Chelation-Controlled Regioselectivity in the Synthesis of Substituted Pyrazolylpyridine Ligands. 1. Bidentates

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En route to novel *C*-linked pyrazole–pyridine bidentate ligands for transition metals, a new, higher-yielding synthesis of diketone **1** was found. It was quantitatively converted to the parent, *C*-linked 3-(pyridin-2-yl)pyrazole **2**. Condensations of **1** with five aromatic hydrazines led to *in*-substituted derivatives of **2** (**4***i*–**8***i*). With CH_3NHNH_2, both *in* and *out* isomers formed, but **3***o* could be isolated pure. In the presence of $ZnCl_2$, CH_3NHNH_2 and methyl 4-hydrazinobenzoate formed the isolable 1:1 complexes (**3***o*)$ZnCl_2$ and (**6***o*)$ZnCl_2$, respectively, which were characterized by NMR and elemental analysis. The bidentate, *out*-substituted **3***o* and **6***o* were freed from the complexes with NH_4OH. Without isolation of complexes, $PhNHNH_2$ and 4-hydrazinobenzoic acid were similarly used to prepare the *out*-substituted derivatives **4***o* and **5***o*, respectively. Nucleophilic aromatic substitution by **2** of 2-bromopyridine and ethyl 4-fluorobenzoate led to the *out* products **8***o* (a novel tridentate) and **9***o*, respectively. Both esters **6***o* and **9***o* could be hydrolyzed to the acid **5***o* in higher overall yield than the direct condensation of 4-hydrazinobenzoic acid. The regiochemistries were assigned by several arguments: Only bidentate *out*-substituted materials were expected to form stable $ZnCl_2$ complexes. It was also shown that **4***o* reacted with $TiCl_4$. The formation of *out* materials in the presence of $ZnCl_2$ could be rationalized by a preferred attack of the metal-activated, *inner* carbonyl of **1** by the more nucleophilic NH_2 ends of the aromatic hydrazines, whereas the *outer* carbonyl is more reactive in the absence of $ZnCl_2$. The formation of *out* materials by nucleophilic aromatic substitutions of **2** could be rationalized as proceeding through a K^+ chelate intermediate that disallows access to the *inner* pyrazole nitrogen. These two mechanistic arguments were tied through the conversion of a product of nucleophilic aromatic substitution (**9***o*) into a product of $ZnCl_2$-mediated condensation (**5***o*). The aromatic ^{1}H-NMR signals were also diagnostic of the regiochemistries: in all cases, the pyridine H-3 doublets lay upfield of the H-4 signals for *in* isomers and downfield for *out* isomers but, in the latter case, the H-3 signals shifted upfield in the Zn complexes (and in the $TiCl_4$ adduct of **4***o*). This pattern was interpreted in conformational terms and the interpretation found support in MM2 calculations: The *out* products, like bipyridine, prefer *anti* orientations of the imino nitrogens due to electronic and steric effects (calculated $\Delta G_{\text{syn-anti}} > 3.3$ kcal/mol for **3***o*–**7***o*). Complexation forces a *syn* orientation which produces a shielding of the pyridine H-3 by a nearby CH_2 group. This same shielding effect is present in either conformation of the *in* isomers, which are much closer in energy (calculated $|\Delta G_{\text{syn-anti}}| < 0.5$ kcal/mol for **3***i*–**7***i*). Finally, the mass spectral fragmentations could be related to the regiochemistry.

Introduction

In order to prepare electroneutral and liposoluble Ru^{2+} and Ru^{3+} complexes, we required lipophilic bipyridine analogues bearing remote ionizable groups. With some precedent,[1] our plan was to prepare *C*-linked pyrazolylpyridines by condensing the lipophilic pyridinyl β-diketone **1** with substituted hydrazines or by *N*-functionalization of the corresponding unsubstituted pyrazolylpyridine **2**. The regioselectivity of such reactions is an old problem,[2] but transient chelation by metal ions provides an opportunity to influence the outcomes. There was no similar opportunity in the syntheses of the several known *N*-linked 2-(pyrazol-1-yl)pyridines.[3] Although such pyrazole-containing ligands may lead to lower $Ru^{2+/3+}$ potentials than in $Ru(bipy)_3^{2+}$, according to the known additivity of ligand effects,[4] electron-withdrawing substituents could then be incorporated in the design to compensate. This paper reports the preparation of several pyrazolylpyridines by these routes and details the determination of the product regiochemistries.

Results and Discussion

In a literature report, 2-picolinoylcyclohexanone (**1**) had been prepared by a Claisen condensation in 28% yield.[5] We obtained a better isolated yield (51%) by the Stork reaction of picolinoyl chloride with 1-morpholinocyclohexene. Its quantitative conversion to the parent pyrazolylpyridine **2** was uneventful. As was found with its tridentate analogue,[6] its ^{1}H-NMR spectrum suggested a *syn* orientation of the pyrazole and pyridine nitrogens by virtue of the upfield position of the pyridine H-3′ doublet,

