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Electronic effects in the reaction of 1,3-diaryl-1,3-diketones with hydrazinopyridines

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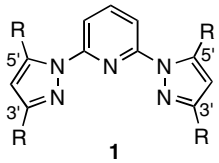
ABSTRACT

The regioselectivity of the condensation of electronically unsymmetrical 1,3-diaryl-1,3-diketones with 2-hydrazinopyridine and 2,6-bis-hydrazinopyridine to form *N*-(2-pyridyl)-3,5-diarylpyrazoles was studied. Significant electronic effects on regioselectivities were observed, and regioselectivities were opposite to those exhibited by perfluoroalkyl/alkyl 1,3-diketones. The electronic effects correlate well to the difference between the Hammett σ^+ coefficients of the *para* substituents on the aryl rings.

The pyrazole ring is an important component of many biologically active compounds.[1] 2-Pyrazolylpyridines and 2,6-bis-pyrazolylpyridines are also robust ligands for a wide variety of transition metals.[2] The most common synthesis of the pyrazole ring involves the reaction of a 1,3-diketone with a hydrazine. When a substituted hydrazine is reacted with an unsymmetrical diketone, the problem of regioselectivity arises. The regioselectivity of the reaction is determined by a combination of steric and electronic factors. Studies of electronic and steric effects in the regioselectivity of pyrazole synthesis have been reported;[3–5] however, these previous studies did not entirely separate electronic effects from steric factors. For example, studies of unsymmetrical perfluoroalkyl/alkyl diketones have been reported.[4,5] However, these diketones are known to exist as single enol tautomers, and thus regioselectivity is more a question of 1,2- versus 1,4-addition and the hardness/softness of the hydrazine used.[5]

We recently developed[6a] a route to 2,6-bis-pyrazolylpyridines (**1**), which, for the first time, allowed for groups larger than methyl at the 5′ positions. This route involves reaction of 2,6-bis-hydrazinopyridine (BHP, **2**)[6] with 1,3-diketones, and accommodates 5′ groups as large as phenyl and even *tert*-butyl with no difficulty. In contrast to the nucleophilic aromatic substitution reactions that were previously used to make unsymmetrical 2,6-bis-pyrazolylpyridines, BHP reacts quite selectively with sterically unsymmetrical 1,3-diketones to place the larger group at the 5′ position. Electronically unsymmetrical (e.g., CF_3 vs CH_3) 1,3-diketones react to selectively place the more electron-withdrawing group at the 5′ positions.[4]



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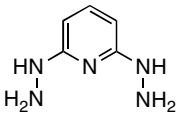

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Given that this new route allowed for aryl groups to be placed at both the 3′ and 5′ positions, we set out to study the regioselectivity of BHP in reactions with 1,3-diaryl-1,3-diketones in which the aryl rings were electronically dissimilar but sterically identical by virtue of *para*-substitution (e.g., **3**, Scheme 1). Although 1,3-diaryl-1,3-diketones are known to be nearly 100% enolic, they tautomerize between the two possible enol forms at an extremely rapid rate through resonance-assisted hydrogen bonding.[7] Indeed, in crystal structures of these compounds, the enol systems are symmetrical.[7c] Thus, products are determined by which of the carbonyl (or enol) carbons is undergoing initial attack by the hydrazine NH_2 group, rather than whether 1,2- or 1,4-addition is occurring. Because pyrazolylpyridines are chelating ligands, we anticipated that electron-donating and electron-withdrawing groups on the aryl rings are likely to influence metal binding through direct resonance with the pyrazole rings, lending synthetic as well as theoretical importance to such a study.

Eight of the requisite diaryl-1,3-diketones (**3a**–**h**) were readily prepared[8] in 60–100% yields by the condensation of the more electron-rich acetophenones with the more electron-deficient methylbenzoates (Scheme 1), followed by purification by recrystallization from hot ethanol. We found that the alternate arrangement led to poor yield or no reaction at all. In these diketones and the derived pyrazolylpyridine products, R_D represents the more electron-donating of the two substituents, and R_W represents the more electron-withdrawing in any given diketone.

