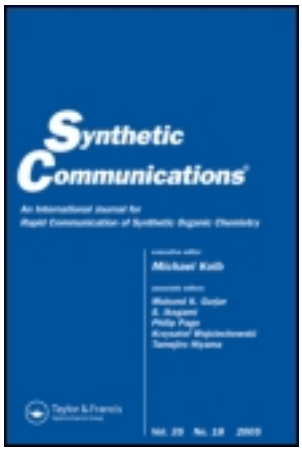

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Introduction of N-Containing Heterocycles into Pyrazole by Nucleophilic Aromatic Substitution

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Introduction of *N*-Containing Heterocycles into Pyrazole by Nucleophilic Aromatic Substitution

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ABSTRACT

The nucleophilic aromatic substitution on 5-chloropyrazoles activated by the electron-withdrawing formyl group offers a useful method to introduce a wide range of *N*-containing heterocycles into them. The rate of reaction was greatly affected by the electronic nature of the N-1 substitution.

Key Words: Pyrazole; Nucleophilic aromatic substitution; Electron-withdrawing group; Heterocyclic system.

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INTRODUCTION

For a long time, nucleophilic aromatic substitution (S_NAr) has been a valuable instrument to prepare a wide variety of functionalized heterocycles and to obtain building blocks for the synthesis of target compounds. The S_NAr reaction of heterocycles[1] containing a nearby halogen atom has offered an efficient method for introducing a wide variety of heteroatom-containing nucleophiles into the heterocyclic ring. This reaction readily allows one to make heteroatom–carbon bond formation, demonstrating relatively high yields, a convenient reaction procedure, and an easy access to various nucleophiles containing nitrogen, oxygen, and sulfur atoms. Due to their conformational rigidity and their wide range of properties, such heterocyclic systems play an essential role as scaffolds in biologically active compounds.[2] Many of them are currently being tested and/or clinically evaluated for new drug discovery.

As part of our study, we are interested in S_NAr reactions of pyrazoles, which produce drug-like structures that are constrained to a limited number of conformations by heterocyclic cores and hindered rotation by substituents. Indeed, the derivatives of pyrazole have shown several biological activities as seen in COX-2 inhibitors,[3] p38 MAP kinase inhibitors,[4] and therefore represent an interesting template for combinatorial as well as medicinal chemistry.[5]

The pyrazole, as an electron-rich heteroaromatic nucleus, does not generally react with nucleophiles. To our knowledge, only a few examples of S_NAr on 5-chloropyrazole have been reported.[6] Such a displacement of halide from a five-membered heterocyclic ring is extremely rare in the absence of electron-withdrawing groups such as formyl or nitro group in a conjugated position of the ring. Thus, it is ambitious that 4-formyl-5-chloropyrazole has a considerable potential for nucleophilic displacement of the halogen, activated by the *ortho*-aldehyde.[1b,6b] Here, we would like to report the introduction of various *N*-containing heterocycles into pyrazole as shown in Sch. 1.

The starting pyrazoles were prepared according to the well-known procedure, in which the required pyrazolones were easily prepared by the condensation of ethyl acetoacetate with methylhydrazine, phenylhydrazine, 2-hydrazinopyridine, and hydrazine monohydrate, respectively. The pyrazolones were then subjected to the Vilsmeier–Haack chloroformylation[6b,7] using DMF and an excess $POCl_3$ to yield the corresponding 5-chloro-4-formylpyrazoles **1–4**.

First, we examined the nucleophilic substitution of **1**[7] (R = Me) with pyrrole in polar solvents such as DMF and DMSO with different alkaline bases. Each run showed a similar reaction profile, but with an increasing time order of KOH, NaOH, $Cs_2CO_3 < K_2CO_3 < LiOH \ll NaHCO_3$. Thus, the reaction was conveniently carried out by heating (ca. 120°C) a mixture

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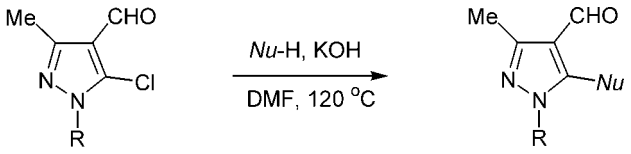

1 (R = Me)
2 (R = Ph)
3 (R = 2-Py)
4 (R = H)

5-27

Scheme 1.

of **1** with pyrrole (3 equiv.) and powdered KOH (1.5 equiv.) in DMF and gave 5-pyrrolopyrazole **5** in 66% yield (entry 1).