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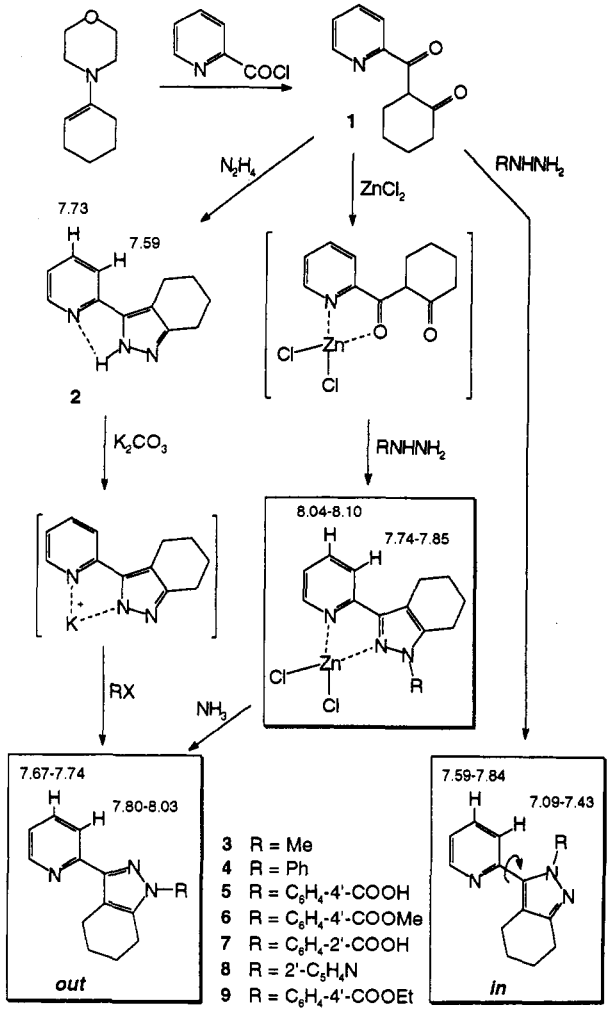
relative to the H-4′ signal, due to shielding by the nearby cyclohexenyl CH_2. This conformation would be stabilized by internal H-bonding between the pyridine N and an *in*-positioned pyrazole N–H. (*In* and *out* refer to the 2- and 1-positions, respectively, on the pyrazole rings.

The condensation of **1** with CH_3NHNH_2 gave a *ca.* 1:1 mixture of isomeric products **3** that were chromatographically inseparable. However, crystallization provided the pure *out* isomer, designated **3*o***, in 35% yield. When the reaction was carried out in the presence of 2 equiv of $ZnCl_2$/Et_2O, the 1:1 complex, (**3*o***)$ZnCl_2$, could be isolated in 77% yield and was characterized by NMR and elemental analysis. Free **3*o*** was liberated from the complex by NH_4-OH treatment in 47% overall yield.



The regiochemistry of this condensation product could be assigned simply on the basis of the complex formation: Only the *out* isomer would be expected to form a stable complex since only this isomer is bidentate. The NMR data supported this. The ^{1}H-NMR spectrum of **3*o*** (Figure 1) included a pyridine H-3′ doublet at a position downfield of the H-4′ signal, a pattern entirely similar to that given by earlier, analogous tridentates.[6] In contrast, spectral subtraction revealed that the H-3′ doublet from the *in* isomer **3*i*** lay upfield of the H-4′ triplet. With (**3*o***)$ZnCl_2$ (Figure 1), the pyridine H-4′ and H-5′ signals migrated downfield by *ca.* 0.4 ppm while the H-3′ doublet (and, curiously, the H-6′ doublet) was almost unaffected. These patterns were interpreted as follows: Whereas the normal conformation of free **3*o*** is *anti* due to electronic repulsions, as is true of bipyridine,[7] the binding to Zn forces **3*o*** into its *syn* form where, as in **2**, the close contact between the pyridine H-3′ and the cyclohexenyl CH_2 leads to a mutual shielding effect that overrides the deshielding caused by the metal. A similar shielding operates in **3*i***, regardless of the conformation. In an equivalent line of reasoning, it has been argued that *syn* lone pairs exert a deshielding influence upon neighboring nuclei.[8] Thus, the pyrazole lone pair in **3*o*** can be viewed as deshielding the pyridine H-3′, relative to the **3*i*** and (**3*o***)$ZnCl_2$ cases.

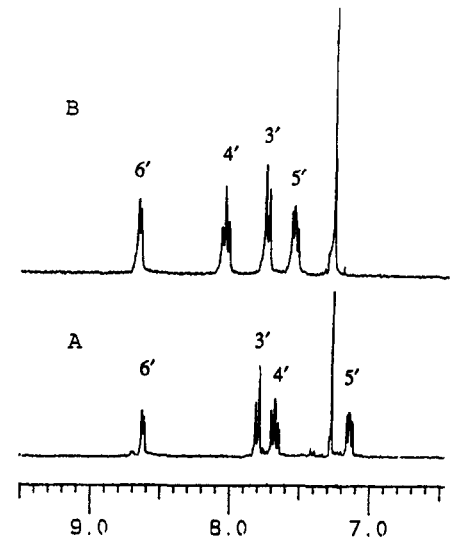


Figure 1. Aromatic regions of the ^{1}H-NMR spectra of (A) free **3*o*** and (B) (**3*o***)$ZnCl_2$.

Direct condensations of **1** with five aromatic hydrazines proceeded to give *in*-substituted products, designated **4*i***–**8*i***, in 44–83% yields after recrystallization. The contrast with the CH_3NHNH_2 case is attributable to the fact that, in reacting with the less-hindered outer carbonyl of **1**, the NH_2 ends of the aromatic hydrazines are both the more nucleophilic *and* the least hindered ends. With three of these aromatic hydrazines, similar condensations in the presence of $ZnCl_2$ led to the *out* products **4*o***–**6*o*** (in 25–52% isolated yields) *via* their Et_2O-insoluble 1:1 $ZnCl_2$ complexes. That of **6*o*** was isolated and characterized by NMR and elemental analysis. As with (**3*o***)$ZnCl_2$, the ^{1}H-NMR spectrum of (**6*o***)$ZnCl_2$ showed downfield migrations for all pyridine signals except that of H-3′, which migrated upfield. The mother liquors from these reactions contained some *in* materials which did not form isolable complexes. The preparation of **5*o*** turned out to be more efficient *via* hydrolysis of ester **6*o*** (42% overall yield) than directly from 4-hydrazinobenzoic acid (25% overall yield).