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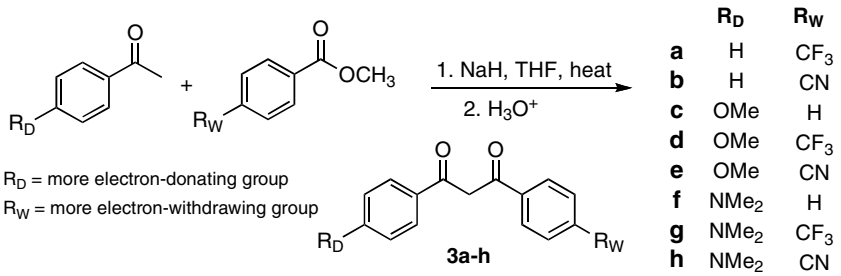
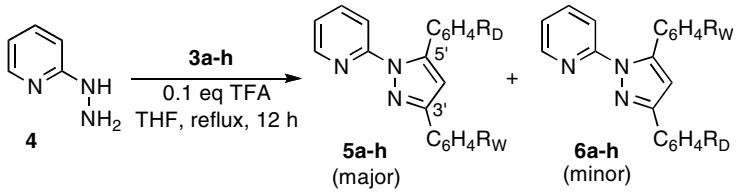


	R_D	R_W
a	H	CF_3
b	H	CN
c	OMe	H
d	OMe	CF_3
e	OMe	CN
f	NMe_2	H
g	NMe_2	CF_3
h	NMe_2	CN

Scheme 1. Synthesis of substituted 1,3-diaryl-1,3-diketones.



Scheme 2. Reaction of **3a–h** with 2-hydrazinopyridine (**4**).

The diketones **3a–h** were first reacted with the simpler and commercially available 2-hydrazinopyridine (**4**) and a catalytic amount of trifluoroacetic acid in THF at reflux for 12 h (Scheme 2).[9] This led to complete conversion to the 3′,5′-diarylpyrazolylpyridines **5a–h** and **6a–h**. The isomer ratios (Table 1) were determined by gas chromatography on HP-5, and generally verified by ^{1}H (and, in three cases, by ^{19}F) NMR. The regioisomers were not easily separable by TLC or column chromatography. However, in three of the eight cases (b, e, and g), fractional crystallization provided X-ray quality crystals that proved the regiochemistry to be that of isomer **5**, and GC of the actual X-ray crystals showed this to be the major isomer in each case. Thus, these reactions regioselectively place the more electron-donating aryl group ($R_DC_6H_4$) at the 5′ position. It should be noted that all of these product mixtures exhibited fluorescence when exposed to UV light at both 254 nm and 365 nm (Fig. 1), particularly those containing dimethylamino substituents.

The regioselectivity of the reaction of 2-hydrazinopyridine with the eight diketones **3a–h** showed a clear correlation with the electronic nature of the *para* substituents, and the electronic effects of the two groups were additive. Thus, the log of the ratio of (**5**/**6**) is linearly related to the difference ($\Delta\sigma^+$) between the Hammett coefficients σ^+ (R_W) and σ^+ (R_D) for the *para* substituents (Graph 1). Because σ^+ values for electron-donating groups are negative, $\Delta\sigma^+$ is always a positive number.

The reaction of diketones **3a–h** was repeated with 2,6-bis-hydrazinopyridine (**2**) (Scheme 3) to prepare 2,6-bis-pyrazolylpyridines **7–9**. The reaction conditions were the same as before, but these higher-boiling product mixtures required analysis on a high-temperature carborane-based GC column. In two cases (**3e** and **3h**), the product mixtures were not separable by GC nor easily analyzed by NMR. The remaining six diketones gave GC-analyzable mixtures of products **7–9** (Table 2). In two of these cases (c and d), fractional recrystallization gave X-ray quality crystals, and the structures were shown to be that of **7c** and **7d**, with both of the 5′ positions being occupied by electron-donating groups. Again, GC of the crystals after X-ray showed that they belonged to the major isomer in both cases. The mixtures of the three regioisomers were again inseparable by silica chromatography, and the product mixtures of **7–9** also exhibited fluorescence at both 254 nm and

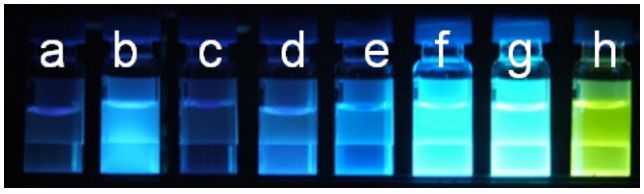
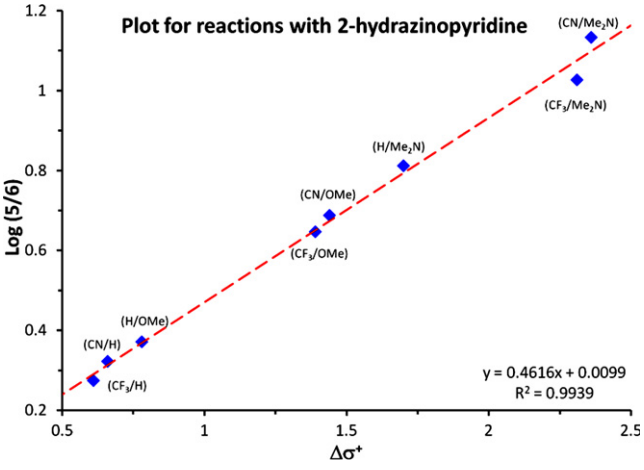