With this promising result, we extended the S_NAr reaction to the readily available *N*-containing heterocycles such as imidazole, pyrazole, indole, pyrrolidine, and morpholine (entries 2–6) as summarized in Table 1. The reaction generously allowed the introduction of a wide range of heterocycles into the pyrazole ring. A brief comparison of the data shows that the aromatic nucleophiles (entries 1–4) react much faster than the saturated heterocycles (entries 5 and 6). Even though the reactions with the aromatics resulted in good yields, the yields from pyrrolidine and morpholine were poor. While the rate of reaction was even slower with morpholine, this led to the formation of the corresponding 5-morpholinopyrazole **10** and by-product **11** (Nu = NMe_2) in only 25% overall yield. The structure of **11** was confirmed by comparison with the product from the reaction with dimethylamine (entry 7). To verify the participation of DMF as a substrate in nucleophilic substitution, **1** was just heated with DMF in KOH without a proper nucleophile. Even though the reaction was not completed for a prolonged time, it gave **11** in 15% and **12** (Nu = H) in 16% yields (entry 8). This result clearly demonstrated that DMF is the source of the nucleophile. Contrary to N-containing nucleophiles, the reactions with oxygen- and sulfur-nucleophiles, such as phenol and thiophenol, resulted in excellent yields (entries 9 and 10).

Analogously, **2** (R = Ph) and **3** (R = 2-Py) were subjected to the S_NAr reactions.[a] The interesting feature was observed that the yields from **3** (entries

[a]General procedure for the S_NAr of **3** with pyrrolidine (entry 20): A mixture of **3** (40 mg, 0.18 mmol), pyrrolidine (45 μL, 0.54 mmol), and powdered KOH (15 mg, 0.27 mmol) in DMF (5 mL) was stirred at 120°C for 2 hr. The reaction mixture was diluted with H_2O (40 mL) and extracted with Et_2O (3 × 20 mL). The combined organic layers were washed successively with brine and water, dried over Na_2SO_4, and then

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18–20) with the saturated heterocycles were substantially superior to those from **1** (entries 5 and 6) and **2** (entries 13 and 14). Indeed, **3**, upon reaction with the cyclic secondary amines such as pyrrolidine, piperidine, and morpholine, afforded the corresponding 5-substituted pyrazoles in good yields (71–89%). Also, it was found that the reaction rates are highly dependent on the blocking groups of pyrazole at N-1 position. Remarkably, the reaction of **3** was completed much faster than that of **1** with morpholine (entries 6 and 20). The difference can be explained in terms of the electronic nature of the substantial groups attached at the adjacent N-1 nitrogen. On the assumption that their stability depends on the relative energies of the transition states, the relative rates reflect their degree of delocalization of negative charge developed on the transition states. Another feature that was observed was the reaction of **3** in DMF without a nucleophile, in less than 2 hr, ended up with **27** (Nu = NMe_2) in 57% yield (entry 22). It is also interesting to note that in the reaction of **4** (R = H) even with imidazole, there was no reaction (entry 23). All new compounds were satisfactorily characterized by ^{1}H NMR, mass spectrometry, and elemental analysis and are shown in Table 2.

When the reaction of **1** with morpholine was carried out in DMSO, the corresponding 5-morpholinopyrazole **10** (18%) and the α,β-unsaturated sulfoxide **28** (20%) were isolated as shown in Sch. 2. It has been known that the dimsyl anion[8] formed in solutions of DMSO containing bases such as sodium hydride or alkali metal alkoxides, undergoes aldol reaction with carbonyl compounds. The structure of the aldol product **28**[b] was determined by NMR and MS, and the *E*-geometry was judged by the coupling constants; δ 7.06 (d, 1H, $J = 15.7$ Hz) and 6.81 (d, 1H, $J = 15.7$ Hz). The yields in DMSO were very similar compared to those obtained in DMF in many other cases.

