A new leaving group in nucleophilic aromatic substitution reactions (S_NAr)

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Nucleophilic aromatic substitution of a 2,4-dinitrophenyl substituted pyrazole **1** with primary amines leads to substitution of the pyrazolo substituent. In these nucleophilic aromatic substitution reactions (S_NAr), 5-amino-1*H*-4-pyrazolecarbonitrile (**3**) acts as a new leaving group.

Keywords: nucleophilic aromatic substitution, leaving group, pyrazole, primary amines

While studying the cyclocondensation reaction of 5-amino-1-(2,4-dinitrophenyl)-1*H*-pyrazole-4-carbonitrile **1** with ethylenediamine in the presence of carbon disulfide to construct an imidazole ring **4**, we observed that the pyrazolo substituent was fairly easily substituted by the diamine (Scheme 1), reminiscent of the nucleophilic aromatic substitution reactions (S_NAr)[1] of 2,4-dinitrochlorobenzene with amines.[2] The success of S_NAr reactions is mainly dependent upon the presence of strongly electron-withdrawing groups in the substrate to stabilise the negative charge in the intermediate anion formed along the reaction path. The stabilising power can be estimated from the δ_p values of the different groups.[3] In the presence of mild electron-withdrawing groups, harsh conditions like high pressure (up to 10^3 M Pa)[4] or long reaction times and high temperatures in dipolar aprotic solvents like DMSO or DMF are needed.[5-6] The greater reactivity of the aryl halides containing strong electron-withdrawing groups reflects an *ipso*-substitution in which the attachment of the nucleophile to the aromatic ring is the rate determining step.[7]

In nucleophilic aromatic substitution the common leaving groups are halides (X) and the leaving group order F >> Cl > Br is commonly observed when activated aromatic derivatives such as 1-X-2,4-dinitrobenzene or 1-X-4-nitrobenzene are subjected to nucleophilic substitution.[7]

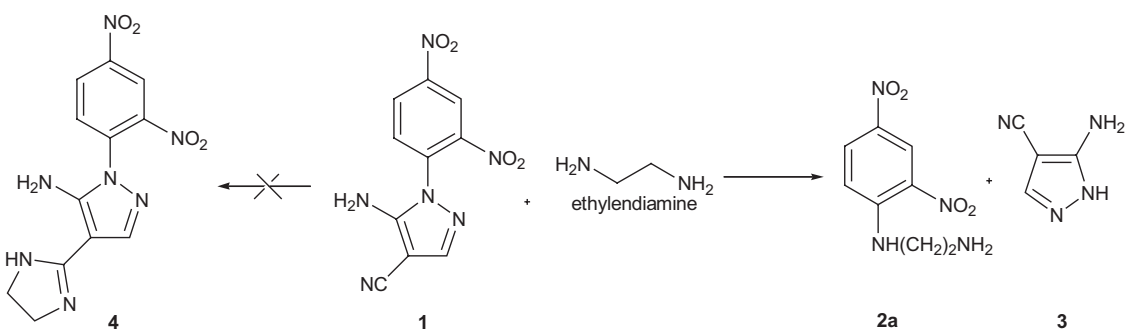
Apart from halides, other potential leaving groups such as amine derivatives[8-9] have been used in S_NAr reactions. Also aminotriazoles[10] have been used as leaving groups in some vicarious nucleophilic substitution (VNS) reactions. We now report on pyrazole as a new leaving group in S_NAr reactions.

In order to study further the leaving potential of the pyrazolo substituent towards nucleophiles, we examined the reaction of 2,4-dinitrophenyl substituted pyrazole **1** with primary amines in refluxing ethanol. All these reactions occurred to give the corresponding substituted products **2a–j**. The compounds **2g–j** are derivatives formed (Scheme 2).

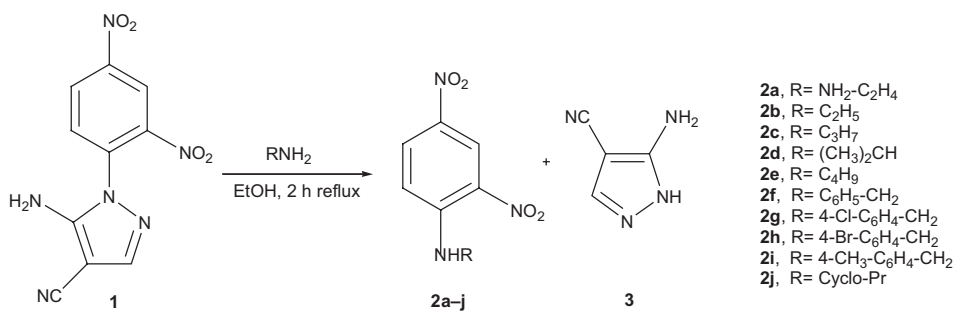
In contrast, weaker nucleophiles such as aryl amines as well as bulkier nucleophiles, like secondary amines *e.g.* morpholine or pyrrolidine, failed to replace the pyrazolo substituent. A rough estimation based on TLC testing indicated that the pyrazolo substituent possibly has a similar leaving ability to chloride ion in S_NAr reactions.

