Facile Synthesis of Polyhalo- and Nitro-pyrazines

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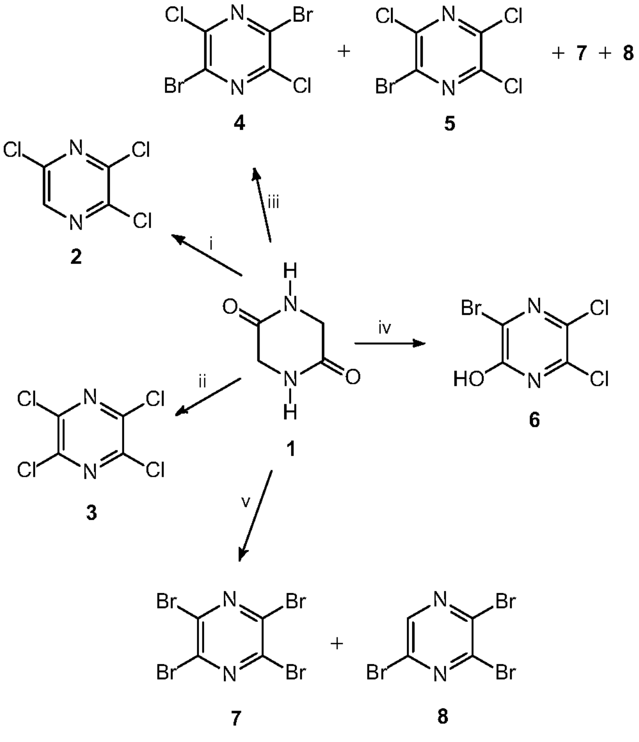
Tandem electrophilic halogenation or nitration and aromatization of 3,6-dihydropyrazines, either as starting material or formed *in situ* from 2,5-dioxopiperazine, provides a simple, facile pathway to polyhalo- and nitro-pyrazines.

In the course of our recent work on the design, synthesis and characterization of novel pharmaceuticals and agrochemicals,[1–5] we were interested in the synthesis of halopyrazines, which are precursors for our target molecules. Although halopyrazines have been studied for many years, their synthesis often requires relatively extreme conditions. Direct halogenation or nitration of the pyrazine ring is very difficult, especially for the introduction of several halogen atoms or nitro groups, and the methodology requires harsh conditions in either case. An alternative approach to halopyrazine synthesis involves treatment of oxopiperazines with phosphoryl chloride or bromide. Several modifications of this method have been reported for halopyrazine formation. However, most of these have proved unsatisfactory for the parent compound, 2,5-dioxopiperazine **1**.[6]

This readily available and attractive precursor, **1**, has now been used herein for the synthesis of polyhalo- and nitro-pyrazines.

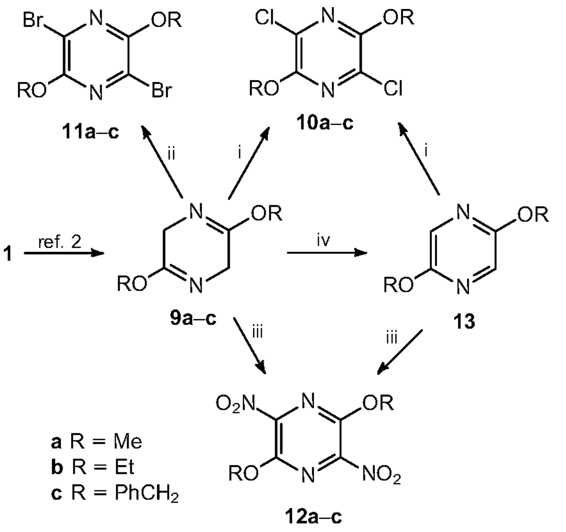
We report the interesting finding that the simple reaction of **1** with $POCl_3$, PCl_5, PBr_5 or their mixtures in the presence of chlorine or bromine can be used to synthesize tri- and tetra-halopyrazines (Scheme 1).



Scheme 1. *Reagents and conditions*: i, $POCl_3/PCl_5/Cl_2$, room temp.; ii, $POCl_3/PCl_5/Cl_2$, 20 °C → 104 °C; iii, $POCl_3/PCl_5/Br_2$, 40 °C → 104 °C; iv, $POCl_3/PCl_5/Br_2$, room temp.; v, PBr_5/Br_2/DMSO, 40 °C → 80 °C.

When compound **1** was treated with chlorine in a mixture of phosphoryl chloride and phosphorus pentachloride at 20 °C and the mixture was stirred for several hours, product **2** was obtained in 83% yield. Passage of chlorine through a similar mixture at an elevated temperature afforded **3** in 92% yield within 2 h. We have also demonstrated that the use of bromine in the analogous system is also effective, as illustrated by Scheme 1. In this case a more complex product mixture was obtained. The products **4**, **5**, **7** and **8** were isolated by silica gel chromatography in 12%, 28%, 7% and 9% yields, respectively. Treatment of **1** with a mixture of phosphorus pentabromide and excess bromine in dimethyl sulfoxide gives two compounds, of which **7** was the major product (65%) and **8** was the minor (21%).

