Unexpected Behavior of 5-Phenoxypyrazole Derivatives

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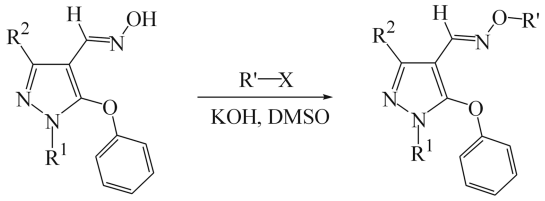
The pyrazole ring is a prominent structural motif found in numerous pharmaceutically active compounds. Due to the easy preparation and rich biological activity, pyrazole framework plays an essential role in biologically active compounds and therefore represents an interesting template for combinatorial as well as medicinal chemistry.[1] Indeed, pyrazole-based derivatives have shown several biological activities as seen in COX-2,[2] p38 MAP kinase,[3] and CDK2/ Cyclin A inhibitors.[4] Many of them are currently being tested and/or clinically evaluated for new drug discovery.

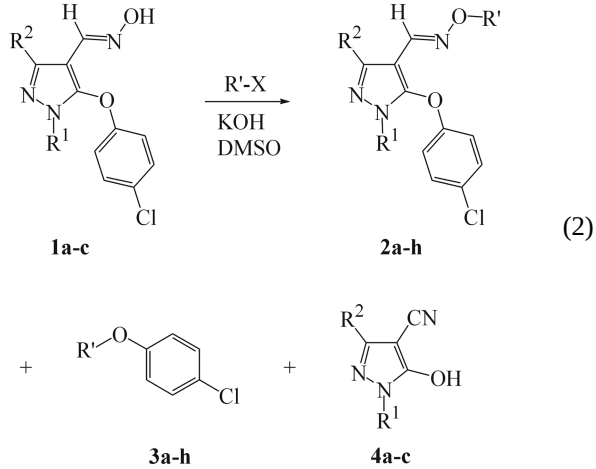
Previously, we studied the facile introduction of nucleophiles into 5-chloropyrazole, activated by the *ortho*-formyl group, by the nucleophilic aromatic substitution.[5] As part of a program, we were interested in 5-phenoxypyrazole derivatives, which produce drug-like structures that are constrained to a limited number of conformations by heterocyclic cores and hindered rotation by substituents. Thus, many pyrazole oxime ethers[6] were prepared by the Williamson synthesis of 5-phenoxypyrazole oximes and alkyl halides, as shown in eq. (1). However, 5-(4-chlorophenoxy)pyrazole derivatives mainly yielded *p*-chlorophenyl ethers derived from alkyl halides in this Williamson synthesis. Here, we would like to report unusual behavior of 5-phenoxypyrazole derivatives, etherification of alkyl halide by aid of 5-(4-chlorophenoxy)pyrazole oxime and nucleophilic displacement of 5-(4-nitrophenoxy)pyrazole.



(1)

The starting pyrazole oximes **1a-c** were readily prepared as single *E*-isomers from the corresponding 4-formylpyrazoles[5] in 72-87% yield (NH_2OH·HCl, NaOH, MeOH, 60 °C, 2 h). Most alkyl and benzyl halides were available from commercial suppliers. Ethyl and *t*-butyl benzoates were prepared from 4-chloromethylbenzoic acid, respectively, by the Fischer esterification and by the acid-catalyzed reaction of isobutene[7] via *in situ* generation from *t*-butanol. *N*-Benzyl piperazine was obtained by the *N*-benzylation of 1-(2-chloroethyl)piperazine, prepared by the chlorination of 1-(2-hydroxyethyl)piperazine.[8]

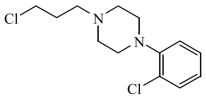
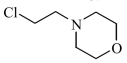
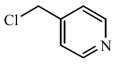
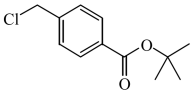
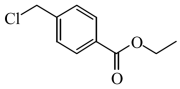
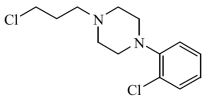
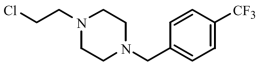
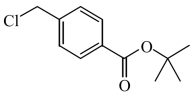
When 5-(4-chlorophenoxy)-1,3-dimethylpyrazole oxime **1a** was subjected to the Williamson synthesis with 1-(2-chlorophenyl)-4-(3-chloropropyl)piperazine, the reaction yielded the corresponding pyrazole oxime ether **2a**, *p*-chlorophenyl ether **3a**, and 4-cyanopyrazole **4a**, as shown in eq. (2). This was a very unique result that 5-(4-chlorophenoxy)pyrazole preferentially produced *p*-chlorophenyl ether when it was reacted with the corresponding halide in the basic conditions. After examining a few examples, we realized that all representing entries uniformly produced *p*-chlorophenyl ethers as major products. The results are summarized in Table 1. Obviously, *p*-chlorophenoxy group plays a crucial role in such unusual etherification of alkyl and benzyl halides comparing to phenoxy group. Conceptually, it is acceptable that an electron-withdrawing group in 5-phenoxypyrazole is a dominating factor to influence the course of the reaction.



