First Nucleophilic Aromatic Substitution of Annelated Pyrazole

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Abstract: 3-Chloropyrazolo[3,4-*c*]quinoline **5**, 3-chloropyrazolo[3,4-*c*]isoquinoline **6**, 1,2-dihydro-1,2-dimethylpyrazolo[3,4-*c*]quinolin-3-one **8,** and 1,2-dihydro-1,2-dimethylpyrazolo[3,4-*c*]isoquinolin-3-one **10** were obtained by acid-induced nucleophilic aromatic substitution (S_NH) of H-3 in *N*-hydroxypyrazolo[3,4-*c*]quinoline **1b** and in *N*-hydroxy pyrazolo[3,4-*c*]isoquinoline **3b**. In the acid-induced chlorination, **3b** was far more reactive than **1b**, whereas the related *N*-hydroxypyrazolo[4,3-*c*]quinoline **2b** and *N*-hydroxypyrazolo[4,3-*c*]isoquinoline **4b** were completely unreactive toward S_NH under identical conditions.

Nucleophilic aromatic substitution of hydrogen (S_NH) constitutes a valuable method for functionalization of heterocycles.[1] While S_NH of six-membered aza-aromatics is widespread, it is less so for the five-membered ring systems. Chichibabin amination of condensed imidazoles[2] and S_NH in triazole *N*-oxides[3,4] and indoles[5] are the only systematically studied examples. Pyrazoles, in particular, show very little susceptibility to S_NH. In the few known cases, the presence of a nitro group[6] or O-activation of pyrazole *N*-oxides[7] was needed to promote attack by a nucleophile. To our knowledge, S_NH of a fused pyrazole has not been reported.

We recently described the synthesis of 1-hydroxy-substituted pyrazolo[3,4-*c*]- and pyrazolo[4,3-*c*]quinolines and corresponding isoquinolines **1**−**4b** from 4- and 5-aryl-substituted 1-benzyloxypyrazoles (Figure 1).[8] An interesting observation was made when we attempted to develop a debenzylation method to access **1**−**4b** from **1**−**4a**. Treatment of **1a** with concentrated HCl at 80 °C for 16 h gave the 3-chloropyrazoloquinoline **5** (Scheme 1) instead of the expected debenzylation product **1b**. This contrasts strikingly with the HCl-induced debenzylation

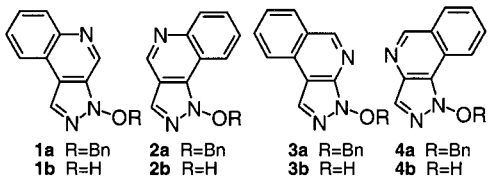


Figure 1.

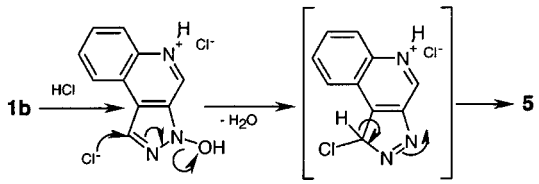
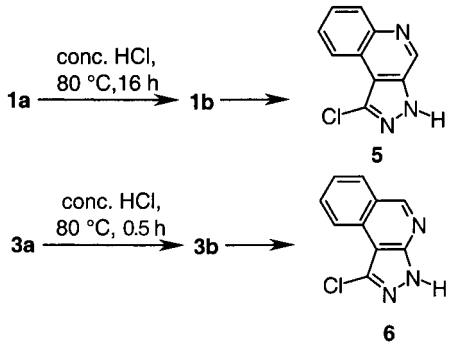


Figure 2. Proposed mechanism for S_NH of **1b**.

Scheme 1



of monocyclic 1-(benzyloxy)pyrazoles, which cleanly leads to 1-hydroxypyrazoles.[9] Treatment of *N*-hydroxypyrazole **1b**[10] with concentrated HCl also gave **5** (Scheme 1). Thus, **5** is likely formed via a formal S_N2' displacement of OH in **1b** with Cl^- as nucleophile, as shown in Figure 2. Acidic conditions were crucial in allowing attack of nucleophile at C-3. Thus, methanolic sodium methoxide gave no reaction with **1a** after 1 h at 60 °C. If Bn in **1a** was replaced for the better leaving Ts group, methoxide ion attacked the sulfonyl group instead of the ring, as observed for monocyclic *N*-tosyloxypyrazoles.[11] Compounds **2**−**4b** were then treated with concentrated HCl the same way as **1b**. Pyrazolo[3,4-*c*]isoquinoline **3b** was by far more reactive toward HCl than **1b**, giving the C-3 chlorinated **6** as the only product after 30 min (Scheme 1), whereas **2b** and **4b** returned only starting materials under these conditions.[12] Interestingly, heating of either **3a** or **3b** to 80−100 °C in concentrated HBr forced departure of the oxy substituent at N-1. Nevertheless, concurrent C-3 bromination was never observed in these reactions, even under drastic conditions. On the other hand, similar HBr treatment of **1a** provided **1b** cleanly.[8]

The S_NH of **1**−**4b** was further investigated using MeOH as nucleophile. Treatment of **1b** with 10% H_2SO_4

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(10) 1-(Benzyloxy)pyrazoles **1**−**4a** are selectively debenzylated to give **1**−**4b** using concentrated H_2SO_4; see ref 8.
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(12) Decomposition instead of the expected C-3 chlorinated products was observed when temperature was raised to 100 °C and the reaction time was prolonged.

