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Modulating N- versus O-arylation in pyrazolone-aryl halide couplings

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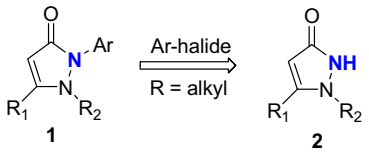
Abstract

The regioselective, copper-catalyzed coupling of a tautomeric pyrazolone/pyrazole with 2-halopyridines was investigated. Conditions were developed to preferentially form either the *N*-aryl or *O*-aryl product.

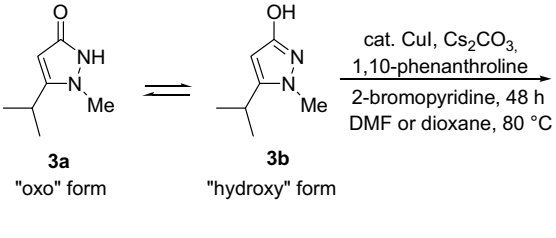
Pyrazolones are useful intermediates in the synthesis of compounds possessing a broad range of pharmacological activities.[1a–d] Within the scope of a medicinal chemistry program, it was necessary to prepare pyrazolone **1** bearing various heterocycles on the acyl ring nitrogen and a methyl group on the adjacent amine (Scheme 1, $R_2 = Me$). Cyclocondensations of aryl hydrazines with acetylenic or β-keto esters are useful methods for installing the *N*-aryl group regioselectively (**1**, $R_2 = H$); however, this strategy required preparation of commercially unavailable aryl hydrazines and a subsequent methylation step for each compound in our library.[2a,b] As an alternative approach, the Cu-mediated coupling of aryl halides with an optimally substituted *NH*-pyrazolone **2** was examined.

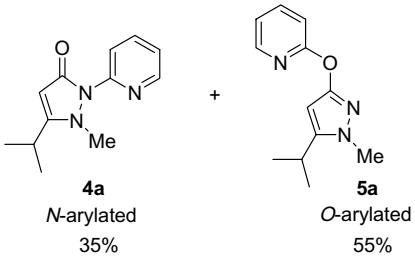
When this study was undertaken, prior art was limited to one example of a regioselective S_nAr N-arylation with 3-methylpyrazolin-5-one (**2**, $R_1 = Me$, $R_2 = H$) and an electronically deactivated 2-fluorophenylnitrile to afford the *N*-phenyl product in 47% yield.[3,4] Given the limited scope of this reaction and several reports describing the N-arylation of amides and acyl hydrazines, contemporary copper-mediated conditions were applied to the coupling of pyrazolone **3** and 2-bromopyridine (Scheme 2).[5,6a–c]

Two regioisomeric compounds were generated and characterized as *N*-pyridyl pyrazolone **4a** and *O*-pyridyl pyrazole **5a**. Proton and ^{13}C NMR data of **4a** were consistent with that reported for structurally similar *N*-aryl pyrazolones.[4] The ^{1}H NMR data of the *N*-phenyl product



Scheme 1.





Scheme 2.

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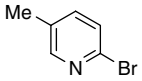
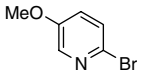
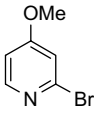
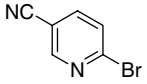
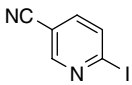
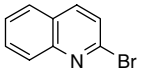
obtained from either Cu-promoted coupling with **3** or cyclocondensation (using $PhNHNH_2$, and subsequent methylation step) were identical. Similarly, spectroscopic data for **5a** compared favorably with that of reported pyrazoles.[8] Diagnostic shifts in ^1H NMR signals and HPLC retention times were found between **4a** and **5a**, and the relative product ratio could be determined from the crude reaction mixture by integrating only those HPLC peaks corresponding to each product. Notably, under these conditions the reaction favored the formation of the less desired *O*-aryl pyrazole. This product was speculated to result from a competing nucleophilic aromatic substitution reaction between the 2-halopyridine and the 'OH' tautomer **3b**, as even in the absence of catalyst, pyrazole **5a** was formed as the only product in 49% yield.[7] Given the ease of surveying this reaction from HPLC integration, the generation of both products in good overall yield, and the broad commercial availability of heterocyclic bromides, 2-bromopyridine was chosen as the substrate with which further optimization was investigated, and a more thorough study aimed at controlling the selective formation of either product was undertaken.