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evaporated under reduced pressure to give a solid residue. The residue was purified by flash chromatography on silica gel with ethyl acetate as the eluent to give 41 mg (89%) of **23** as a solid: mp 135–137°C; EIMS m/z (rel. intensity) 256 (M^+, 3), 227 (3), 213 (4), 199 (3), 118 (18), 78 (100); ^{1}H NMR ($CDCl_3$) δ 1.88–1.94 (m, 4H), 2.46 (s, 3H), 3.36 (t, 4H, $J = 6.5$ Hz), 7.27–7.30 (m, 1H), 7.62 (d, 1H, $J = 8.0$ Hz), 7.82–7.88 (m, 1H), 8.51 (dd, 1H, $J = 4.8$, 1.6 Hz), 9.98 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 15.4, 26.2, 53.6, 109.6, 120.8, 123.1, 139.0, 148.6, 152.2, 153.4, 153.6, 183.4. Anal. Calcd for $C_{14}H_{16}N_4O$: C, 65.61%; H, 6.29%; N, 21.86%. Found: C, 65.92%; H, 6.46%; N, 21.63%.

[b]**28**: Mp 111–113°C; EIMS m/z (rel. intensity) 220 ($M^+ + 2$, 14), 218 (M^+, 47), 203 (70), 185 (38), 167 (74), 154 (100); HRMS (EI) calcd for $C_8H_{11}ClN_2OS$: 218.0281 found 218.0280; ^{1}H NMR ($CDCl_3$) δ 7.06 (d, 1H, $J = 15.7$ Hz), 6.81 (d, 1H, $J = 15.7$ Hz), 3.80 (s, 3H), 2.70 (s, 3H), 2.34 (s, 3H).

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Table 1. Introduction of nucleophiles into 4-formyl-5-chloropyrazoles **1–4** in DMF.

Entry	R	Nu-H	Reaction time (hr)	Product (yield, %)	Mp (°C)
1	Me	Pyrrole	2	**5** (66)	100
2	Me	Imidazole	2	**6** (75)	92–94
3	Me	Pyrazole	2	**7** (77)	92
4	Me	Indole	2	**8** (76)	Oil
5	Me	Pyrrolidine	5	**9** (34)	Oil
6	Me	Morpholine	22	**10** (14)	68–70
				11[a] (11)	Oil
7	Me	Dimethylamine[b]	21	**11**[a] (68)	Oil
8	Me	DMF[c]	80[d]	**11**[a] (15)	Oil
				12[e] (16)	43–46
9	Me	Phenol	2	**13** (91)	Oil
10	Me	Thiophenol	2	**14** (87)	Oil
11	Ph	Imidazole	4	**15** (80)	125–127
12	Ph	Pyrazole	4	**16** (83)	135
13	Ph	Pyrrolidine	3	**17** (33)	152
14	Ph	Morpholine	5	**18** (10)	132–134
				19[a] (15)	Oil
15	Ph	Phenol	2	**20** (82)	94–95
16	2-Py[f]	Imidazole	2	**21** (79)	130
17	2-Py	Pyrazole	2	**22** (81)	121–125
18	2-Py	Pyrrolidine	2	**23** (89)	135–137
19	2-Py	Piperidine	2	**24** (75)	95
20	2-Py	Morpholine	2	**25** (71)	101–103
21	2-Py	1-Methylpiperazine	2	**26** (50)	108
22	2-Py	DMF[c]	2	**27**[a] (57)	Oil
23	H	Imidazole	24	—[g]	—[g]

[a]Nu = NMe_2.
[b]40 wt.% solution in water (8 equiv.) was used.
[c]DMF was used as a source of dimethylamine.
[d]The reaction was not completed.
[e]Nu = H.
[f]2-Py = 2-pyridinyl.
[g]No reaction observed.

In conclusion, the S_NAr reactions on 4-formyl-5-chloropyrazole offer a useful method to introduce a wide range of *N*-containing heterocycles into them. Such reactivity can be explained in terms of a combination of the electron-withdrawing effects of formyl group in a conjugated position and

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Table 2. Compounds **5–27** prepared.