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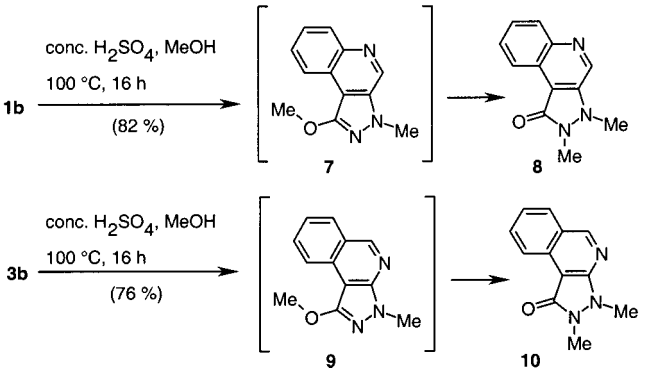
Scheme 2



in refluxing methanol, conditions employed successfully in other heterocyclic systems,[13] gave no reaction. However, harsh treatment (conc H_2SO_4 - MeOH at 100 °C for 16 h) did allow acid-induced S_NH of **1b** and dimethylpyrazolo[3,4-*c*]quinolin-3-one **8** was isolated in 82% yield as the only product (Scheme 2). The isolated compound was unambiguously assigned as **8** with the aid of the characteristic ^{13}C NMR shift values of the two methyl groups (35.33 ppm, 28.83 ppm), these are in keeping with the values reported for the related 1,2-dimethyl-5-nitroindazol-3-one (35.48 ppm, 28.97 ppm).[14] Although the tautomeric 1-methyl-3-methoxy-pyrazolo[3,4-*c*]quinoline **7** was not isolated,[15] it could very well be the intermediate initially formed by MeOH attack at C-3, followed by dehydration/N-1 methylation with a mechanism at work similar to that proposed in Figure 2 for the reaction of **1b** with HCl. The isolated pyrazolone **8** is possibly the product of the subsequent *O,N*-alkyl shift. These conditions (conc H_2SO_4 - MeOH at 100 °C for 16 h) were then also tried for **2**−**4b**. Reaction of **3b** afforded 1,2-dimethyl-1,2-dihydro-pyrazolo[3,4-c]isoquinolin-3-one **10** (with Me signals at 33.53 ppm, 28.99 ppm) in 76% yield (Scheme 2). The presumed intermediate (**9**) of initial MeOH attack at C-3 was not detected. Similarly as observed in reaction with conc HCl, **2b** and **4b** did not undergo S_NH at C-3 at all, returning only starting material, and extensive degradation resulted upon prolonged reaction times.

In summary, acid-induced nucleophilic substitution of hydrogen in an annelated pyrazole system was observed for the first time. 3-Chloropyrazolo[3,4-*c*]quinoline **5**, 3-chloropyrazolo[3,4-*c*]isoquinoline **6**, 1,2-dimethyl-1,2-dihydropyrazolo[3,4-*c*]quinolin-3-one **8,** and 1,2-dimethyl-1,2-dihydropyrazolo[3,4-*c*]isoquinolin-3-one **10** were accessed starting from *N*-hydroxypyrazolo[3,4-*c*]quinoline **1b** and *N*-hydroxypyrazolo[3,4-*c*]isoquinoline **3b**, while *N*-hydroxypyrazolo[4,3-*c*]quinoline **2b** and *N*-hydroxypyrazolo[4,3-*c*]isoquinoline **4b** did not undergo S_NH under the same conditions.

(13) Under these conditions, (±)-1-acetyloxytryptophan methyl ester was methoxylated at C-5 in 71% yield: Somei, M.; Fukui, Y. *Heterocycles* **1993**, *36*, 1859.

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(15) The two Me groups of **7** could be expected to have ^{13}C NMR shift values ca. 56.50 ppm (OMe) and 35.46 ppm (NMe), as observed for 3-methoxy-1-methyl-5-nitroindazolone; see ref 14.

Experimental Section

General Considerations. Compounds **1**−**4a** and **1**−**4b** were prepared as previously reported.[8] All solvents and reagents were commercially available and used without further purification. Elemental analyses were performed by Microanalytical Laboratory, Department of Physical Chemistry, University of Vienna, Austria. Melting points are uncorrected. LC−MS analyses were obtained on a Hewlett-Packard 1100 system, binary pump, degasser, injector, column oven, and DAD detector and MSD single quadrupole mass spectrometer. NMR spectra were recorded on a 300 MHz Bruker or Varian spectrometer with tetramethylsilane as internal standard.