Table 1
Effect of changing the halopyridine on product ratio and yield in the O-arylation and N-arylation procedures with **3**

Entry	Halopyridine	Conditions[a]	HPLC ratio[b] **4a**:**5a**	**4a**:**5a** Isolated (%)	Overall yield, isolated (%)
1	2-Chloropyridine	a	0:100	0:84	84
2	2-Chloropyridine	b	0	0	0
3	2-Bromopyridine	a	30:70	14:77	91
4	2-Bromopyridine	b	71:29	72:7	79
5	2-Iodopyridine	a	61:39	64:31	95
6	2-Iodopyridine	b	70:30	77:19	96

[a] Reagents and conditions: (a) 0.50 g pyrazolone, halopyridine, 5 mol % CuCN, 11 mol % ethylenediamine, Cs_2CO_3, DMF, 110 °C, 48 h; (b) 0.50 g pyrazolone, halopyridine, 5 mol % CuBr, 11 mol % 1,10-phenanthroline, K_3PO_4, ^{i}PrOH, 110 °C, 48 h.
[b] Ratio determined from the crude reaction mixture using reverse phase HPLC (5 min run, 0.1% formic acid in CH_3CN/H_2O) at 215 nm between peak areas at ca. $R_T = 2.4$ and ca. $R_T = 2.9$ (**4a** and **5a**, respectively). Other peaks, not integrated, may have been present, such as those corresponding to starting material or ligand.

Table 2
Results of N-arylation study with **3** using optimized conditions[a]

Entry	Halide	Product	Yield **4**[b] (%)	Yield **5**[b] (%)	Overall yield (%)
1		**4a**, **5a**	72	7	79
2		**4b**, **5b**	70	5	75
3		**4c**, **5c**	68	15	83
4		**4d**, **5d**	78	9	87
5		**4e**, **5e**	14	61	75
6		**4e**, **5e**	22	61	83
7		**4f**, **5f**	80	10	90
8		**4g**, **5g**	51	47	98

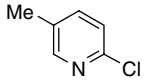
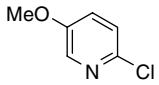
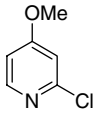
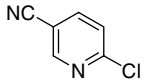
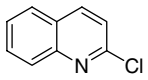
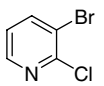
[a] Reagents and conditions: 0.50 g pyrazolone, 1 equiv halide, 5 mol % CuBr, 11 mol % 1,10-phenanthroline, 1.4 equiv K_3PO_4, ^{i}PrOH, 110 °C, 48 h.
[b] Isolated yields.

The influence of several parameters on the reaction between 2-bromopyridine and **3** was examined. The choice of copper catalyst (CuCl, CuBr, CuI, CuCN, CuOAc, $CuSO_4$, and $CuSO_4{\cdot}5H_2O$), inorganic base (K_3PO_4 or Cs_2CO_3), amine ligand (1,10-phenanthroline, 3,4,7,8-tetramethylphenanthroline, ethylenediamine, and a few examples with either *N*,*N*′-dimethylethylenediamine or *trans*-1,2-diaminocyclohexane), and solvent (DMF, dioxane, and ^{i}PrOH) were surveyed.[9] From this preliminary screen, product distribution was determined to be profoundly impacted by choice of solvent. A majority of reactions in DMF resulted in near 1:1 production of **4a** to **5a**; however, reagent combinations that resulted in significant shifts in the product ratio away from 1:1 predominantly favored pyrazole product **5a**. Alternatively, reactions employing ^{i}PrOH generally favored pyrazolone **4a** formation. Use of dioxane typically required longer heating times (>90–120 h) to reach completion and did not offer advantages over other solvents. The use of ethylenediamine notably shifted product ratios in favor of pyrazolone formation; however, significant amounts of starting material remained after 72–108 h, thus limiting the utility of this base due to poor overall yield. Once conditions were identified that promoted a product ratio in favor of either **4a** or **5a**, yields were established by isolation and then the optimized conditions were used to study the effect of using 2-chloro- or 2-iodopyridine instead of 2-bromopyridine (Table 1).

The formation of *N*-aryl product with 2-bromopyridine was optimally achieved using CuBr and 1,10-phenanthroline in the presence of K_3PO_4 and ^{i}PrOH for 48 h at 110 °C. This reagent combination provided **4a** in 72% yield with a 7% yield of pyrazole **5a** (entry 4). Exchange of 2-chloropyridine for the bromide afforded neither product, presumably due to a competitive side reaction with ^{i}PrOH (entry 2). The use of 2-iodopyridine resulted in an isolated ratio of **4a**:**5a** that was similar to that obtained when the corresponding bromide was employed (entry 6).