In all cases, the positions of the pyridine H-3′ doublets relative to the H-4′ signals were diagnostic: they lay upfield for *in* isomers and downfield for *out* isomers (as in Figure 2) but shifted upfield in the Zn complexes. In a further test, a $CDCl_3$ solution of **4*o*** was treated with $TiCl_4$ in the NMR tube. Some precipitation occurred but the ^{1}H-spectrum of the supernatant (Figure 2) showed much less signal crowding and strong downfield migrations of the H-4′, H-5,′ and H-6′ signals but an upfield shift for the H-3′ doublet. The CH_2 region in this case exemplified particularly well the reciprocity of the shielding interaction.

This interpretation of the NMR shifts was supported by molecular mechanics calculations on both conformers

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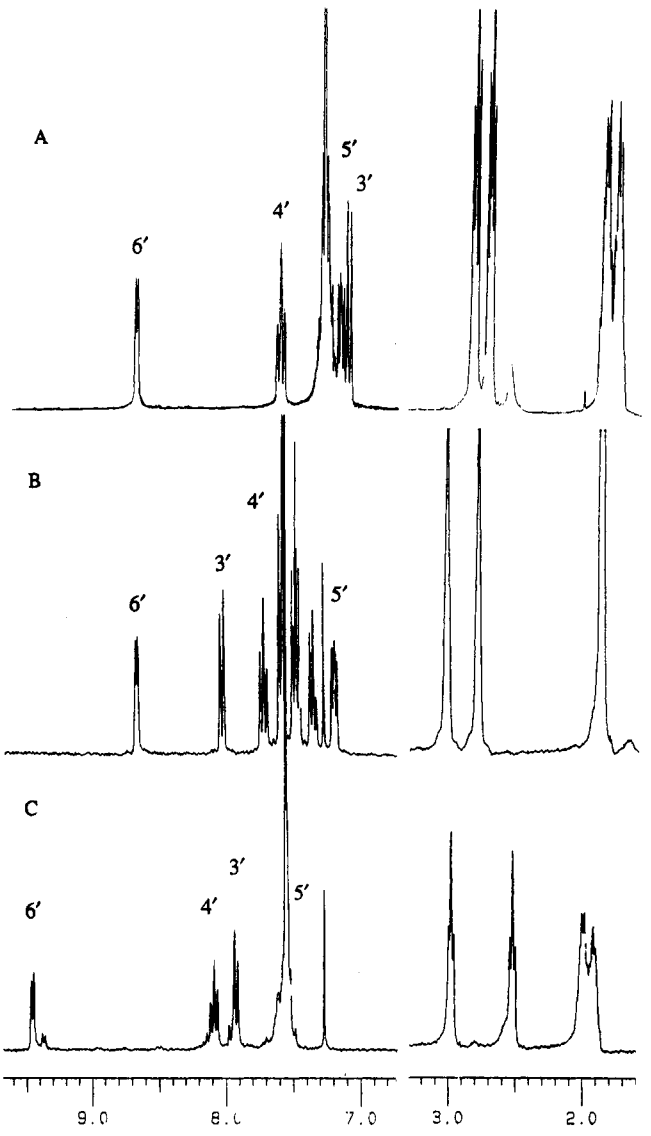

Figure 2. Aromatic and CH_2 regions of the ^{1}H-NMR spectra of (A) 4*i*, (B) 4*o*, and (C) 4*o* with $TiCl_4$.

Table 1. MM2 Conformational Energy Differences ($\Delta G_{syn\text{-}anti}$ in kcal/mol

substituent	*out* isomers	*in* isomers
CH_3 (3)	4.40	−0.44
C_6H_5 (4)	3.39	0.07
C_6H_4-4-COOH (5)	4.28	−0.34
C_6H_4-4-COOMe (6)	4.36	0.17
C_6H_4-2-COOH (7)	4.20	−0.40

of both isomers of compounds 3–7 (Table 1). With *out* substitution, there was a relatively large energy difference between *syn*/*anti* conformers ($\Delta G_{syn\text{-}anti} > 3.3$ kcal/mol) strongly favoring the *anti* form, which is devoid of steric congestion. In contrast, the conformers of *in*-substituted products, which suffer steric encumbrance in either form, were much closer in energy ($|\Delta G_{syn\text{-}anti}| < 0.5$ kcal/mol). The rotation about the pyridine–pyrazole link must be rapid on the NMR timescale since only single sets of signals were ever visible.

The observed shift in regioselection in the presence of $ZnCl_2$ suggests that chelation to the pyridine and the *inner* carbonyl groups of 1 is involved (as drawn), whereby the metal can serve as a template to deliver the hydrazine or to increase the reactivity of the *inner* carbonyl toward external attack. We obtained some NMR evidence of this type of coordination. The formation of an oily deposit from treatment of 1 with $ZnCl_2$ in $CHCl_3$ requires only 1 equiv, suggesting a 1:1 complex. It can be converted to a solid by trituration with ether, but this is too hygroscopic to manipulate with ease. When dissolved in acetone-d_6, the ^{1}H-NMR spectrum revealed an impure mixture dominated by one set of severely broadened signals. These included one from the doubly activated C*H*, indicating no ionization of 1. (In contrast, the use of CD_3OD resulted in apparent ionization but produced a complex mixture of species.) Relative to the free ligand positions in acetone-d_6, the signals had migrated downfield, depending in degree on the sample concentration and the signal type, with the pyridine signals most strongly shifted and the aliphatic signals almost unaffected. For example, in one concentrated sample, the overlapping pyridine H-4 and H-5 signals had resolved into distinct resonances and the H-6 signal had migrated by 0.8 ppm, compared with ≤0.2 ppm for the aliphatic signals. This is consistent with the proposed mode of chelation. Unfortunately, the ^{13}C-NMR spectra were uninformative, with only very broad signals from the major component, and the *C*=O peaks were undetectable or overlapping that from the solvent. We concluded that the chelation is weak in acetone-d_6; it is driven forward by precipitation out of $CHCl_3$ and by the presence of excess $ZnCl_2$, which may also trap the H_2O produced by condensation with a hydrazine. Using an equimolar amount of $ZnCl_2$ provided lower yields of the *out* products.