The intrinsic leaving potential of the pyrazolo substituent is attributable to the electron-withdrawing inductive and mesomeric effects exerted by the nitrogen atoms and the nitrile moiety.

Note that unlike aryl halides, 2, 4-dinitrophenyl substituted pyrazole **1** on subjection to non-anionic polarisable nucleophiles in S_NAr reactions does not produce hydrogen halide in the



Scheme 1



Scheme 2

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course of the reaction. Therefore the pH value of the reaction mixture is not altered and the protonation of the nucleophile does not occur. Another feature of this reaction is the high solubility in ethanol of the separated pyrazole **3** which allows the easy work-up of the reaction mixture.

In summary, we have introduced a new leaving group in S_NAr reactions with relatively high leaving potential and no impact on the pH value of the reaction mixture, therefore leaving the nucleophile free from protonation so that it can function effectively.

Experimental

Melting points were recorded on an Electrothermal type 9100 melting point apparatus. The ^{1}H NMR (100 MHz) spectra were recorded on a Bruker AC 100 spectrometer. Chemical shifts are reported in ppm downfield from TMS as internal standard; coupling constants *J* are given in Hertz. The mass spectra were scanned on a Varian. Mat CH-7 at 70 eV. Elemental analysis was performed on a Thermo Finnigan Flash EA microanalyser.

Compound **1** was obtained according to the published method.[11] Other reagents were commercially available.

General procedure for the synthesis of **2a–j**

To a solution of **1** (3.65 mmol) in EtOH (20 ml), ethylendiamine (3.9 mmol) was added. The solution was refluxed for 2 h and then poured into water. The precipitate was collected by filtration and recrystallised from EtOH to give **2a.**

N-1-(2,4-dinitrophenyl)-1,2-ethanediamine **(2a):** Yellow crystals (EtOH), yield (90%), m.p. 146–148 °C (Lit. m.p. 145–147 °C);[12] ^{1}H NMR (100 MHz, acetone-d_6) δ 2.98 (br s, 2H), 3.45–4.85 (m, 4H), 7.35 (d, *J* = 10.0 Hz, 1H), 8.35 (dd, *J* = 10.0, 4.5 Hz, 1H), 8.65 (br s, 1H), 8.96 (d, *J* = 4.5 Hz, 1H). MS (*m/z*) 226 (M^+). Found: C, 42.8; H, 4.5; N, 25.0. Calcd. for $C_8H_{10}N_4O_4$ (226.2): C, 42.48; H, 4.46; N, 24.77.

N-(2,4-dinitrophenyl)-N-ethylamine **(2b):** Yellow crystals (EtOH), yield (82%), m.p. 110–112 °C (Lit. m.p. 114–115 °C)[13]; ^{1}H NMR (100 MHz, acetone-d_6) δ 1.35 (t, *J* = 9.0 Hz, 3H), 3.55–3.75 (m, 2H), 7.37 (d, *J* = 10.0 Hz, 1H), 8.29 (dd, *J* = 10.0, 4.5 Hz, 1H), 8.75 (br s, 1H), 8.92 (d, *J* = 4.5 Hz, 1H). MS (*m/z*) 211 (M^+). Found: C, 45.3; H, 4.3; N, 20.1. Calcd. for $C_8H_9N_3O_4$ (211.2): C, 45.50; H, 4.30; N, 19.90.

N-(2,4-dinitrophenyl)-N-propylamine **(2c):** Yellow crystals (EtOH), yield (86%), m.p. 101–103 °C (Lit. m.p. 99–101 °C)[14]; ^{1}H NMR (100 MHz, acetone-d_6) δ 1.21 (t, *J* = 9.0 Hz, 3H), 1.45–1.77 (m, 2H), 3.45–3.65 (m, 2H), 7.38 (d, *J* = 10.0 Hz, 1H), 8.28 (dd, *J* = 10.0, 4.5 Hz, 1H), 8.75 (br s, 1H), 8.91(d, *J* = 4.5 Hz, 1H). MS (*m/z*) 225 (M^+). Found: C, 47.6; H, 4.8; N, 18.90. Calcd. for $C_9H_{11}N_3O_4$ (225.2): C, 48.00; H, 4.92; N, 18.66.

N-(2,4-dinitrophenyl)-N-isopropylamine **(2d):** Yellow crystals (EtOH), yield (71%), m.p. 92–94 °C (Lit. m.p. 94–95 °C)[14]; ^{1}H NMR (100 MHz, acetone-d_6) δ 1.14 (d, *J* = 9.0, 6H), 3.53–3.71 (m, 1H), 7.37 (d, *J* = 10.0 Hz, 1H), 8.29 (dd, *J* = 10.0, 4.5 Hz, 1H), 8.75 (br s, 1H), 8.92 (d, *J* = 4.5 Hz, 1H). MS (*m/z*) 225 (M^+). Found: C, 47.9; H, 4.9; N, 18.9. Calcd. for $C_9H_{11}N_3O_4$ (225.2): C, 48.00; H, 4.92; N, 18.66.