Conditions were also identified that reversed the observed ratio in favor of pyrazole **5a**. Use of CuCN and ethylenediamine in the presence of Cs_2CO_3 and DMF at 110 °C for 48 h afforded **5a** in 77% yield and **4a** in 14% yield (entry 3). The *N*-aryl coupling predominated with iodopyridine under these conditions; however, substituting 2-chloropyridine in this reaction exclusively provided the pyrazole in 84% yield (entry 1), implying that the rate of the aromatic substitution reaction is faster than the *N*-aryl copper-mediated coupling with 2-chloropyridine. However, it is important to note that copper plays an integral role in accelerating or promoting the conversion to the *O*-aryl product, since in the absence of catalyst the reaction with

Table 3
Results of O-arylation study with **3** using optimized conditions[a]

Entry	Halide	Product	Yield **4**[b] (%)	Yield **5**[b] (%)	Overall yield (%)
1		**4a**, **5a**	0	84	84
2		**4b**, **5b**	0	17[c]	17
3		**4c**, **5c**	0	16	16
4		**4d**, **5d**	0	82	82
5		**4e**, **5e**	10	72	82
6		**4f**, **5f**	0	98	98
7		**4g**, **5g**	0	95	95
8		**4h**, **5h**	0	84	84

[a] Reagents and conditions: 0.50 g pyrazolone, 1.0 equiv halopyridine, 5 mol % CuCN, 11 mol % ethylenediamine, 1.4 equiv Cs_2CO_3, DMF, 110 °C, 48 h.
[b] Isolated yields.
[c] Heated for 72 h.

2-chloropyridine gave only a marginal yield of **5a** (41%, single product after 48 h).

With conditions in place that favored either product in a controlled manner, the scope of each reaction was studied mainly using 5-substituted, 2-halopyridines to ascertain what effect electronic factors may have on the product distribution. The conditions used to preferentially form pyrazolone **4a** were then applied to the substrates shown in Table 2. The presence of a methyl or methoxy group on the pyridine ring had little effect on the product ratio; however, the introduction of an electron-withdrawing group promoted the competitive substitution reaction such that primarily the *O*-aryl product was formed (Table 2, entry 5).

Having already determined experimentally in the preliminary screen that the use of iodopyridine predominately led to the *N*-aryl pyrazolone regardless of what conditions were used (Table 1, entries 5 and 6), 6-iodonicotinonitrile was tested in an attempt to suppress pyrazole formation (Table 2, entry 6). However, the bromo- and iodonicotinonitriles produced virtually identical results, indicating the importance of the electronic nature of the substituent on the prevalence of pyrazole formation. Use of 2-bromopyrazine (entry 8) likewise eroded the product ratio to nearly 1:1, presumably due to the inductively deactivating effect of the second nitrogen in the ring. Surprisingly, 2-bromoquinoline[10] showed good selectivity toward pyrazolone formation despite the anticipated electron-withdrawing effect of the conjugated fused ring system (entry 7).

Based on the results with 2-chloropyridine (Table 1), it was expected that the analogous substituted 2-chloropyridines would afford high yields of the corresponding pyrazoles. To test this idea, the conditions favoring *O*-aryl product formation were then used with the substituted 2-chloro heterocycles in Table 3. Experimentally, 2-chloro-5-methylpyridine was found to be very unreactive, and a substantial amount of starting material was recovered unchanged (entry 2). In the case of entry 3, pyrazole **5c** was not stable to purification conditions, resulting in a poor isolated yield; however, the 4-substituted methoxy derivative delivered an acceptable yield of the expected pyrazole **5d**. The presence of the strongly electron withdrawing nitrile group (entry 5) only marginally affected the product ratio such that a minor amount of pyrazolone product **4e** was formed; however, in all other cases only the expected pyrazole was detected. Use of 2-chloroquinoline or 2-chloropyrazine resulted in excellent yields of the corresponding pyrazoles, and the 2-chloro-3-bromopyridine reacted selectively at the 2-position in accordance with the proposed mechanism.

