OXIDATION METHODS FOR AROMATIC DIAZINES. PART II. CHLORINATED PYRAZINE *N*-OXIDES

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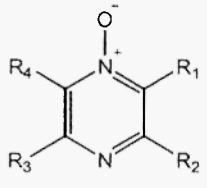
Abstract: Chlorinated pyrazines are directly oxidized to the *N*-oxides using dimethyldioxirane. The reactions were found to be completely regioselective and the products were easily isolated in good yields. These oxidations were comparable to the conversion of methylated pyrazines to pyrazine monoxides and dioxides described by us in part I. Oxidation with dimethyldioxirane in acetone overcomes problems associated with the isolation of hydrophilic pyrazine *N*-oxides obtained by using other oxidation reagents.

Introduction

In this work we describe a convenient and regioselective conversion of chlorinated pyrazines to chlorinated pyrazine *N*-oxides. In part I[1] we described the efficient conversion of methylated pyrazines and terpyridines to the mono- and di-*N*-oxides by using the reagent OXONE® / acetone (dimethyldioxirane). Dimethyldioxirane[2-5] (DMD) proved to be a convenient oxidizing agent for acetone soluble compounds. Herein we extend the methodology for the regioselective conversion of halogenated pyrazines to the halogenated pyrazine *N*-oxides.

Chlorinated pyrazines have been oxygenated previously to the *N*-oxides with varying success. The typical methods of oxygenation of *N*-heterocyclic compounds with hydrogen peroxide,[6-8] Caro's reagent,[9] sodium perborate,[10] and OXONE®[1] have significant disadvantages in the preparation of pyrazine *N*-oxides. The inherent solubility of the *N*-oxide in highly acidic and aqueous media makes isolation of the *N*-oxide problematic. The method described herein has the advantages of utilizing a commercially available oxidizing agent at ambient reaction conditions and eliminates the possibility of dangerous peroxide isolation. Caro's reagent is highly acidic and will provide complementary regioselectivity with less acidic oxygenation reactants such as OXONE® and DMD.



1a $R_1, R_3, R_4 = H$; R_2=Cl
1b $R_1, R_3 = CH_3$; R_2 = Cl; R_4=H
1c $R_1, R_4 = H$; R_2, R_3=Cl

Several mono- and dichlorinated pyrazines were selected to develop this methodology. Halogenation deactivates pyrazine to *N*-oxidation and the pyrazine ring is further deactivated by *N*-oxidation, therefore no dioxide was found in

the *N*-oxidation of chlorinated pyrazines with dimethyldioxirane. Other reagents such as trifluoroperacetic acid can be used to prepare chlorinated *N*,*N*-dioxides.[11] The oxidation of 2-chloropyrazine, 2,6-dichloropyrazine, and 3-chloro-2,5-dimethylpyrazine with dimethyldioxirane could in principle provide two isomeric pyrazine *N*-oxides in each case. All three of the above reactions were found to be completely regioselective. All reactions were monitored with GCMS to detect oxygenated isomers and extent of oxygenation. Previously, difficult isolation procedures involving aqueous phases provided poor isolated yields and the products were not easily characterized by GC. The use of dimethyldioxirane in acetone allowed the explicit isomeric distribution to be established.

2-Chloropyrazine 4-oxide (**1a**) was prepared in 91% yield, 2-chloro-3,6-dimethylpyrazine 4-oxide (**1b**) in 86% yield and 2,6-dichloropyrazine 4-oxide (**1c**) in 40% yield. As a result of the simplicity of the dimethyldioxirane oxygenation procedure the yields were comparable or better than most previously reported. Halogenated pyrazine *N*-oxides sublime very easily. In order to reduce the loss of yield the acetone was stripped as a pentane azeotrope. Several attempts to oxygenate 2,3-dichloropyrazine were unsuccessful. Calculated[12] PM3[13] Mulliken[14] charges at the nitrogens of 2,3-dichloropyrazine (–0.019 and -0.019) compared to the Mulliken charges of the parent nitrogens (–0.042 and –0.042) illustrate significant deactivation of the halogenated pyrazine to *N*-oxygenation. The nitrogen atoms of 2,6-dichloropyrazine have Mulliken values of -0.439 and -0.464 (6-31G**)[15] which are consistent with the oxygenation regioselectivity found in the experiment.