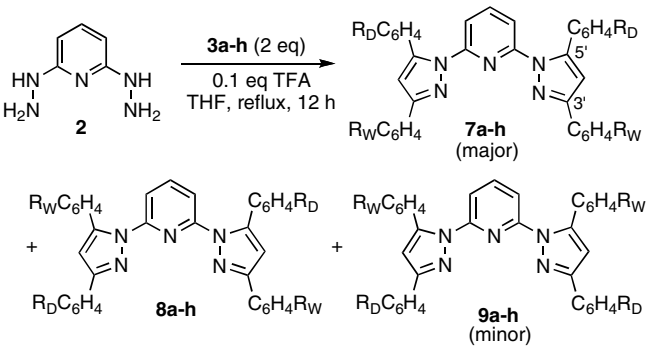
Figure 1. Fluorescence in the mixtures of **5**/**6a–h** at 365 nm.



Graph 1. Log of (**5**/**6**) versus $\Delta\sigma_p^+$.

Table 1
Product ratios from reaction of **3a–h** with **4**

3	R_D	R_W	(**5**/**6**)
a	H	CF_3	1.88
b	H	CN	2.10
c	OMe	H	2.35
d	OMe	CF_3	4.43
e	OMe	CN	4.87
f	Me_2N	H	6.48
g	Me_2N	CF_3	10.56
h	Me_2N	CN	13.58



Scheme 3. Reaction of **3a–h** with 2,6-bis-hydrazinopyridine (**2**).

Table 2
Inherent selectivity in reactions of **3a–h** with **2** calculated from product ratios

3	R_D	R_W	Ratio **7**:**8**:**9**	Inherent selectivity
a	H	CF_3	2.43:3.30:1	1.69
b	H	CN	3.97:3.91:1	1.99
c	OMe	H	7.22:5.72:1	2.69
d	OMe	CF_3	22.79:9.55:1	4.78
e	OMe	CN	N/A	N/A
f	Me_2N	H	63.87:15.08:1	7.99
g	Me_2N	CF_3	137.12:23.42:1	11.7
h	Me_2N	CN	N/A	N/A

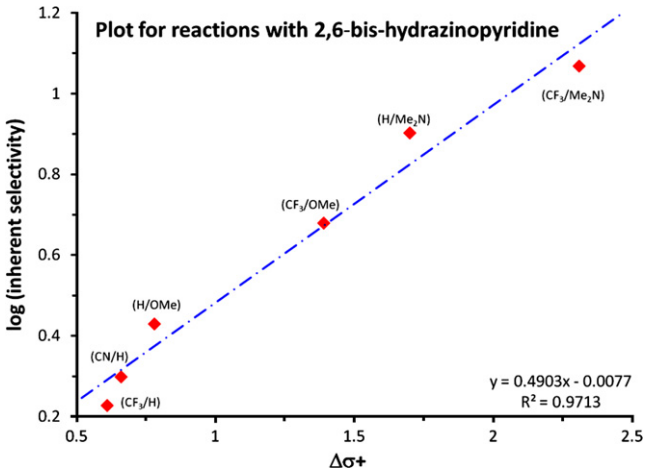
365 nm (Fig. 2), particularly in cases where dimethylamino substituents were present.

Given that reactions with BHP require two separate selective reactions, we sought to determine the average selectivity of an individual reaction. Thus, if X and Y represent the fractional probabilities in the reaction of any one hydrazino group placing the electron donating group in the 5′ or 3′ positions, respectively, the fraction of product **7** should be X^2, that of product **9** would be Y^2, and that of product **8** would be 2XY. This analysis revealed that the selectivities observed for 2-hydrazinopyridine were very similar to those calculated for BHP (Table 3). Indeed, the Hammett plot (Graph 2) for BHP reactions is nearly superimposable on that of 2-hydrazinopyridine. Thus, the selectivity of the reaction of the first

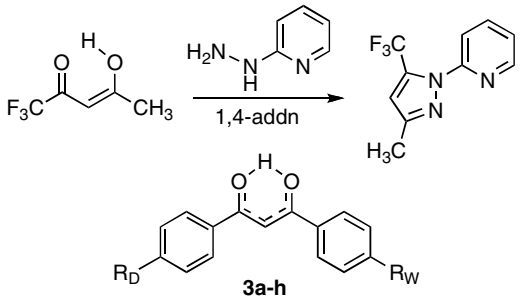
Figure 2. Fluorescence in the mixtures of **7**/**8**/**9a–h** at 365 nm.