In conclusion, Cu-mediated coupling conditions have been identified that promote the selective N-arylation of a pyrazolone scaffold with 2-bromopyridines in reasonable yields.[11] We have demonstrated that a competing O-arylation pathway can be suppressed and that pyrazolone product formation is sensitive to electronically deactivating substituents on the heterocyclic bromide. Additionally, conditions were also developed to preferentially generate the corresponding pyrazoles in good yield.[12]

Acknowledgments

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Supplementary data

Summarized results from the preliminary screen of conditions, experimental procedures, and full characterization data for **4a–g** and **5a–h** are provided. Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2007.11.185.

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J.; Millerais, S.; Powell, K. L.; Reynolds, K.; Spacey, G. D.; Stables, J. N.; Tatlock, M. A.; Wheeler, K. A.; Wishart, G.; Woo, C.-K. *J. Med. Chem.* **2001**, *44*, 78–93.

9. Summarized results from the entire array of screened reactions can be found in the Supplementary data.
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11. Procedure for the N-arylation of **3**: *3-isopropyl-2-methyl-1-(pyridin-2-yl)-1,2-dihydropyrazol-5-one*, **4a**: In a sealed tube were combined 3-isopropyl-2-methyl-1,2-dihydropyrazol-5-one **3** (0.50 g, 3.6 mmol), Cs_2CO_3 (1.63 g, 4.99 mmol), 1,10-phenanthroline (0.0707 g, 0.392 mmol), CuBr (0.026 g, 0.178 mmol), 2-bromopyridine (0.35 ml, 3.57 mmol) and ^{i}PrOH (7.5 mL). The vessel was flushed with argon, sealed, and heated for 48 h at 110 °C. After cooling to rt, LCMS data were collected, and the reaction was concentrated under reduced pressure to remove the solvent. At rt, the solids were suspended in EtOAc, adsorbed onto silica, and purified by flash chromatography (25%- 60% EtOAc/Hex) to afford **4a** as a white solid (0.56 g, 72%) and **5a** as a colorless oil (0.055 g, 7% yield). Data for **4a**: ^{1}H NMR (400 MHz, chloroform-*d*) δ ppm 8.44–8.52 (m, 1H), 7.91–7.98 (m, 1H), 7.76–7.84 (m, 1H), 7.10–7.17 (m, 1H), 5.36 (s, 1H), 3.27–3.42 (s, 3H), 2.74–2.91 (m, 1H), 1.31 (d, $J = 6.8$ Hz, 6H); ^{13}C NMR (100.6 MHz, chloroform-*d*) δ ppm 168.4, 166.3, 148.6, 148.1, 138.0, 120.5, 117.8, 94.8, 36.5, 26.4, 21.7; EI-MS (M^{+}+H) *m*/*z*: calculated: 218.1, observed: 218.1; $R_T = 2.40$; ESI-HRMS (M^{+}+H) *m*/*z* calculated: 218.1288, found: 218.1281.
12. Procedure for the O-arylation of **3**: *2-(5-isopropyl-1-methyl-1H-pyrazol-3-yloxy)pyridine*, **5a**: In a sealed tube was combined 3-isopropyl-2-methyl-1,2-dihydropyrazol-5-one **3** (0.50 g, 3.6 mmol), CuCN (0.016 g, 0.18 mmol), 2-chloropyridine (0.34 ml, 3.6 mmol), Cs_2CO_3 (1.6 g, 5.0 mmol) and anhydrous DMF (7.5 mL). The vessel was flushed with argon, sealed, and then ethylendiamine (0.026 ml, 0.39 mmol) was added via syringe through the sealed septum. The reaction was heated for 48 h at 110 °C and then cooled to rt. LCMS data were collected, and the reaction was concentrated under reduced pressure to remove the solvent. At rt the solids were suspended in EtOAc, adsorbed onto silica, and purified by flash chromatography (25–50% EtOAc/Hex) to afford **5a** as a colorless oil (0.65 g, 84%). ^{1}H NMR (300 MHz, chloroform-*d*) δ ppm 8.16–8.27 (m, 1H) 7.58–7.73 (m, 1H) 6.90–7.06 (m, 2H) 5.81 (s, 1H) 3.74 (s, 3H) 2.81–3.01 (m, 1H) 1.28 (d, $J = 6.87$ Hz, 6H); ^{13}C NMR (75.5 MHz, chloroform-*d*) δ ppm 162.9, 156.7, 150.8, 147.6, 139.3, 118.7, 111.5, 91.9, 36.0, 25.9, 22.1; EI-MS (M^{+}+H) *m*/*z*: calculated: 218.1, observed: 218.1; $R_T = 2.85$; ESI-HRMS (M^{+}+Na) *m*/*z* calculated: 240.1107, found: 240.1102.