N-butyl-N-(2,4-dinitrophenyl)amine **(2e):** Yellow crystals (EtOH), yield (83%), m.p. 87–90 °C (Lit. m.p. 89–90 °C)[15]; ^{1}H NMR (100 MHz, acetone-d_6) δ 0.98 (t, *J* = 9.0 Hz, 3H), 1.35–1.86 (m, 4H), 3.47–3.67 (m, 2H), 7.35 (d, *J* = 10.0 Hz, 1H), 8.34 (dd, *J* = 10.0, 4.5 Hz, 1H), 8.74 (br s, 1H), 8.95(d, *J* = 4.5 Hz, 1H). MS (*m/z*) 239 (M^+). Found: C, 49.9; H, 5.4; N, 17.7. Calcd. for $C_{10}H_{13}N_3O_4$ (239.2): C, 50.21; H, 5.48; N, 17.56.

N-benzyl-N-(2,4-dinitrophenyl)amine **(2f):** Yellow crystals (EtOH), yield (90%), m.p. 109–111 °C (Lit. m.p. 107–109 °C)[14]; ^{1}H NMR (100 MHz, acetone-d_6) δ 4.88 (d, *J* = 9.5 Hz, 2H), 7.18 (d, *J* = 10.0 Hz, 1H), 7.23–7.52 (m, 5H), 8.14 (dd, *J* = 10.0, 4.5 Hz, 1H), 8.93(d, *J* = 4.5 Hz, 1H), 9.19 (br s, 1H),. MS (*m/z*) 273 (M^+). Found: C, 57.35; H, 4.2; N, 23.7. Calcd. for $C_{13}H_{11}N_3O_4$ (273.2): C, 57.14; H, 4.06; N, 23.42.

N-(4-chlorobenzyl)-N-(2,4-dinitrophenyl)amine **(2g):** Yellow crystals (EtOH), yield (81%), m.p. 135–137 °C; ^{1}H NMR (100 MHz, acetone-d_6) δ 4.91 (d, *J* = 9.5 Hz, 2H), 7.16 (d, *J* = 10.0 Hz, 1H), 7.25 (d, *J* = 9.50 Hz, 2H), 7.31 (d, *J* = 9.50 Hz, 2H), 8.17 (dd, *J* = 10.0, 4.5 Hz, 1H), 8.95(d, *J* = 4.5 Hz, 1H), 9.17 (br s, 1H),. MS (*m/z*) 307 (M^+). Found: C, 50.55; H, 3.3; N, 13.8. Calcd. for $C_{13}H_{10}ClN_3O_4$ (307.7): C, 50.75; H, 3.28; N, 13.66.

N-(4-bromobenzyl)-N-(2,4-dinitrophenyl)amine **(2h):** Yellow crystals (EtOH), yield (83%), m.p. 137–139 °C; ^{1}H NMR (100 MHz, acetone-d_6) δ 4.92 (d, *J* = 9.5 Hz, 2H), 7.17 (d, *J* = 10.0 Hz, 1H), 7.26 (d, *J* = 9.50 Hz, 2H), 7.32 (d, *J* = 9.50 Hz, 2H), 8.15 (dd, *J* = 10.0, 4.5 Hz, 1H), 8.93(d, *J* = 4.5 Hz, 1H), 9.19 (br s, 1H),. MS (*m/z*) 287 (M^+). Found: C, 43.95; H, 2.7; N, 12.2. Calcd. for $C_{13}H_{10}BrN_3O_4$ (287.3): C, 44.34; H, 2.86; N, 11.93.

N-(2,4-dinitrophenyl)-N-(4-methylbenzyl)amine **(2i):** Yellow crystals (EtOH), yield (89%), m.p. 125–127 °C; ^{1}H NMR (100 MHz, acetone-d_6) δ 2.68 (s, 3H), 4.90 (d, *J* = 9.5 Hz, 2H), 7.19 (d, *J* = 10.0 Hz, 1H), 7.23 (d, *J* = 9.50 Hz, 2H), 7.28 (d, *J* = 9.50 Hz, 2H), 8.18 (dd, *J* = 10.0, 4.5 Hz, 1H), 8.97(d, *J* = 4.5 Hz, 1H), 9.15 (br s, 1H),. MS (*m/z*) 352 (M^+). Found: C, 58.3; H, 4.4; N, 14.9. Calcd. for $C_{14}H_{13}N_3O_4$ (352.1): C, 58.53; H, 4.56; N, 14.63.

N-cyclopropyl-N-(2,4-dinitrophenyl)amine **(2j):** Yellow crystals (EtOH), yield (71%), m.p. 115–117 °C; ^{1}H NMR (100 MHz, acetone-d_6) δ 0.65–0.79 (m, 4H), 0.91–1.12 (m, 1H), 7.55 (d, *J* = 10.0 Hz, 1H), 8.35 (dd, *J* = 10.0, 4.5 Hz, 1H), 8.65 (br s, 1H), 8.91 (d, *J* = 4.5 Hz, 1H). MS (*m/z*) 223 (M^+). Found: C, 48.2; H, 3.9; N, 19.1. Calcd. for $C_9H_9N_3O_4$ (223.2): C, 48.43; H, 4.06; N, 18.83.

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