Finally, the high-temperature nucleophilic aromatic substitutions of 2 with 2-bromopyridine[9] (K_2CO_3/DMSO/120 °C/1 d/22%) or with ethyl 4-fluorobenzoate[10] (K_2CO_3/DMSO/120–140 °C/3 d/52%) produced *out* materials 8*o* (a novel terpyridine analogue) and 9*o*, respectively. Beside starting materials, no other products were detected. The modest yields reflect incomplete reactions, losses during purification and, in the case of 9*o*, partial hydrolytic decomposition by adventitious water of ethyl 4-fluorobenzoate. Presumably, these reactions proceeded through the intermediacy of a K^+ chelate that disallowed access to the inner pyrazole N of 2. In contrast, the benzylation of similar compounds under basic, phase-transfer conditions (*i.e.* without chelation) gave significant amounts of *in* products.[8] The hydrolysis of 9*o* provided a third, still higher yielding route to 5*o* (50% overall from 1).

The EI mass spectra showed fragmentation patterns common for all of the pyrazolylpyridines, the notable common ions being attributable to pyridine (79), 2-cyanopyridine (104), loss of the pyrazole substituent (198), and subsequent loss of N_2 (170). Interestingly, the *in*-substituted materials tended to additionally lose fragments of 54 and 68 mass units. Consistent with the assigned regiochemistries, these are attributable to C_2H_4CN and C_3H_6CN, respectively.

Experimental Section

General. THF was distilled over K and benzophenone. The petroleum ether (PE) used was the light fraction (30–60 °C). Unless noted otherwise, column chromatography was on "flash" silica gel using 3:7 EtOAc–PE as eluent. Melting points are not corrected. NMR spectra were recorded on a 300-MHz instrument

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in $CDCl_3$. For assignments of the pyridine and pyrazole signals, made with the help of correlation spectra, and for coupling constants, see the tables in the Supplementary Material. Mass spectra are from EI at 70 eV, measured by Dr. B. Khouw. In mass spectral peak assignments, pyridine is abbreviated py. Elemental analyses were performed by Guelph Chemical Laboratories, Ltd., Guelph, ON and by Galbraith Laboratories, Inc., Knoxville, TN. Molecular modeling was performed using PC-MODEL version 4 (Serena Software, Bloomington, IN).

2-Picolinoylcyclohexanone (1). A mixture of picolinic acid (2.46 g, 20 mmol) and $SOCl_2$ (8 mL) was refluxed for 2 h, and then rid of volatiles under vaccum. The residue was dissolved in 20 mL of dry THF and then treated with a solution of 1-morpholinocyclohexene (Aldrich, 3.34 g, 20 mmol) and Et_3N (2.22 g, 22 mmol) in 100 mL of dry THF, with cooling to 0 °C. After stirring at room temperature overnight, the mixture was acidifed by the addition of 50 mL of H_2O and 10 mL of HOAc. After 2 h, the solution was evaporated to dryness and the residue was extracted with CH_2Cl_2. After stripping the extract of solvent, the dark brown oil was purifed by flash chromatography to a light-yellow oil, which was crystallized in petroleum ether. This gave 2.1 g (51%) of white crystals, mp 68–71 °C (lit.[5] mp 70–73 °C); ^{1}H-NMR δ 1.74–2.65 (m, 8H), 5.03 (dd, 1H, J = 7.3, 10.2 Hz), 7.44 (ddd, 1H), 7.83 (td, 1H), 8.06 (d, 1H), 8.61 (d, 1H) ppm; MS (m/z) 203 ($M^{+\cdot}$), 202 ($M^{+\cdot}$ – H), 175 ($M^{+\cdot}$ – CO), 160 ($M^{+\cdot}$ – H – C_3H_6), 147 ($M^{+\cdot}$ – C_4H_8), 125 ($M^{+\cdot}$ – C_5H_4N), 106 ($M^{+\cdot}$ – C_6H_9O), 79 (100%, py), 78 (C_5H_4N), 51. Anal. Calcd for $C_{12}H_{13}NO_2$: C, 70.92; H, 6.45; N, 6.89. Found: C, 70.54; H, 6.69; N, 6.95.

2*H*-3-(pyridin-2-yl)-4,5,6,7-tetrahydroindazole (2). To a solution of 1 (2.0 g, 10 mmol) in 30 mL of CH_2Cl_2 was added N_2H_4 hydrate (0.55 mL, 11 mmol). The mixture was stirred overnight and stripped of solvent and then the oily residue was recrystallized from PE, affording 1.87 g (94%) of crystals: mp 103–105 °C; ^{1}H-NMR δ 1.85 (m, 4H), 2.75 (t, 2H) 2.84 (t, 2H), 7.19 (ddd, 1H), 7.59 (d, 1H), 7.73 (td, 1H), 8.64 (d, 1H) ppm; ^{13}C-NMR δ 22.4, 22.8, 23.2, 23.4, 114.0, 120.1, 121.8, 136.5, 139.1, 148.5, 149.3, 150.0 ppm; MS (m/z) 199 ($M^{+\cdot}$), 198 ($M^{+\cdot}$ – H), 184, 170 ($M^{+\cdot}$ – H – C_2H_4 or $M^{+\cdot}$ – H – N_2), 145 ($M^{+\cdot}$ – C_2H_4CN), 131 ($M^{+\cdot}$ – C_3H_6CN), 121 ($M^{+\cdot}$ – C_5H_4N), 105 (pyCNH), 104 (pyCN), 95 ($M^{+\cdot}$ – pyCN), 79 (py), 78 (C_5H_4N), 52, 51. Anal. Calcd for $C_{12}H_{13}N_3$: C, 72.33; H, 6.58; N, 21.09. Found: C, 72.23; H, 6.88; N, 20.92.