Product	Molecular formula[a]	^{1}H NMR[b] δ (J, Hz)	MS (70 eV) m/z (rel. intensity, %)
5	$C_{10}H_{11}N_3O$ (189.2)	9.59 (s, 1H), 6.86–6.84 (m, 2H), 6.45–6.43 (m, 2H), 3.66 (s, 3H), 2.50 (s, 3H)	189 (M^+, 100), 160 (25), 133 (11), 117 (14), 105 (3)
6	$C_9H_{10}N_4O$ (190.2)	9.62 (s, 1H), 7.74 (s, 1H), 7.33 (s, 1H), 7.18 (s, 1H), 3.68 (s, 3H), 2.51 (s, 3H)	190 (M^+, 27), 163 (100), 147 (11), 134 (9), 119 (13)
7	$C_9H_{10}N_4O$ (190.2)	9.66 (s, 1H), 7.83–7.81 (m, 2H), 6.54–6.51 (m, 1H), 3.76 (s, 3H), 2.46 (s, 3H)	190 (M^+, 82), 162 (41), 147 (25), 120 (29)
8	$C_{14}H_{13}N_3O$ (239.2)	9.52 (s, 1H), 7.74–7.70 (m, 1H), 7.30–7.12 (m, 4H), 6.83–6.81 (m, 1H), 3.58 (s, 3H), 2.56 (s, 3H)	239 (M^+, 56), 210 (24), 167 (20), 139 (9), 119 (13)
9	$C_{10}H_{15}N_3O$ (193.2)	9.86 (s, 1H), 3.69 (s, 3H), 3.49–3.42 (m, 4H), 2.39 (s, 3H), 2.04–2.00 (m, 4H)	193 (M^+, 100), 164 (27), 150 (59), 137 (23)
10	$C_{10}H_{15}N_3O_2$ (209.2)	9.96 (s, 1H), 3.85–3.81 (m, 4H), 3.71 (s, 3H), 3.20–3.16 (m, 4H), 2.41 (s, 3H)	209 (M^+, 21), 191 (65), 178 (28), 162 (17)
11	$C_8H_{13}N_3O$ (167.2)	9.88 (s, 1H), 3.61 (s, 3H), 2.85 (s, 6H), 2.34 (s, 3H)	167 (M^+, 100), 152 (85), 150 (61), 136 (22)
12	$C_6H_8N_2O$ (124.1)	9.86 (s, 1H), 7.81 (s, 1H), 3.88 (s, 3H), 2.48 (s, 3H)	124 (M^+, 100), 82 (6)
13	$C_{12}H_{12}N_2O_2$ (216.2)	9.52 (s, 1H), 7.40–7.32 (m, 2H), 7.21–7.13 (m, 1H), 7.03–6.98 (m, 2H), 3.64 (s, 3H), 2.46 (s, 3H)	216 (M^+, 53), 188 (100), 124 (24)

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14	$C_{12}H_{12}N_2OS$ (232.3)	10.01 (s, 1H), 7.33–7.22 (m, 2H), 7.13–7.08 (m, 3H), 3.80 (s, 3H), 2.52 (s, 3H)	232 (M^+, 21), 204 (84), 176 (23), 124 (18)
15	$C_{14}H_{12}N_4O$ (252.2)	9.70 (s, 1H), 7.58 (s, 1H), 7.32–7.29 (m, 2H), 7.09–7.04 (m, 3H), 7.15 (s, 1H), 6.96 (s, 1H), 2.53 (s, 3H)	252 (M^+, 43), 225 (81), 210 (11), 196 (7), 143 (18)
16	$C_{14}H_{12}N_4O$ (252.2)	9.65 (s, 1H), 8.17 (s, 1H), 7.84 (s, 1H), 7.54–7.40 (m, 3H), 7.16–7.13 (m, 2H), 6.59 (s, 1H), 3.34 (s, 3H)	252 (M^+, 2), 249 (9), 223 (3), 209 (18), 143 (23)
17	$C_{15}H_{17}N_3O$ (255.3)	9.96 (s, 1H), 7.48–7.36 (m, 5H), 3.31–3.23 (m, 4H), 2.49 (s, 3H), 1.90–1.82 (m, 4H)	255 (M^+, 71), 226 (24), 212 (39), 184 (14)
18	$C_{15}H_{17}N_3O_2$ (271.3)	9.97 (s, 1H), 7.52–7.38 (m, 5H), 3.68 (t, 4H, $J = 4.5$), 3.15 (t, 4H, $J = 4.8$), 2.47 (s, 3H)	271 (M^+, 59), 240 (72), 211 (100), 183 (73)
19	$C_{13}H_{15}N_3O$ (229.2)	9.93 (s, 1H), 7.52–7.44 (m, 2H), 7.44–7.39 (m, 3H), 2.78 (s, 6H), 2.33 (s, 3H)	229 (M^+, 5), 212 (19), 197 (12), 171 (9), 144 (9)
20	$C_{17}H_{14}N_2O_2$ (278.3)	9.51 (s, 1H), 7.55 (d, 2H, $J = 6.0$), 7.35–7.26 (m, 8H), 2.47 (s, 3H)	278 (M^+, 21), 250 (52), 186 (18), 143 (20)
21	$C_{13}H_{11}N_5O$ (253.2)	9.71 (s, 1H), 8.31–8.29 (m, 1H), 7.83 (dd, 1H, $J = 7.6, 1.8$), 7.74 (s, 1H), 7.62 (d, 1H, $J = 7.6$), 7.30–7.22 (m, 1H), 7.21 (s, 1H), 7.16 (s,1H), 2.61 (s, 3H)	253 (M^+, 3), 224 (36), 210 (9), 184 (10), 156 (14), 145 (19)
22	$C_{13}H_{11}N_5O$ (253.2)	9.80 (s, 1H), 8.74 (d, 1H, $J = 3.0$), 7.93 (m, 1H), 7.91–7.80 (m, 1H), 7.48 (d, 1H, $J = 9.0$), 7.29 (t, 1H, $J = 6.2$), 6.51–6.42 (m, 1H), 2.63 (s, 3H)	253 (M^+, 33), 225 (100), 224 (76), 197 (41), 184 (52)

