



Practical synthesis of 1,3-diaryl-5-alkylpyrazoles by a highly regioselective *N*-arylation of 3,5-disubstituted pyrazoles with 4-fluoronitrobenzene

Xiao-jun Wang,^{a,*} Jonathan Tan,^a Karl Grozinger,^a Raj Betageri,^b Tom Kirrane^b
and John R. Proudfoot^b

^aDepartment of Chemical Development, Boehringer Ingelheim Pharmaceuticals Inc., Ridgefield, CT 06877, USA

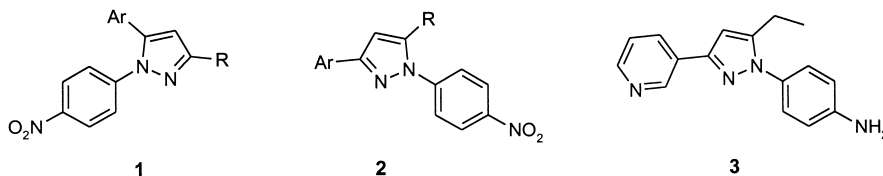
^bDepartment of Medicinal Chemistry, Boehringer Ingelheim Pharmaceuticals Inc., Ridgefield, CT 06877, USA

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Abstract

3-Aryl-5-alkylpyrazoles undergo a highly regioselective arylation on N-1 atom with 4-fluoronitrobenzene in the presence of base to yield the corresponding 1-(4-nitrophenyl)pyrazoles. © 2000 Elsevier Science Ltd. All rights reserved.

The most common route to *N*-arylpyrazoles involves condensation of 1,3-diketones with arylhydrazines. In this reaction unsymmetrical 1,3-diketones generally yield a mixture of two regioisomers in a ratio which depends on the nature of 1,3-diketones.¹ We recently required an efficient entry into a variety of 1-(4-nitrophenyl)-3-aryl-5-alkylpyrazoles **2**, and since direct condensation of aryl alkyl 1,3-diketones with arylhydrazines proceeded to give the undesired isomeric 1-(4-nitrophenyl)-3-alkyl-5-arylpyrazole **1** as a major component,² we sought an alternative approach to these molecules. We were particularly interested in a practical synthesis of pyrazole **3**, which we needed in large quantities.

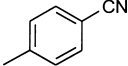
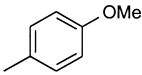
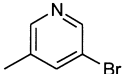
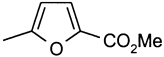


In this communication we describe our findings that direct *N*-arylation of pyrazoles **4** with 4-fluoronitrobenzene (**5**) using potassium *tert*-butoxide as a base in DMSO at 70°C for 1 hour

* Corresponding author.

affords pyrazoles **2** with high regioselectivity in excellent yields (Scheme 1 and Table 1).^{3,4} We found that the previously reported conditions,^{2c,5a–d} such as K_2CO_3 /DMF, K_2CO_3 /DMSO, KOH/Bu_4NBr , KO^tBu and NaH/THF , required longer times and gave moderate to good yields, with similar regioselectivity observed. A practical synthesis of pyrazole **3** was developed using this approach. The starting pyrazoles **4** were prepared by condensation of the corresponding 1,3-diketones with hydrazine.⁶

Table 1
N-Arylation of pyrazole **4** with 4-fluoronitrobenzene (**5**) (Scheme 1)

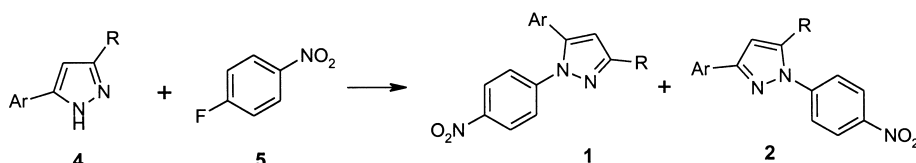
Entry	Ar	R	Ratio of 2:1 ^a	Yield (%) ^{b,c}
1		CH ₂ CH ₃	22:1	92
2		CH(CH ₃) ₂	3.8:1	89 ^d
3		CH ₂ CH ₃	30:1	85
4		CH ₂ CH ₃	17:1	87
5		CH ₂ CH ₃	38:1	94
6		CH ₂ CH ₃	99:1	88
7		CH ₂ CH ₃	99:1	84
8		CH ₂ CH ₃	99:1	96
9		CH ₂ CH ₃	9:1	74
10		CH ₂ CH ₃	11:1	90

^a Determined by ¹H NMR of crude products.