1-Methyl-3-(pyridin-2-yl)-4,5,6,7-tetrahydroindazole (3*o*). By direct condensation: A solution of 1 (0.41 g, 2 mmol) and methylhydrazine (0.1 g, 2.2 mmol) in 20 mL of $CHCl_3$ was stirred overnight. After removing the solvent, the oily residue was flash-chromatographed using EtOAc as eluent. Crystallization from PE gave 0.17 g (40%) of crystals: mp 93–94 °C; ^{1}H-NMR δ 1.82 (m, 4H, CH_2), 2.60 (t, 2H, J = 6.2 Hz), 2.87 (t, 2H, J = 6.0 Hz), 3.80 (s, 3H), 7.13 (ddd, 1H), 7.67 (td, 1H), 7.80 (dd, 1H), 8.63 (dd, 1H) ppm; ^{13}C-NMR δ 21.6, 22.4, 22.6, 23.1, 35.7, 115.5, 120.6, 121.3, 136.0, 139.9, 146.5, 149.2, 153.8 ppm; MS (m/z) 213 ($M^{+\cdot}$), 212 ($M^{+\cdot}$ – H), 198 ($M^{+\cdot}$ – CH_3), 185 ($M^{+\cdot}$ – C_2H_4), 184 ($M^{+\cdot}$ – H – C_2H_4), 170 ($M^{+\cdot}$ – CH_3 – N_2), 135 ($M^{+\cdot}$ – py), 105 (pyCNH), 79 (py), 78 (C_5H_4N), 51, 39 (100%). Anal. Calcd for $C_{13}H_{15}N_3$: C, 73.21; H, 7.09; N, 19.70. Found: C, 72.97; H, 7.27; N, 19.79.

By demetallation of the $ZnCl_2$ complex: Treatment of 0.27 g of solid (3*o*)$ZnCl_2$ with 10% NH_3 and extraction into CH_2Cl_2 gave 0.10 g (50% overall) of 3*o*.

(3*o*)$ZnCl_2$. To a solution of 1 (0.2 g, 1 mmol) in 20 mL of $CHCl_3$ was added 1.0 M Et_2O solution of $ZnCl_2$ (Aldrich, 2.2 mL, 2.2 mmol). To the resulting precipitate was added methylhydrazine (0.055 g, 1.2 mmol) and the mixture was stirred overnight and then freed of solvent to give an oily residue. Crystallization from EtOAc gave 0.27 g (77%) of crystals: mp 243–244 °C, ^{1}H-NMR δ 1.91 (m, 4H), 2.68 (t, 2H, J = 5.6 Hz), 2.82 (t, 2H, J = 5.6 Hz), 3.99 (s, 3H), 7.55 (dd, 1H), 7.74 (d, 1H), 8.04 (td, 1H), 8.67 (d, 1H) ppm; ^{13}C-NMR δ 21.4, 21.6, 22.2, 36.4, 115.9, 121.5, 125.00, 140.8, 144.7, 147.8, 149.2 ppm. Anal. Calcd for $C_{13}H_{15}Cl_2N_3Zn$: C, 44.67; H, 4.33; N, 12.02. Found C, 44.58; H, 4.04; N, 11.78.

2-Phenyl-3-(pyridin-2-yl)-4,5,6,7-tetrahydroindazole (4*i*). Using the same procedure as for 3*o*, 1 (0.20 g, 1 mmol) and $PhNHNH_2$ (0.12 g, 1.1 mmol) in $CHCl_3$ provided 0.20 g (73%) of crystals from Et_2O: mp 135–136 °C; ^{1}H-NMR δ 1.85 (m, 4H), 2.71 (t, 2H, J = 6.1 Hz), 2.81 (t, 2H, J = 6.3 Hz), 7.09 (d, 1H), 7.17 (dd, 1H), 7.26 (m, 5H), 7.59 (td, 1H), 8.61 (d, 1H) ppm; ^{13}C-NMR δ 21.3, 23.1, 23.2, 23.3, 118.4, 122.0, 124.3, 124.6, 126.6, 128.6, 135.9, 137.4, 140.4, 149.5, 150.2, 150.3 ppm; MS (m/z) 275 ($M^{+\cdot}$), 274 (100%, $M^{+\cdot}$ – H), 246 ($M^{+\cdot}$ – H – C_2H_4), 221 ($M^{+\cdot}$ – C_2H_4CN), 207 ($M^{+\cdot}$ – C_3H_6CN), 198 ($M^{+\cdot}$ – Ph), 170 ($M^{+\cdot}$ – Ph – N_2), 104 (pyCN), 78 (C_5H_4N), 77 (Ph), 51. Anal. Calcd for $C_{18}H_{17}N_3$: C, 78.52; H, 6.22; N, 15.26. Found: C, 78.22; H, 6.26; N, 14.92.

