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

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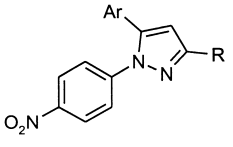
Abstract

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.

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.



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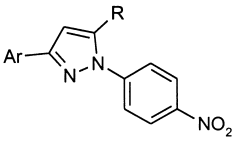

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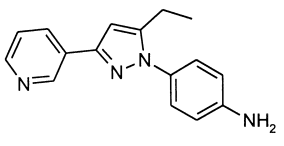

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In this communication we describe our findings that direct *N*-arylation of pyrazoles **4** with 4-fluoronitrobenzene (**5**) using potassium *tert*-butoxide as a base in DMSO at 70°C for 1 hour

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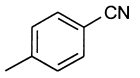
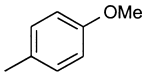
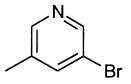
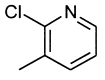
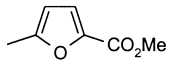
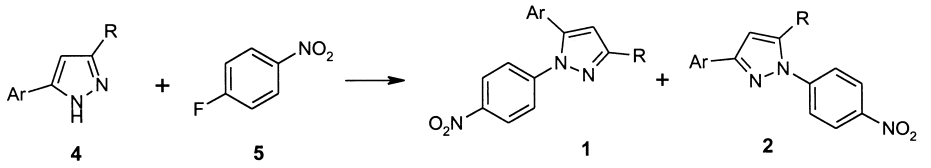
affords pyrazoles **2** with high regioselectivity in excellent yields (Scheme 1 and Table 1).[3,4] We found that the previously reported conditions,[2c,5a–d] such as K_2CO_3/DMF, K_2CO_3/DMSO, KOH/Bu_4NBr, KO^{t}Bu and NaH/THF, required longer times and gave moderate to good yields, with similar regioselectivity 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_2CH_3	22:1	92
2		$CH(CH_3)_2$	3.8:1	89[d]
3		CH_2CH_3	30:1	85
4		CH_2CH_3	17:1	87
5		CH_2CH_3	38:1	94
6		CH_2CH_3	99:1	88
7		CH_2CH_3	99:1	84
8		CH_2CH_3	99:1	96
9		CH_2CH_3	9:1	74
10		CH_2CH_3	11:1	90

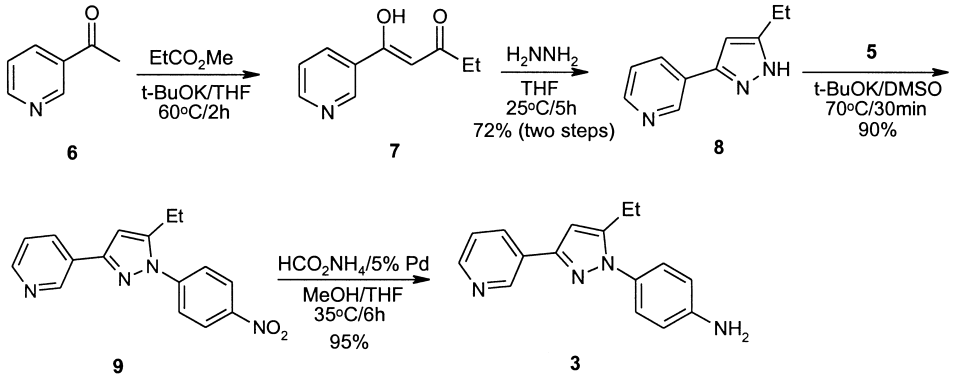
[a] Determined by ^{1}H NMR of crude products.
[b] Isolated yield of **2** unless otherwise stated.
[c] All products gave satisfied proton and carbon NMR, high resolution MS or elemental analysis.
[d] Combined yield of **1** and **2**. Both isomers were separated by column chromatography on silica gel.



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 HCO_2NH_4/5% 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

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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. ^{1}H NMR (400 MHz, $CDCl_3$): 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, CH_2CH_3), 1.38 (t, $J=7.52$ Hz, 3H, CH_2CH_3). MS *m*/*e* 294 (20, MH^+), 265 (25), 264 (100). Anal. calcd for $C_{17}H_{15}N_3O_2$: C, 69.61; H, 5.15; N, 14.32. Found: C, 69.65; H, 5.19; N, 14.43.
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8. Some minor regioisomers **1** were independently synthesized by a known procedure,[2] if not isolated from the *N*-arylation.