Table 3
Comparison of selectivity in reactions of **3a–h** with **4** and **2**

3	R_D	R_W	From **4** (Ratio **5**/**6**)	Selectivity from reactions with **2**
a	H	CF_3	1.88	1.69
b	H	CN	2.10	1.99
c	OMe	H	2.35	2.69
d	OMe	CF_3	4.43	4.78
e	OMe	CN	4.87	N/A
f	Me_2N	H	6.48	7.99
g	Me_2N	CF_3	10.56	11.7
h	Me_2N	CN	13.58	N/A



Graph 2. Log of inherent selectivity in reaction of **3a–h** with **2** versus $\Delta\sigma_p^+$.



Scheme 4. Enolization in perfluoroalkyl/alkyl 1,3-diketones and in 1,3-diaryl-1,3-diketones.

hydrazino group in BHP does not appear to significantly influence the selectivity of the second one.

For both 2-hydrazinopyridine and BHP, the observed regiochemistry is consistent with initial reaction of the hydrazine NH_2 group at the carbonyl (or enol) carbon closer to the more electron-withdrawing aryl group. This regiochemistry is opposite of that observed for perfluoroalkyl/alkyl 1,3-diketones, where the perfluoroalkyl groups occupy the pyrazole 5′ positions. In these cases, the reactions proceed by 1,4-addition to a single enol form (Scheme 4). For 1,3-diaryl-1,3-diketones, the data suggest that the regiochemistry of the reaction depends simply on the relative electrophilicity of each carbonyl (or enol) carbon rather than on the location of an enolic double bond or whether 1,2- or 1,4-addition occurs. This is consistent with the resonance-assisted hydrogen bonding model in that a high degree of delocalization makes it impossible to distinguish between 1,2- versus 1,4-addition.

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8. The procedure used in all cases was a modification of Soto, Y.; Morimoto, M.; Segawa, H.; Shimidzu, T. *J. Phys. Chem* **1995**, 99, 35–39. The dimethylamino/cyano example is typical: to a flask under nitrogen atmosphere containing 470 mg of NaH (19.6 mmol, 1.06 equiv) in refluxing THF was added dropwise a THF solution containing 3.05 g of 4-dimethylaminoacetophenone (18.4 mmol, 1.0 equiv) and 3.10 g of methyl 4-cyanobenzoate (18.6 mmol, 1.01 equiv). The solution was allowed to reflux for 16 h, was cooled, acidified to pH 2 with 1 M HCl and extracted three times with 50 mL of CH_2Cl_2. After concentration, the crude solid was recrystallized from ethanol to give small fluorescent yellow needles (5.27 g, 98%; lit. 35%), spectroscopically identical with known[8] material.
9. 2-Hydrazinopyridine (110 mg, 1.00 mmol, 1.01 equiv) was placed in a 25 mL round-bottomed flask with 279 mg (1.00 mmol, 1 equiv) of 4-cyano-4′-methoxydibenzoylmethane, and was placed under nitrogen atmosphere. The mixture was dissolved in 10 mL of THF, then 7 μL of trifluoroacetic acid (0.094 mmol, 0.094 equiv) was added and the reaction was heated to reflux for 12 h. After cooling, the reaction mixture was added to 50 mL of 1 M NaOH and extracted three times with 25 mL of CH_2Cl_2. The combined organic extracts were washed with saturated NaCl (50 mL) and dried over $MgSO_4$ and concentrated by rotary evaporation to yield 306 mg (87%) of a mixture of two isomers. Major isomer: *N*-(2-pyridyl)-3-(4′-cyanophenyl)-5-(4′-methyoxyphenyl)pyrazole. MS: 352 (M^+), 351 (base), 337, 308, 280, 250, 224, 207, 176, 154, 127, 78, 51. Minor isomer: *N*-(2-pyridyl)-3-(4′-methyoxyphenyl)-5-(4′-cyanophenyl)pyrazole. MS: 352 (M^+), 351 (base), 337, 308, 280, 253, 230, 218, 192, 175, 154, 127, 102, 78, 51.