1-Phenyl-3-(pyridin-2-yl)-4,5,6,7-tetrahydroindazole (4*o*). In a preparation entirely analogous to that of 3*o via* (3*o*)$ZnCl_2$, 1 (0.2 g, 1 mmol), 1.0 M $ZnCl_2$ in Et_2O (2.2 mL, 2 mmol), and phenylhydrazine (0.13 g, 1.2 mmol) provided 0.26 g (63%) of white solid, mp >300 °C. This was treated with 10% NH_3 and extracted into $CHCl_3$. The $CHCl_3$ phase was evaporated and the oily product was crystallized in hexane, giving 0.14 g (52%) of white crystals: mp 118–120 °C; ^{1}H-NMR δ 1.84 (m, 4H), 2.77 (t, 2H), 3.00 (t, 2H), 7.17 (ddd, 1H), 7.33 (t, 1H, J = 8.2 Hz), 7.46 (t, 2H, J = 8.1 Hz), 7.58 (d, 2H, J = 8.4 Hz), 7.70 (td, 1H), 8.01 (d, 1H), 8.65 (dd, 1H) ppm; ^{13}C-NMR δ 22.80, 22.85, 23.01, 23.94, 117.5, 121.1, 121.7, 123.5, 126.9, 129.0, 136.0, 140.0, 148.6, 149.1, 154.0 ppm; MS (m/z) 275 ($M^{+\cdot}$), 274 ($M^{+\cdot}$ – H), 246 ($M^{+\cdot}$ – H – C_2H_4), 207 ($M^{+\cdot}$ – C_3H_6CN), 197 ($M^{+\cdot}$ – C_5H_4N), 170 ($M^{+\cdot}$ – Ph – N_2), 143, 105 (pyCNH), 79 (py), 78 (C_5H_4N), 77 (Ph), 69, 51 (100%), 41, 39. Anal. Calcd for $C_{18}H_{17}N_3$: C, 78.52; H, 6.22; N, 15.26. Found: C, 78.09; H, 6.36; N, 15.27.

2-(4-Carboxyphenyl)-3-(pyridin-2-yl)-4,5,6,7-tetrahydroindazole (5*i*). As for 3*o*, 4-hydrazinobenzoic acid (0.38 g, 2.5 mmol) and 1 (0.51 g, 2.5 mmol) in THF afforded 0.66 g (83%) of crystals from Et_2O: mp 217–220 °C; ^{1}H-NMR δ 1.85 (m, 4H), 2.68 (t, 2H, J = 6.1 Hz), 2.83 (t, 2H, J = 6.2 Hz), 7.22–7.25 (m, 2H), 7.32 (d, 2H, J = 8.6 Hz), 7.70 (td, 1H), 7.99 (d, 2H, J = 8.6 Hz), 8.65 (d, 1H) ppm; ^{13}C-NMR δ 21.4, 23.1, 23.2, 23.5, 119.6, 122.6, 123.9, 124.5, 127.4, 130.9, 136.5, 137.6, 144.6, 149.9, 150.0, 151.5, 170.0 ppm; MS (m/z) 319 ($M^{+\cdot}$), 290 ($M^{+\cdot}$ – H – C_2H_4), 275 ($M^{+\cdot}$ – CO_2), 265 ($M^{+\cdot}$ – C_2H_4CN), 251 ($M^{+\cdot}$ – C_3H_6CN), 241 ($M^{+\cdot}$ – py), 198 ($M^{+\cdot}$ – C_6H_4COOH), 170 (198 – N_2), 78 (C_5H_4N), 77 (Ph), 55 (100%), 51. Anal. Calcd for $C_{19}H_{17}N_3O_2$: C, 71.46; H, 5.37; N, 13.16. Found: C, 71.42; H, 5.46; N, 13.00.

1-(4-Carboxyphenyl)-3-(pyridin-2-yl)-4,5,6,7-tetrahydroindazole (5*o*). By condensation: To a mixture of 1 (0.41 g, 2 mmol) and 0.5 M $ZnCl_2$ solution in THF (Aldrich, 8 mL, 4 mmol) in 20 mL of $CHCl_3$ was added 4-hydrazinobenzoic acid. The suspension was stirred for 72 h. Filtration gave 0.7 g of solid which was treated with 40 mL of a 0.1 M solution of disodium EDTA and then extracted into $CHCl_3$. After evaporation of solvent, the organic phase provided 0.16 g (25%) of crystalline 5*o*: mp 239–241 °C; ^{1}H-NMR δ 1.87 (m, 4H), 2.87 (t, 2H), 3.00 (t, 2H), 7.24 (t, 1H), 7.76 (m, 3H, J = 8.7 Hz), 8.02 (d, 1H), 8.21 (d, 2H, J = 8.6 Hz), 8.70 (d, 1H) ppm; ^{13}C-NMR δ 22.77, 22.82, 22.91, 24.59, 118.8, 121.5, 122.2, 122.3, 127.0, 131.3, 136.3, 140.3, 144.3, 149.2, 149.5, 153.4, 170.0 ppm; MS (m/z) 319 ($M^{+\cdot}$), 318 ($M^{+\cdot}$ – H), 290 ($M^{+\cdot}$ – H – C_2H_4), 274 ($M^{+\cdot}$ – H – CO_2), 241 ($M^{+\cdot}$ – py), 198 ($M^{+\cdot}$ – C_6H_4COOH), 187, 170 (198 – N_2), 123, 79 (py), 78 (C_5H_4N), 77 (Ph), 51, 43 (100%), 39. Anal. Calcd for $C_{19}H_{17}N_3O_2$: C, 71.46; H, 5.37; N, 13.16. Found: C, 71.18; H, 5.28; N, 13.06.

By hydrolysis of esters 6o and 9o: A mixture of 6*o* (1.17 g, 3.5 mmol), 12 mL of 10% NaOH, and 50 mL of THF was refluxed overnight. After evaporating the THF, the mixture was diluted with 20 mL of H_2O and acidified with HOAc. Filtration of the precipitate gave 1.1 g (97%) of 5*o*, identical to that produced directly. Similarly, 0.35 g of 9*o* produced 0.31 g (97%) of 5*o*.