(2)

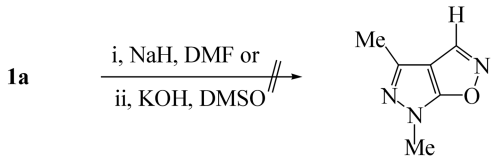
At a glance, a possible explanation for the above observation should include the generation of *p*-chlorophenoxide anion in the reaction mixtures. We thought a facile intramolecular cyclization of **1a** to such as pyrazoloisoxazole **5** under the basic conditions might kick out *p*-chlorophenoxy group, and then which are trapped by the existing alkyl halide to produce *p*-chlorophenyl ether **3a**. But, we could not observe the formation of **5**, even though **1a** was treated with sodium hydride or potassium hydroxide without alkyl halide. Later, we knew that this is consistent with previous

Table 1. Unusual ether formation of alkyl halides by aid of 5-(4-chlorophenoxy)pyrazole oxime derivatives

Entry	**1**	R^1	R^2	R'-X	Yield (%)[a]	
1	**1a**	Me	Me		**2a** (30)	**3a** (53)
2	**1a**				**2b** (8)	**3b** (40)
3	**1a**				**2c** (4)	**3c** (14)
4	**1b**	Ph	Me		**2d** (17)	**3d** (72)
5	**1b**				**2e** (16)	**3e** (54)
6	**1b**				**2f** (53)	**3f** (32)
7	**1b**				**2g** (9)	**3g** (13)
8	**1c**	Ph	*i*-Pr		**2h** (10)	**3h** (85)

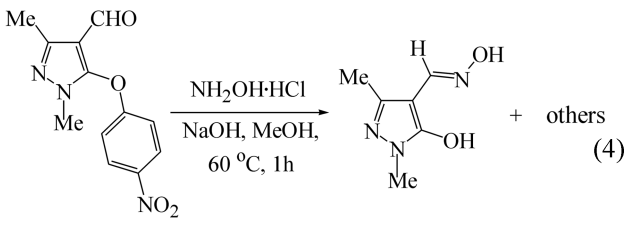
[a]The nitrile **4** was readily removed during the aqueous work-up and the yield was not determined except entry 1.

finding that such *E*-configuration in **1a** does not readily undergo cyclization even under forcing conditions.[9] The second choice was that a nucleophilic attack at the 5-position would liberate the phenoxide anion. An attempted synthesis of 5-(4-nitrophenoxy)pyrazole oxime was failed, instead **6a** readily lose the *p*-nitrophenoxy group and afforded 5-hydroxy-pyrazole **7** in 60% yield (eq. 4). This result strongly suggested that the phenoxy groups with stabilization by the electron-withdrawing groups, serve as good leaving groups toward nucleophilic substitution, and are not formed by aid of the intramolecular cyclization.



(3)

5



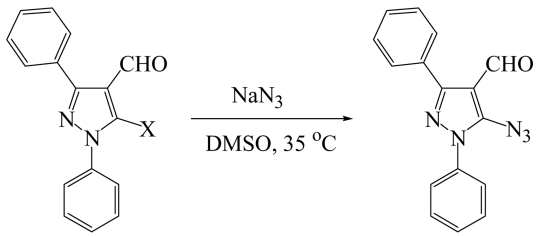
(4)

6a **7**

Table 2. Azide displacement of 5-substituted pyrazole derivatives

Entry	**6**	X	Reaction Time (h)	**8** (yield, %)
1	**6b**	Cl	23	74
2	**6c**	*p*-chlorophenoxy	160	48
3	**6d**	*p*-nitrophenoxy	45	92

The pyrazole, as an electron-rich heteroaromatic nucleus, does not generally react with nucleophiles. To our knowledge, only a few examples of nucleophilic aromatic substitution on 5-chloro-pyrazole have been reported.[5,10] It is very interesting to figure out a potential of **6b-d** for nucleophilic substitution, as shown in eq. (5). Thus, 4-formyl-5-(4-nitrophenoxy)pyrazole **6d** was reacted with sodium azide to afford 5-azidopyrazole **8** in 92% yield (Table 2, entry 3). The result supports that **6d** is a suitable substrate for the nucleophilic aromatic substitution and chemically equivalent to 5-chloropyrazole **6b**. It is also noteworthy that 5-aminopyrazole is an important class of antitumor and antiinflammatory agents for new drug discovery.[2-4]



