflects a steric contact between O(15) and the H atom bound to

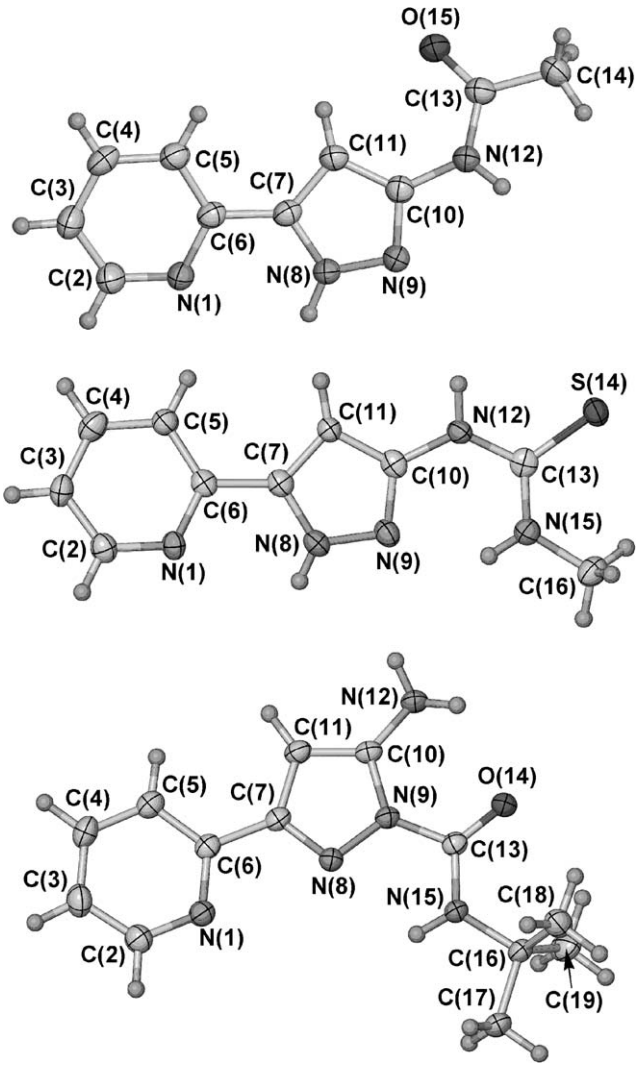


Figure 1. Views of the single crystal structures of **III**·*n*-CH_2Cl_2 (top), **VI** (centre) and **XI** (bottom). Only one of the two crystallographically independent molecules in **III**·*n*-CH_2Cl_2 is shown. The other molecule is visually near-identical to this one, but shows some disorder in its amide group. Thermal ellipsoids are at the 50% displacement level, except for H atoms which have arbitrary radii. A view of **X** is given in Supplementary data.

C(11), which are 2.5 Å apart (with the H atom in an idealised calculated position). For comparison, the sum of the van der Waals radii of an H and O atom is 2.6 Å.[19] The thiourea function in **VI** adopts the *Z*,*E* conformation that is usually preferred for *N*,*N*′-disubstituted thioureas,[20] giving rise to an intramolecular N–H···N hydrogen bond from the distal N–H group N(15) to the pyrazole pyridinic N atom N(9) (Fig. 1). Chelation of an anion to this group would require rotation of the thiourea group to a *Z*,*Z* conformation (for which there is substantial precedent)[8] and cleavage of this hydrogen bond. The dihedral angle between the pyrazole and thiourea groups in this structure is 3.0(2)°, showing that they are effectively coplanar. The conformations of **X** and **XI** in the crystal are essentially identical, with near-coplanar pyrazole and carboxamido functions positioned to afford two intramolecular hydrogen bonds (Fig. 1): between the NH_2 group N(12) and carbonyl O atom O(14); and, from the amide NH group N(15) to the pyrazole pyridinic N atom N(8). All four compounds also take part in intermolecular hydrogen bonding in their crystal lattices. In **III**·*n*-CH_2Cl_2, **X** and **XI** this leads to three-connected 2-D hydrogen-bond networks with 6^3 'herringbone' topologies,[21] while in **VI** the molecules associate into 1D hydrogen-bonded chains zig-zagging along the crystallographic [0 1 1] direction.