Pews and Mixan describe complementary mechanisms for the oxygenation of pyrazines using Caro's reagent and peroxyacids.[9] The mechanism recognized for the highly acidic conditions of the Caro's reagent involves protonation of the most basic nitrogen atom first allowing oxidation to take place on the remaining nitrogen of the pyrazine ring. In the less acidic medium of peroxyacid, nucleophilic attack on the peroxy oxygen by the most basic nitrogen on the heterocycle occurs first. Finally, in the mechanism put forth by Adam et al.[16] for oxygenation by dimethyldioxirane a nucleophilic attack by the most basic nitrogen via an S_N2 mechanism has been suggested. The observed regioselective formation of 2-chloropyrazine-4-oxide, 2,6-dichloropyrazine 4-oxide, and 2-chloro-3,6-dimethylpyrazine 4-oxide is consistent with previous work[8,9,11,17-20] and putative mechanisms.[9,16]

Conclusion

Oxygenation with dimethyldioxirane is an efficient and simple method to prepare monoxygenated chlorodiazines. The oxygenation regioselectivity is complementary to Caro's well established and highly acidic oxygenation procedure. This method alleviates many of the isolation problems associated with aqueous layers generated in the peroxide or Caro's method.

Experimental

Melting points were obtained with a Mel-Temp apparatus and are uncorrected. Infrared spectra were recorded on a Perkin Elmer Model 1725X spectrophotometer. ^{1}H NMR spectra (270 MHz) were determined on a Jeol-270 instrument. Gas chromatography/ mass spectroscopy was conducted on a Varian CP-3800 and Varian Saturn 2200 instruments using a CP-Sil 8 column (30m x .25μm). Solvents including acetone (ACS reagent grade) were obtained from Fisher. Potassium peroxymonosulfate was obtained from Aldrich. $CDCl_3$ (CIL or Aldrich) was stored over 3-Å sieves.

2-Chloropyrazine-4-oxide (1a). A solution of dimethyldioxirane in acetone (0.08 M, 34 mL) was stirred with 2-chloropyrazine (0.179 g, 1.56 mmol) at 25 °C for 42 h. A GC – MS analysis showed the presence of one isomer. The

solvent was removed *in vacuo* by azeotropic distillation with pentane. The remaining solid was dissolved in a large excess of dichloromethane (250 mL) and the solution was dried with anhydrous magnesium sulfate. Removal of the solvent *in vacuo* provided **1a** as a white solid (0.18 g, 91%); mp 93.8-95.0 °C (lit.[9] mp 94-95 °C). ^{1}H NMR 8.25 (m); MS m/z 130 (M^+ ,100%), 132 (M^+ 36%).

2-Chloro-3,6-dimethylpyrazine-4-oxide (1b). A solution of dimethyldioxirane in acetone (~0.08 M, 39.0 mL) was stirred with 3-chloro-2,5-dimethylpyrazine (0.254 g, 1.78 mmol) at 25 °C for 18 h. A GC – MS analysis showed the presence of one isomer. The solvent was removed *in vacuo* by azeotropic distillation with pentane. The remaining solid was dissolved in a large excess of dichloromethane (250 mL) and the solution was dried with anhydrous magnesium sulfate. Removal of the solvent *in vacuo* provided **1b** as an off-white solid (0.244 g, 1.54 mmol, 86%); mp 111.3-113.5 °C (lit.[9] mp 110-112°C). ^{1}H NMR 7.96 (s, 1H), 2.55 (s, 3H), 2.44 (s, 3H); MS m/z 142 (M^+, 100%), 144 (M^+, 36%), 107 (M^+ -35). The 1-oxide was prepared using Caro's reagent conditions for mp and spectra comparison.

2,6-Dichloropyrazine-4-oxide (1c). A solution of dimethyldioxirane in acetone (~0.08M, 41.0 mL) was stirred with 2,6-dichloropyrazine (0.098g, 0.66 mmol) at 25 °C for 48 h. A GC-MS analysis showed the presence of substrate (59%) and one product (**1c**, 40%). The solvent was removed *in vacuo* by azeotropic distillation with pentane. The remaining solid was dissolved in a large excess of dichloromethane (250 mL) and the solution was dried with anhydrous sodium sulfate. The removal of solvent *in vacuo* provided crude **1c** as a tan solid (0.116 g). The crude 2,6-dichloropyrazine-4-oxide was further purified by column chromatography to provide **1c** as an off-white solid (0.043 g, 0.26 mmol, 40%); mp 117-119 °C (lit.[9] mp 119-121 °C). Product **1c** can be further purified by crystallization from pentane; ^{1}H NMR 8.05 (s) [lit.[9] 8.02 (s)].

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