2-[4-(Methoxycarbonyl)phenyl]-3-(pyridin-2-yl)-4,5,6,7-tetrahydroindazole (6*i*). Using the same procedure as for 3*o*, 1 (0.41 g, 2 mmol) and methyl 4-hydrazinobenzoate (0.33 g, 2 mmol) provided 0.58 g (87%) of crystals from Et_2O: mp 138–139 °C; ^{1}H-NMR δ 1.85 (m, 4H), 2.68 (t, 2H, J = 6.1 Hz), 2.82 (t, 2H, J = 6.3 Hz), 3.90 (s, 3H), 7.19 (dd, 1H), 7.21 (ddd, 1H), 7.30 (d, 2H, J = 8.8 Hz), 7.66 (td, 1H), 8.46 (d, 2H, J = 8.8 Hz), 8.60 (d, 1H) ppm; ^{13}C-NMR δ 21.4, 23.1, 23.2, 23.5, 52.1, 119.5, 122.5, 123.8, 124.4, 127.9, 130.3, 136.4, 137.5, 144.1, 149.7, 149.9, 151.4, 166.5 ppm; MS (m/z) 333 (100%, $M^{+\cdot}$), 332 ($M^{+\cdot}$ – H), 304 ($M^{+\cdot}$ – H – C_2H_4), 279 ($M^{+\cdot}$ – C_2H_4CN), 274, 265 ($M^{+\cdot}$ – C_3H_6CN), 255 ($M^{+\cdot}$ – py), 198 ($M^{+\cdot}$ – $C_6H_4COOCH_3$), 170 (198 – N_2), 136 (C_6H_5-$COOCH_3$), 78 (C_5H_4N), 77 (Ph), 51. Anal. Calcd for $C_{20}H_{19}N_3O_2$: C, 72.05; H, 5.74; N, 12.60. Found: C, 72.00; H, 5.65; N, 12.66.

(6*o*)$ZnCl_2$. In a preparation entirely analogous to that of (3*o*)-$ZnCl_2$, 4.4 mL of 1.0 M $ZnCl_2$ in Et_2O, 1 (0.41 g, 2 mmol), and methyl 4-hydrazinobenzoate (0.33 g, 2 mmol) provided 0.46 g (49%) of crystals from EtOAc; mp 285–289 °C; ^{1}H-NMR δ 1.96 (m, 4H), 2.78 (t, 2H, J = 5.8 Hz), 2.94 (t, 2H, J = 5.9 Hz), 3.97 (s, 3H), 7.62 (dd, 1H), 7.85 (m , 3H, J = 8.7 Hz), 8.10 (td, 1H), 8.28 (d, 2H, J = 8.7 Hz), 8.71 (d, 1H) ppm; ^{13}C-NMR δ 21.7, 21.8, 22.1, 23.4, 117.3, 122.0, 124.5, 125.6, 131.3, 131.5, 139.9, 140.9, 144.8, 145.2, 147.2, 149.2, 165.7 ppm. Anal. Calcd for $C_{20}H_{19}Cl_2N_3O_2Zn$: C, 51.14; H, 4.08; N, 8.95. Found: C, 50.81; H, 3.81; N, 8.51.

1-[4-(Methoxycarbonyl)phenyl]-3-(pyridin-2-yl)-4,5,6,7-tetrahydroindazole (6*o*). In the same fashion as with (3*o*)-$ZnCl_2$, the demetalation of 0.46 g of (6*o*)$ZnCl_2$ provided 0.30 g (45%) of crystals from EtOAc: mp 170–172 °C; ^{1}H-NMR δ 1.85 (m, 4H), 2.85 (t, 2H), 3.01 (t, 2H), 3.96 (s, 3H), 7.22 (ddd, 1H), 7.72 (d, 2H, J = 8.7 Hz), 7.74 (td, 1H), 8.03 (d, 1H), 8.15 (d, 2H, J = 8.7 Hz), 8.68 (d, 1H) ppm; ^{13}C-NMR δ 22.73, 22.77, 22.84, 24.46, 52.2, 118.6, 121.4, 122.1, 122.3, 128.0, 130.6, 136.4, 140.2, 143.6, 149.0, 149.2, 153.3, 166.4 ppm; MS (*m*/*z*) 333 ($M^{+\cdot}$), 332 ($M^{+\cdot}$ – H), 304 ($M^{+\cdot}$ – H – C_2H_4), 255 ($M^{+\cdot}$ – py), 228, 170 ($M^{+\cdot}$ – $C_6H_4COOCH_3$ – N_2), 136 ($C_6H_5COOCH_3$), 107, 105 (PyCNH), 78 (C_5H_4N), 77 (Ph), 51. Anal. Calcd for $C_{20}H_{19}N_3O_2$: C, 72.05; H, 5.74; N, 12.60. Found: C, 71.85; H, 5.81; N, 12.39. The mother liquor yielded an oil which was chromatographed to provide 0.35 g (52%) of *in* product 6*i* identical to that prepared directly.

2-(2-Carboxyphenyl)-3-(pyridin-2-yl)-4,5,6,7-tetrahydroindazole (7*i*). Using the same procedure as for 3*o*, 2-hydrazinobenzoic acid hydrochloride (0.23 g, 1.2 mmol) and 1 (0.20 g, 1.0 mmol) in THF provided 0.14 g (44%) of crystals from 1:1 EtOH–Et_2O: mp 188–190 °C; ^{1}H-NMR δ 1.85 (m, 4H), 2.68 (t, 2H, J = 6.1 Hz), 2.78 (t, 2H, J = 6.2 Hz), 6.92 (d, 1H, J = 7.8 Hz), 7.26 (m, 1H), 7.32 (td, 1H), 7.43 (dd, 1H), 7.46 (t, 1H), 7.83 (d, 1H, J = 7.9 Hz), 7.84 (t, 1H), 8.36 (dd, 1H) ppm; ^{13}C-NMR δ 21.2, 22.9, 23.1, 23.3, 117.8, 123.0, 124.0, 128.7, 129.2, 130.0, 131.1, 133.9, 137.9, 138.0, 138.4, 147.8, 148.1, 151.1, 168.1 ppm; MS (*m*/*z*) 319 ($M^{+\cdot}$), 275 ($M^{+\cdot}$ – CO_2), 241 ($M^{+\cdot}$ – py), 198 ($M^{+\cdot}$ – C_6H_4COOH), 170 (198 – N_2), 78 (C_5H_4N), 77 (Ph), 69 (100%), 51. Anal. Calcd for $C_{19}H_{17}N_3O_2$: C, 71.46; H, 5.37; N, 13.16. Found: C, 71.72; H, 5.42; N, 12.88.