(*continued*)

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Table 2. Continued.

Product	Molecular formula[a]	^{1}H NMR[b] δ (J, Hz)	MS (70 eV) m/z (rel. intensity, %)
23	$C_{14}H_{16}N_4O$ (256.3)	9.98 (s, 1H), 8.51 (dd, 1H, $J = 7.8, 1.6$), 7.88–7.82 (m, 1H), 7.62 (d, 1H, $J = 8.0$), 7.30–7.27 (m, 1H), 3.36 (t, 4H, $J = 6.5$), 2.46 (s, 3H), 1.94–1.88 (m, 4H)	256 (M^+, 3), 227 (3), 213 (4), 199 (3), 118 (18), 78 (100)
24	$C_{15}H_{18}N_4O$ (270.3)	9.93 (s, 1H), 8.55–8.53 (m, 1H), 7.82–7.79 (m, 1H), 7.59–7.57 (m, 1H), 7.28–7.24 (m, 1H), 3.12 (d, 4H, $J = 2.9$), 2.43 (s, 3H), 1.55 (s, 3H)	270 (M^+, 44), 241 (32), 212 (19), 160 (31), 145 (69)
25	$C_{14}H_{16}N_4O_2$ (272.3)	9.85 (s, 1H), 8.48–8.46 (m, 1H), 7.78–7.75 (m, 1H), 7.55 (d, 1H, $J = 9.0$), 7.23–7.21 (m, 1H), 3.64 (t, 4H, $J = 3.3$), 3.13 (t, 4H, $J = 3.1$), 2.37 (s, 3H)	272 (M^+, 17), 241 (15), 213 (17), 185 (21), 158 (24)
26	$C_{15}H_{19}N_5O$ (285.3)	9.85 (s, 1H), 8.58–8.56 (m, 1H), 8.05–7.99 (m, 1H), 7.64 (d, 1H, $J = 9.0$), 7.49–7.45 (m, 1H), 3.10 (t, 4H, $J = 4.8$), 2.34 (s, 3H), 2.30 (t, 4H, $J = 4.8$), 2.15 (s, 3H)	285 (M^+, 32), 268 (11), 228 (13), 215 (100), 228 (13), 215 (100), 200 (25)
27	$C_{12}H_{14}N_4O$ (230.2)	9.95 (s, 1H), 8.57 (d, 1H, $J = 3.1$), 7.90–7.84 (m, 1H), 7.63–7.61 (m, 1H), 7.33–7.28 (m, 1H), 2.94 (s, 6H), 2.47 (s, 3H)	230 (M^+, 36), 215 (15), 187 (28), 160 (24)

[a]Satisfactory microanalyses obtained: C $\pm$ 0.31, H $\pm$ 0.18, N $\pm$ 0.23.
[b]$CDCl_3$.

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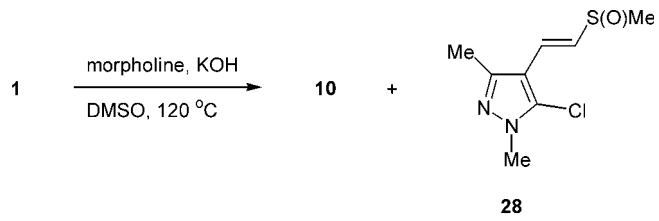

Scheme 2.

of the adjacent N-1 ring nitrogen. The rate of S_NAr reaction was greatly affected by the electronic nature of the N-1 substituted pattern.

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