The regioisomeric structures of the products in Scheme 2 are also evident from their ^{1}H NMR spectra in $(CD_3)_2SO$. Compounds **III**–**V** and **VI**–**VIII** afford two and three N–H NMR signals, respectively, lying between 10 and 13 ppm and with equal integrals (but see below). That is the distribution expected if the primary amine group has been functionalised in these compounds, as observed. Conversely, **IX**–**XI** show two N–H NMR peaks with a 2:1 integral ratio, one near 6.5 ppm (2H) from the primary NH_2 amino group, and one at a more variable chemical shift of between 7 and 10 ppm (1H) from the urea N–H function. The ^{1}H spectra of the amide derivatives **III**–**V** in $(CD_3)_2SO$ all show two distinct pairs of N–H peaks. The two resonances within a pair have equal integrals, and the integrals of the major and minor peaks for each H environment sum to 1H relative to the other peaks in the spectra. We ascribe this behaviour to the existence of both the 3-pyridyl-5-amido and 5-pyridyl-3-amido tautomers of the pyrazole ring in solution, since it is quite common to resolve the different tautomers of pyrazole derivatives by NMR in this strongly associating solvent.[18] The NMR spectra show that the minor tautomer forms have no more than 25% of the samples under these conditions, although it is unfortunately not possible to assign which of the two tautomeric structures is the major one from these data alone.[18] In $CDCl_3$, **III**–**V** show only a single pair of N–H NMR resonances, implying that the tautomeric equilibrium occurs more rapidly, or that only a single tautomeric form is populated in this solvent. Thioureas **VI**–**VIII** all exhibit only one set of three N–H NMR peaks in both $(CD_3)_2SO$ and $CDCl_3$.

In conclusion, we have shown that **I** can be prepared on a multi-gram scale in two steps from commercial reagents, and that it is a versatile precursor for amide (**III**–**V**) and thiourea (**VI**–**VIII**) derivatives that have the potential to chelate concurrently to both metal cations and anions. However, attempts to prepare urea derivatives analogous to **VI**–**VIII** instead afforded the 3-(pyridin-2-yl)-5-aminopyrazole-1-carboxylic acid amides **IX**–**XI**. We ascribe the different regiochemistry of addition of isocyanates and cyanates to **I** to the particular hardness of the cyanate electrophiles. This generates a more polar transition state during the cyanate addition reactions that can be delocalised around the pyrazole ring more effectively when attack takes place at a heterocyclic N atom. Preliminary investigations have shown that reaction of **IX**–**XI** with first-row transition metal ions results in their rapid, Lewis acid-effected deacylation to regenerate **I**. Studies of the binding

properties of **III–VIII** towards metal salts are more promising, and will be reported separately.

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Supplementary data

Electronic supplementary data: experimental procedures and characterisation data for the compounds in this study, and further detail about the crystal structures, their data collection and refinement. Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2006.02.053.

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10. Crystal data for **III**·*n*-CH_2Cl_2 ($n \approx 0.25$): $C_{10.25}H_{10.5}Cl_{0.5}N_4O$, M_r 223.45, monoclinic, space group $C2/c$, $a = 18.1473(7)$, $b = 25.0031(10)$, $c = 9.3864(4)$ Å, $\beta = 97.153(2)°$, $V = 4225.8(3)$ Å^3, $Z = 16$, $D_c = 1.405$ g cm^{-3}, μ(Mo-Kα) = 0.217 mm^{-1}, $\lambda = 0.71073$ Å, $T = 150$ K, $R_1 = 0.073$, $wR_2 = 0.227$. The asymmetric unit contains two molecules of **III**, with essentially identical conformations although the amide group in one of them is disordered; and, a region of ca. 0.5 mol equiv of disordered solvent occupying channels in the crystal lattice. See Supplementary data for more details. CCDC 293593.
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15. Crystal data for **VI**: $C_{10}H_{11}N_5S$, M_r 233.30, orthorhombic, space group $Pna2_1$, $a = 14.7900(6)$, $b = 6.9094(2)$, $c = 10.5119(3)$ Å, $V = 1074.21(6)$ Å^3, $Z = 4$, $D_c = 1.443$ g cm^{-3}, μ(Mo-Kα) = 0.280 mm^{-1}, $\lambda = 0.71073$ Å, $T = 150$ K, $R_1 = 0.048$, $wR_2 = 0.103$, Flack parameter = 0.06(12). CCDC 293596.
16. Crystal data for **X**: $C_{15}H_{19}N_5O$, M_r 285.35, monoclinic, space group $P2_1/c$, $a = 12.4597(17)$, $b = 10.2158(16)$, $c = 12.0416(16)$ Å, $\beta = 91.997(7)°$, $V = 1531.8(4)$ Å^3, $Z = 4$, $D_c = 1.237$ g cm^{-3}, μ(Mo-Kα) = 0.082 mm^{-1}, $\lambda = 0.71073$ Å, $T = 100$ K, $R_1 = 0.066$, $wR_2 = 0.197$. CCDC 293595.
17. Crystal data for **XI**: $C_{13}H_{17}N_5O$, M_r 259.32, orthorhombic, space group $Pbca$, $a = 13.6978(3)$, $b = 11.4417(3)$, $c = 17.2288(5)$ Å, $V = 2700.20(12)$ Å^3, $Z = 8$, $D_c = 1.276$ g cm^{-3}, μ(Mo-Kα) = 0.086 mm^{-1}, $\lambda = 0.71073$ Å, $T = 150$ K, $R_1 = 0.042$, $wR_2 = 0.107$. CCDC 293594.
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