2,3-Di(pyridin-2-yl)-4,5,6,7-tetrahydroindazole (8*i*). To a mixture of 1 (0.51 g, 2.5 mmol) and 2-hydrazinopyridine dihydrochloride (0.46 g, 2.5 mmol) in 20 mL of CH_2Cl_2 was added sufficient Et_3N to dissolve the suspension. The mixture was allowed to stir overnight and then was washed with 15 mL of H_2O. The CH_2Cl_2 phase was separated and evaporated to give an oily residue. Crystallization from 1:1 Et_2O–PE gave 0.4 g (58%) of crystalline product: mp 167–170 °C; ^{1}H-NMR δ 1.85 (m, 4H), 2.66 (t, 2H, J = 6.1 Hz), 2.82 (t, 2H, J = 6.2 Hz), 7.11 (dd, 1H), 7.18 (dd, 1H), 7.31 (d, 1H), 7.57 (d, 1H), 7.68 (t, 1H), 7.72 (t, 1H), 8.19 (d, 1H), 8.52 (d, 1H) ppm; ^{13}C-NMR δ 21.3, 23.2, 23.3, 23.6, 117.6, 119.2, 121.4, 122.0, 124.1, 135.8, 137.9, 147.8, 149.3, 151.1, 151.3, 153.0 ppm; MS (*m*/*z*) 276 ($M^{+\cdot}$), 275 ($M^{+\cdot}$ – H), 247 ($M^{+\cdot}$ – H – C_2H_4), 222 (100%, $M^{+\cdot}$ – C_2H_4CN), 208 ($M^{+\cdot}$ – C_3H_6CN), 198 ($M^{+\cdot}$ – py), 171, 170 ($M^{+\cdot}$ – py – N_2), 104 (PyCN), 79 (Py), 78 (C_5H_4N), 51. Anal. Calcd for $C_{17}H_{16}N_4$: C, 73.89; H, 5.84; N, 20.27. Found: C, 73.49; H, 6.05; N, 19.92.

1,3-Di(pyridin-2-yl)-4,5,6,7-tetrahydroindazole (8*o*). A mixture of compound 2 (0.20 g, 1.0 mmol), 2-bromopyridine (0.24 g, 1.5 mmol), and K_2CO_3 (0.55 g, 4.0 mmol) in 20 mL of DMSO was stirred at 120 °C for 24 h. The solids were filtered off and washed with $CHCl_3$. After extraction with H_2O, the $CHCl_3$ layer was dried ($MgSO_4$) and evaporated to dryness. The oily residue was chromatographed, using 15:85 EtOAc–PE, to give 0.062 g (22%) of crystalline material: mp 104–6 °C; ^{1}H-NMR δ 1.85 (m, 4H), 2.97 (t, 2H, J = 5.4 Hz), 3.22 (t, 2H, J = 5.6 Hz), 7.14 (dd, 1H), 7.20 (ddd, 1H), 7.72 (td, 1H), 7.79 (td, 1H), 8.03 (d, 1H), 8.05 (d, 1H), 8.41 (d, 1H), 8.67 (d, 1H) ppm; ^{13}C-NMR δ 22.9, 25.7, 115.1, 118.7, 120.5, 121.3, 121.9, 136.0, 138.0, 141.7, 147.3, 149.1, 149.2, 153.7 ppm. Anal. Calcd for $C_{17}H_{16}N_4$: C, 73.89; H, 5.84; N, 20.27. Found: C, 74.13; H, 6.01; N, 19.95.

1-[4-(Ethoxycarbonyl)phenyl]-3-(pyridin-2-yl)-4,5,6,7-tetrahydroindazole (9*o*). As for 8*o*, 2 (2.42 g, 12 mmol), K_2CO_3 (3.32 g, 24 mmol), and ethyl 4-fluorobenzoate (2.5 g, 15 mmol) were stirred in dry DMSO at 120–140 °C for 72 h. After a similar workup, chromatography and recrystallization from Et_2O yielded 2.17 g (52%) of white crystals: mp 130–131 °C; ^{1}H-NMR δ 1.42 (t, 3H, J = 7.1 Hz), 1.85 (m, 4H), 2.83 (t, 2H), 3.00 (t, 2H), 4.40 (q, 2H, J = 7.1 Hz), 7.20 (dd, 1H), 7.70 (d, 2H, J = 8.6 Hz), 7.72 (td, 1H), 8.02 (d, 1H), 8.14 (d, 1H, J = 8.7 Hz), 8.66 (d, 1H) ppm; ^{13}C-NMR δ 14.30, 22.77, 22.79, 22.86, 24.45, 61.0, 118.5, 121.2, 122.0, 122.2, 128.3, 130.5, 136.1, 140.1, 143.5, 149.1, 149.2, 153.6, 165.9 ppm; MS (*m*/*z*) 347 ($M^{+\cdot}$), 318 ($M^{+\cdot}$ – H – C_2H_4), 269 ($M^{+\cdot}$ – py), 198 ($M^{+\cdot}$ – C_6H_4COOEt), 170 (198 – N_2), 105 (pyCNH), 104 (pyCN), 79 (py), 78 (C_5H_4N), 77 (Ph), 51, 39. Anal. Calcd for $C_{21}H_{21}N_3O_2$: C, 72.60; H, 6.09; N, 12.10. Found: C, 72.55; H, 5.86; N, 12.00.

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Supplementary Material Available: Assignments and coupling constants for pyridine and pyrazole ^{1}H- and ^{13}C-NMR signals for all new compounds (3 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.