^b Isolated yield of **2** unless otherwise stated.

^c All products gave satisfied proton and carbon NMR, high resolution MS or elemental analysis.

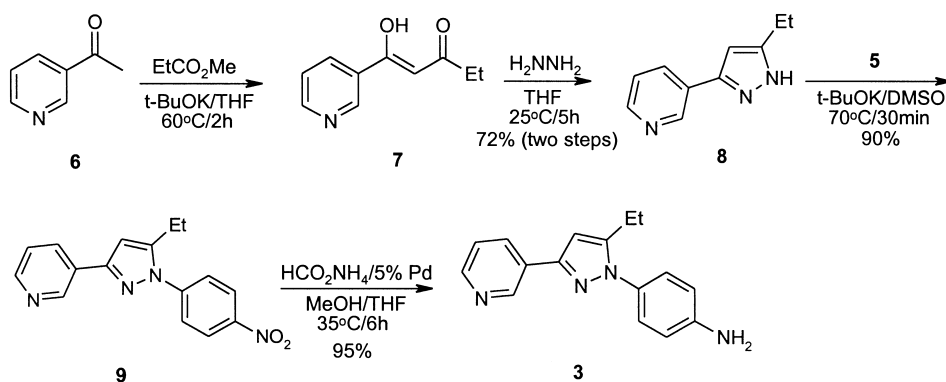
^d Combined yield of **1** and **2**. Both isomers were separated by column chromatography on silica gel.



Scheme 1.

For the pyrazole anion of **4**, there are two equivalent resonance forms, and therefore a regioisomeric mixture of **1** and **2** would be expected from *N*-arylation (Scheme 1). The observed regioselectivity of this process may be attributable to the steric hindrance of the non-twisted aryl ring^{1,7} that prohibits access to the nitrogen atom next to the aromatic ring by the electrophile leading to isomer **2**. With the opposing isopropyl group instead of ethyl (Entry 2), the regioselectivity was lower, suggesting a steric effect for both the aryl and isopropyl groups. Consistent with our rationale, the less sterically demanding furan ring leads to lower selectivity (Entries 9 and 10). Electronic effects may also be affecting the regioselectivity.¹ It is noteworthy that pyrazoles with electron-withdrawing groups on the aryl ring (Entries 3 and 10) showed higher regioselectivity than did the parent substrates (Entries 2 and 9), while a lower selectivity was observed for pyrazole with an electron-donating group (Entry 4). In general, pyrazoles with more electron-deficient aromatic substituents (Entries 5 through 8) gave higher regioselectivity. The structures of isomeric products **1** and **2** were supported by NOE experiments: a strong NOE effect was observed between the methylene protons of the alkyl group and the *ortho*-proton of the nitrophenyl group in isomer **2** and was absent in isomer **1**.⁸

Using this highly regioselective *N*-arylation as a key step, we developed a scalable, three-step synthesis of pyrazole **3**, a key intermediate for our program, with an overall yield of 60% (Scheme 2). Thus, condensation of 3-acetylpyridine (**6**) with methyl propionate in the presence of *t*-BuOK yielded 1,3-diketone **7** as the enol. In a one-pot operation, the reaction mixture was neutralized with concentrated HCl, and then treated with hydrazine. Pyrazole **8** was isolated in 72% yield by concentration, followed by adding water. *N*-Alkylation of **8** with 4-fluoronitrobenzene (**5**) gave the desired regioisomer **9** in 90% isolated yield after removal of the other regioisomer (2.5%) by trituration with a 1:1 mixture of hexane and ethyl acetate. Reduction of **9** was carried out using HCO₂NH₄/5% Pd on carbon in a mixture of methanol and THF to give pyrazole **3**. This



Scheme 2.

operation was carried out on a greater than 500 g scale, and proved to be very practical. Analogous pyrazoles were also scaled up along the same lines.