(5)

6b-d **8**

In summary, we found that 5-(4-chlorophenoxy)pyrazole oximes **1a-c** preferentially produced *p*-chlorophenyl ethers when they reacted with the halides under the basic conditions. This situation can be explained that the 4-chlorophenoxy group serves as a good leaving group toward nucleophilc substitution, with the stabilization by the electron-withdrawing group. It is interesting to note that 5-(4-nitrophenoxy)pyrazole **6d** is a suitable substrate for the nucleophilic aromatic substitution.

Experimental Section

A representative procedure for etherification of alkyl halide (Table 1, entry 1). A mixture of **1a** (400 mg, 1.5 mmol), 1-(2-chlorophenyl)-4-(3-chloropropyl)piperazine (620 mg, 2 mmol), and powdered KOH (226 mg, 3.9 mmol) in DMSO (6 mL) was stirred at 50-60 °C for 4 h. The reaction mixture was partitioned EtOAc (60 mL) and H_2O (50 mL). The organic layer was washed successively with brine and water and dried over Na_2SO_4, then evaporated under reduced pressure to give a residue. The residue was purified by flash chromatography on silica gel (hexane/EtOAc = 4/1) to give **2a** (228 mg, 30%) and **3a** (292 mg, 53%). The aqueous layer was thoroughly evaporated under

reduced pressure to give a solid residue, which was then purified by flash chromatography on silica gel (EtOH/EtOAc = 1/1) to give **4a** (62 mg, 30%). **2a**: oil; ^{1}H NMR ($CDCl_3$) δ 7.76 (s, 1H), 7.30-7.27 (m, 2H), 7.17 (t, 1H, J = 8.1 Hz), 6.89-6.78 (m, 5H), 4.03 (t, 2H, J = 6.4 Hz), 3.61 (s, 3H), 3.23-3.20 (m, 4H), 2.59-2.56 (m, 4H), 2.45 (t, 2H, J = 6.4 Hz), 2.38 (s, 3H), 1.81 (m, 2H); EIMS (70eV) *m/z* (rel intensity) 502 (M^+, 11), 250 (100), 209 (66), 166 (71), 70 (37). **3a**: mp 67-68 °C; ^{1}H NMR ($CDCl_3$) δ 7.18-7.12 (m, 2H), 6.87-6.75 (m, 6H), 3.62 (t, 2H, J = 6.6 Hz), 3.20-3.17 (m, 4H), 2.60-2.56 (m, 4H), 2.56-2.51 (m, 2H), 1.98 (m, 2H); EIMS (70eV) *m/z* (rel intensity) 364 (M^+, 48), 247 (27), 209 (100), 70 (49). **4a**: ^{1}H NMR (DMSO-d_6) δ 3.18 (s, 3H), 2.59 (s, 1H), 1.99 (s, 3H); ^{13}C NMR (CD_3OD) δ 12.2, 31.1, 40.0, 71.7, 148.9, 168.3; EIMS (70eV) *m/z* (rel. intensity) 137 (M^+, 100), 78 (10), 69 (25), 66 (90), 52 (15); HR-EIMS Calcd for $C_6H_7N_3O$: 137.0588, Found: 137.0589; IR (KBr) 3423, 2919, 2198, 1587, 1508, 1436, 1027, 736, 536 cm^{-1}.

A representative procedure for azide displacement (Table 2, entry 3). The 5-(4-nitrophenoxy)pyrazole **6d** (150 mg, 0.39 mmol) was dissolved in DMSO (2 mL) and to this solution was added sodium azide (76 mg, 1.17 mmol). The reaction mixture was stirred for 45 h at 35 °C in the absence of light. The mixture was diluted with H_2O (50 mL) and extracted with EtOAc (40 mL). The organic phase was washed with brine and H_2O, dried over Na_2SO_4, then evaporated under reduced pressure to give **8** (104 mg, 92%) as a solid: mp 118-120 °C; ^{1}H NMR ($CDCl_3$) δ 9.89 (s, 1H), 7.62-7.58 (m, 4H), 7.46-7.18 (m, 6H); EIMS (70 eV) *m/z* (rel intensity) 289 (M^+, 1), 261 (3), 127 (2), 77 (100).

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