3-Chloropyrazolo[3,4-*c*]quinoline (5). A solution of **1b** (52 mg, 0.3 mmol) in concentrated HCl (5 mL) was heated to 80 °C for 16 h, and then the pH of the reaction was adjusted to pH 10 with 4 M NaOH and extracted with diethyl ether (3 × 20 mL). The combined organic layers were $MgSO_4$ dried and concentrated. Chromatographic purification (silica gel, 20% EtOAc in petroleum ether) gave **5** (51 mg, 84%) as off-white crystals: mp >300 °C (EtOAc); R_f (EtOAc/*n*-heptane, 2/1) 0.27; NMR δ_H (300 MHz, CD_3OD) 9.15 (1H, s), 8.72 (1H, d, J = 8.8 Hz), 8.18 (1H, d, J = 8.8 Hz), 7.81−7.69 (2H, m); NMR δ_C (75 MHz, DMSO-d_6) 142.2, 138.7, 136.1, 132.5, 130.0, 128.3, 127.3, 121.7, 120.7, 116.2; LC−MS *m*/*z* 204.6 (MH^+). Anal. Calcd: C, 58.98; H, 2.97; N, 20.64. Found: C, 58.81; H, 2.97; N, 20.14.

3-Chloropyrazolo[3,4-*c*]isoquinoline (6). Similar treatment of **3b** (52 mg, 0.3 mmol) for 30 min followed by workup and purification afforded **6** (49 mg, 84%) as white crystals: mp 226−227 °C (MeOH); R_f (EtOAc/*n*-heptane, 2/1) 0.59; NMR δ_H (300 MHz, CD_3OD) 9.13 (1H, s), 8.68 (1H, d, J = 8.1 Hz), 8.18 (1H, d, J = 8.1 Hz), 7.93 (1H, dt, J = 7.7, 1.2 Hz) 7.69 (1H, dt, J = 7.7, 1.0 Hz); NMR δ_C (75 MHz, DMSO-d_6): 155.1, 149.2, 132.6, 131.7, 129.9, 128.8, 126.0, 125.0, 121.0; LC−MS *m*/*z* 204.6 (MH^+). Anal. Calcd: C, 58.98; H, 2.97; N, 20.64. Found: C, 59.01; H, 2.95; N, 20.22.

1,2-Dihydro-1,2-dimethylpyrazolo[3,4-*c*]quinolin-3-one (8). A solution of **1b** (52 mg, 0.3 mmol) in 10 mL of concentrated H_2SO_4 and 2 mL of MeOH was stirred at 100 °C and worked up as for **5**. Flash chromatography (FC) (EtOAc/*n*-heptane 1/1) gave **8** (49 mg, 82%) as green crystals: mp 188−189 °C (methanol); R_f (EtOAc/*n*-heptane/methanol, 4/1/1) 0.24; NMR δ_H (300 MHz, CD_3OD) 9.03 (1H, s), 8.62 (1H, d, J = 7.7 Hz), 8.03 (1H, d, J = 7.7 Hz), 7.72−7.60 (2H, m), 3.70 (3H, s), 3.61 (3H, s); NMR δ_C (75 MHz, CD_3OD) 161.7, 143.6, 141.6, 138.7, 130.2, 130.0, 128.4, 124.6, 123.6, 113.9, 35.3, 28.8; LC−MS *m*/*z* 214.4 (MH^+). Anal. Calcd: C, 67.59; H, 5.20; N, 19.71. Found: C, 67.61; H, 5.23; N, 19.60.

1,2-Dihydro-1,2-dimethylpyrazolo[3,4-*c*]isoquinolin-3-one (10). Following the procedure described for synthesis of **8** using **3b** (52 mg, 0.3 mmol), FC (EtOAc/*n*-heptane 1/1) gave **10** (45 mg, 76%) as yellow crystals: mp 218−219 °C (methanol); R_f (EtOAc/*n*-heptane/methanol, 4/1/1) 0.43; NMR δ_H (300 MHz, CD_3OD) 9.22 (1H, s), 8.61 (1H, d, J = 8.3 Hz), 8.14 (1H, d, J = 8.2 Hz), 7.89 (1H, dt, J = 7.6, 1.2 Hz), 7.60 (1H, dt, J = 7.6, 1.0 Hz), 3.70 (3H, s), 3.61 (3H, s); NMR δ_C (75 MHz, CD_3OD) 162.5, 159.4, 155.8, 134.4, 134.0, 130.7, 127.5, 126.8, 122.9, 100.2, 33.5, 29.0; LC−MS *m*/*z* 214.4 (MH^+).

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Supporting Information Available: Spectral data of compounds **5**, **6**, **8**, and **10**. This material is available free of charge via the Internet at http://pubs.acs.org.

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