In conclusion, *N*-arylation of 3-aryl-5-alkylpyrazoles yields 1,3-aryl-5-alkylpyrazoles in a highly regioselective manner, and it can serve as a general approach to this type of molecules.

References

1. Kost, A. N.; Grandberg, I. I. In *Advances in Heterocyclic Chemistry*; Kartrizky, A. R.; Boulton, A. J., Ed.; Academic Press: New York, 1966; Vol. 6, 347.
2. For examples, see: (a) Murray, W.; Wachter, D. B.; Barton, D.; Forero-Kelly, Y. *Synthesis* **1991**, 18–20; (b) Kashima, C.; Harada, H.; Kita, I.; Fukuchi, I.; Hosomi, A. *Synthesis* **1994**, 61–65. (c) Luo, Y.; Potvin, P. G. *J. Org. Chem.* **1994**, 59, 1761–1765.
3. Elguero, J. In *Comprehensive Heterocyclic Chemistry*; Katritzky, A. R.; Rees, C. W., Ed.; Pergamon Press: Oxford, 1984; Vol. 5, 167.
4. A representative procedure: To a solution of 3-phenyl-5-ethylpyrazole (1.0 g, 5.81 mmol) in DMSO (5 mL) was added solid potassium *tert*-butoxide (0.72 g, 6.39 mmol) followed by addition of 4-fluoronitrobenzene (0.65 mL, 6.10 mmol) through a syringe. The resulting mixture was heated to 70°C and kept at this temperature for 30 min. It was then cooled to room temperature and quenched with water (50 mL). The precipitate was collected by filtration and oven-dried in vacuo. The solid was triturated in a 2:1 mixture of hexane and ethyl acetate (20 mL) for 30 min, then collected by filtration and dried to give 1-(4-nitrophenyl)-3-phenyl-5-ethylpyrazole (1.70 g, 92%); m.p. 112–113°C. ¹H NMR (400 MHz, CDCl₃): 8.39, 7.79 (ABq, *J* = 9.1 Hz, 4H, ArH), 7.90 (m, 2H, PhH), 7.45 (m, 2H, PhH), 7.38 (m, 1H, PhH), 6.66 (s, 1H, PyH), 2.86 (q, *J* = 7.52 Hz, 2H, CH₂CH₃), 1.38 (t, *J* = 7.52 Hz, 3H, CH₂CH₃). MS *m/e* 294 (20, MH⁺), 265 (25), 264 (100). Anal. calcd for C₁₇H₁₅N₃O₂: C, 69.61; H, 5.15; N, 14.32. Found: C, 69.65; H, 5.19; N, 14.43.
5. (a) Sugaya, T.; Mimury, Y.; Ikuta, M.; Mimury, T.; Kasai, M.; Tomioka, S. *Synthesis* **1994**, 73–76. (b) Cerrada, M. L.; Elguero, J.; De La Fuente, J.; Pardo, C.; Ramos, M. *Synth. Commun.* **1993**, 23, 1947–1952. (c) Park, K. H.; Cho, S. Y.; Yum, E. K.; Yu, C. M.; Hwang, K. J. *Bull. Korean Chem. Soc.* **1995**, 16, 799–801. (d) Finar, I. L.; Hurlock, R. J. *J. Chem. Soc.* **1957**, 3024–3026.
6. Wiley, R. H.; Hexaner, P. E. *Org. Synth. Coll. Vol. IV* **1963**, 351–353.
7. Kashima, C.; Fukuchi, I.; Takahashi, K.; Hosomi, A. *Tetrahedron Lett.* **1993**, 34, 8305–8308.
8. Some minor regioisomers **1** were independently synthesized by a known procedure,² if not isolated from the *N*-arylation.