Alkylation of **1**, thus fixing the reactive dihydro derivative, followed by halogenation or nitration resulted in electrophilic displacement and aromatization. The corresponding diagonally-substituted pyrazines resulted from this process.

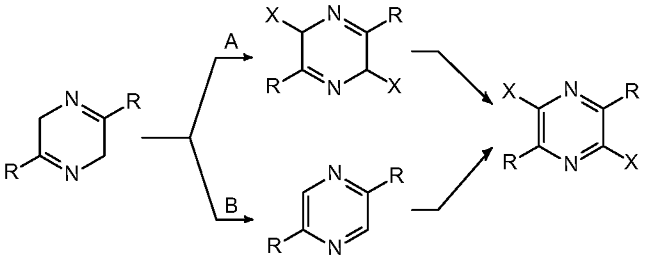


Scheme 2 *Reagents and conditions*: i, NCS, MeCN, reflux; ii, Br_2, MeCN, reflux; iii, N_2O_4, MeCN, 20 °C → 50 °C, or KNO_3, $(CF_3CO)_2O$, room temp.; iv, $FClO_3$, MeCN, 20 °C.

Thus, dichloro derivatives **10a–c** can be prepared by treatment of **9a–c** in acetonitrile for 1 h with *N*-chlorosuccinimide (NCS). However, the isolated yields in this reaction were only 40–65% and substantial insoluble by-product formation was also observed. In contrast, a similar reaction in chloroform was earlier found[7] to afford **13** in high yield, not chloro derivatives. It should be noted that compound **13b** also gave **10b** by chlorination in acetonitrile for 2.5 h in 15% yield. The conversion of **9a–c** into **11a–c** occurred on bromination with bromine in boiling acetonitrile. However, the yields of **11a–c** were about 30–40%. Such a brominating agent as *N*-bromosuccinimide gave a complicated mixture of products in the reaction. Fluorination of **9b** using perchloryl fluoride afforded no fluoro derivatives, only aromatization occurred in this case and **13** was formed in 87% yield.

An attempted nitration of both **9b** and **13b** using a mixture of concentrated nitric and sulfuric acids, conditions we successfully used earlier[8] in the nitration of 2-chloro-6-methoxypyrazine, caused extensive degradation of the starting materials. However, under mild conditions oxidative nitration of **9a,b** with nitrogen dioxide gave dinitro derivatives **12a,b**. A similar result arose from treatment with alkali nitrate in trifluoroacetic anhydride (trifluoroacetyl nitrate). These methods afforded a low yield of the product (about 30%). In contrast, under the same conditions aromatic compound **13b** gave **12b** in poor yield (8%). The nitration of **9c** was complicated by an additional nitration of the phenyl group. No attempt was made to optimize the yield of these nitropyrazines.[9]

The mechanism of the process is by no means certain: we could either have *in situ* formation and immediate reaction of 3,6-dihalo(nitro)-3,6-dihydropyrazine (route A); alternatively, initial aromatization could be expected (route B). However, the fact that dihydropyrazines easily and quickly yielded dihalo and dinitro derivatives rather than the corresponding pyrazines gave grounds for considering route A to be more preferable.



R = OAlk, Hal
X = Hal, NO_2

The structure of these compounds was confirmed by elemental analysis, MS, IR and ^1H and ^{13}C NMR spectroscopy.[†]

In conclusion, we have shown a straightforward method for polyhalopyrazine synthesis from available 2,5-dioxopiperazine. No previous study has established the possibility of such a simple and quick procedure for preparing these compounds. We assume that optimising the nitration procedure will also provide a convenient route to nitropyrazines.

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Received: Moscow, 6th June 1995
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[†] All new compounds gave satisfactory combustion analyses and accurate mass measurements. Some selected data: for **10b**, m.p. 101–102 °C; MS *m/z*: 237 (M^+), 209 ($M^+-C_2H_4$); ^1H NMR ($CDCl_3$) δ 1.40 (Me), 4.36 (CH_2); ^{13}C NMR ($CDCl_3$) δ 149.3 (*C*-OEt), 129.2 (*C*-Cl), 64.2 (CH_2), 14.3 (Me). For **11b**: m.p. 133–134.5 °C; MS *m/z*: 327 (M^+), 299 ($M^+-C_2H_4$); ^1H NMR ($CDCl_3$) δ 1.42 (Me), 4.38 (CH_2); ^{13}C NMR ($CDCl_3$) δ 161.5 (*C*-OEt), 131.5 (*C*-Br), 75.1 (CH_2), 24.3 (Me). For **12b**: m.p. 118–120 °C; MS *m/z*: 258 (M^+), 230 ($M^+-C_2H_4$); ^1H NMR ($CDCl_3$) δ 1.48 (Me), 4.55 (CH_2); ^{13}C NMR ($CDCl_3$) δ 144.3 (*C*-OEt), 139.4 (*C*-NO_2), 67.3 (CH_2), 14.35 (Me).