Tetrahedron Letters No.56, pp. 5931-5934, 1968. Pergamon Press. Printed in Great Britain.

# THE ABNORMAL NUCLEOPHILIC SUBSTITUTION OF 2-TRICHLOROMETHYLPYRAZINE AND 2-CHLORO-3-DICHLOROMETHYLPYRAZINE[1]

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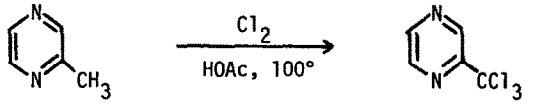
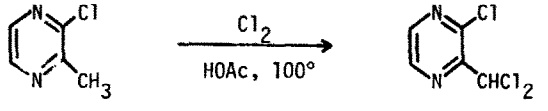
(Received in USA 15 July 1968; received in UK for publication 24 October 1968)

Recent reports concerning the biological activity of a variety of substituted pyrazines have prompted further interest in the development of synthetic methods for the preparation of this class of compounds.[2] This communication is a preliminary account of our studies concerning some unusual nucleophilic displacements which are relevant to the general problem of the synthesis of substituted pyrazines.

We have prepared 2-trichloromethylpyrazine (II) by chlorination of 2-methylpyrazine (I) in acetic acid at 100°.[3] 2-Chloro-3-dichloromethylpyrazine (IV) was prepared under the same conditions from 2-chloro-3-methylpyrazine (III).[4] Under these conditions no 2-chloro-3-trichloromethylpyrazine was formed, indicative of the steric crowding about the dichloromethyl group of IV.



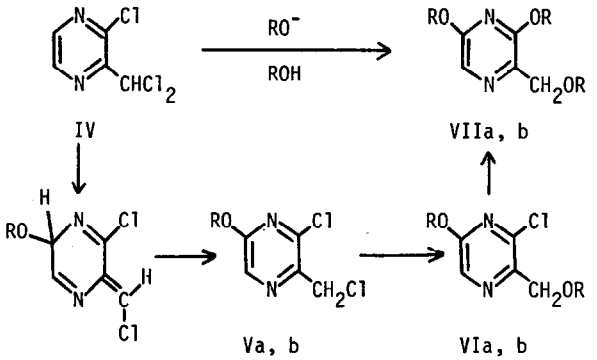

I II




III IV

Treatment of 2-chloro-3-dichloromethylpyrazine (IV) with three equivalents of methoxide ion in refluxing methanol afforded a quantitative yield of 3,5-dimethoxy-2-methoxymethylpyrazine (VIIa). No other products could be detected by nmr or vpc.[5] The nmr spectrum of VIIa

displayed singlets at τ 2.35 (ArH), 5.62 ($ArCH_2$), 6.05 and 6.10 (2 $ArOCH_3$), and 6.71 ($CH_2OCH_3$). We believe that the formation of VIIa involves a displacement of chloride ion from the dichloromethyl group of IV by attack of methoxide ion at $C_6$,[6] followed by proton transfer to yield Va, which undergoes an Sn2 displacement to afford VIa, which then undergoes an SnAr2 displacement to afford VIIa. In support of our postulated reaction path, IV reacted with: a) one equivalent of ethoxide ion in ethanol at 0° to afford Vb as the principal reaction product; b) two equivalents of ethoxide ion in ethanol at 25° to afford VIb as the principal reaction product; and c) three equivalents of ethoxide ion in refluxing ethanol to afford a quantitative yield of VIIb.

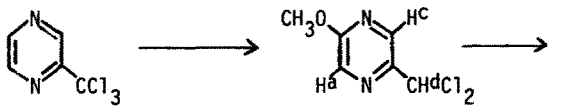



a. R = $CH_3$ b. R = $CH_3CH_2$

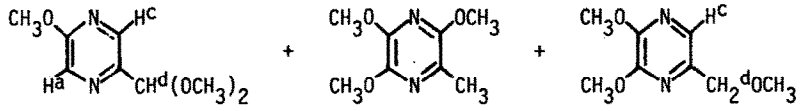
The initial abnormal nucleophilic displacement of chloride ion from IV, similar to that reported for other heterocyclic and aromatic compounds,[7] is a result of the susceptibility of the pyrazine ring to nucleophilic substitution,[8] the electron withdrawing nature of the substituents present in IV, and the steric bulk of these substituents which retards initial Sn2 displacement.

Treatment of 2-trichloromethylpyrazine (II) with three equivalents of methoxide ion in refluxing methanol afforded a quantitative yield of three isomeric pyrazines. The reaction mixture was analyzed by vpc.[5,9] The principal product, (75%) 2-dimethoxymethyl-5-methoxypyrazine (VIII), exhibited the following nmr spectrum: τ 1.80 ($ArH^c$, q, $J_{H^aH^c}$ = 1.5 Hz, $J_{H^cH^d}$ = 0.6 Hz), 1.92 ($ArH^a$, d, $J_{H^aH^c}$ = 1.5 Hz), 4.75 ($ArCH^d$, d, $J_{H^cH^d}$ = 0.6 Hz), 6.07 ($ArOCH_3$, s), 6.69 ($C(OCH_3)_2$, s). The $H^aH^c$ coupling constant is in accord with 2,5-substitution.[10] The second reaction product (15%) was 2,3,5-trimethoxy-6-methylpyrazine (IX). Its nmr spectrum

displayed four singlets of equal area at τ 6.12, 6.15, 6.17 and 7.79. No additional resonances were present in the spectrum. The third product (10%) was 2,3-dimethoxy-5-methoxymethylpyrazine (X), which exhibited the following nmr spectrum: τ 2.45 (Ar$\underline{H}^c$, t, $J_{HCHd}$ = 0.8 Hz), 5.66



II XI



VIII IX X

(Ar$\underline{CH}_2$O, d, $J_{HCHd}$ = 0.8 Hz), 6.05 (2 ArO$\underline{CH}_3$, apparent singlet), 6.60 ($CH_2O\underline{CH}_3$, s).

Subsequent treatment of II with one equivalent of methoxide ion in methanol at 5° yielded 2-dichloromethyl-5-methoxypyrazine (XI) as the only reaction product. Compound XI, an unstable colorless oil, was isolated by preparative vpc, and exhibited the following nmr spectrum: τ 1.48 (Ar$\underline{H}^c$, q, $J_{HaHc}$ = 1.4 Hz, $J_{HCHd}$ = 0.4 Hz), 1.93 (Ar$\underline{H}^a$, d, $J_{HaHc}$ = 1.4 Hz), 3.30 (Ar$\underline{CH}^dCl_2$ d, $J_{HCHd}$ = 0.4 Hz), 6.00 (ArO$\underline{CH}_3$, s). Reaction of XI with excess methoxide in refluxing methanol afforded products VIII, IX and X in the same yields as previously obtained.

A number of possible reaction paths for the formation of isomeric pyrazines VIII, IX and X can be formulated. These include various combinations of displacements (normal and abnormal), solvation of unsaturated bonds, elimination of hydrogen chloride and elimination of methanol. Evidence is being sought to differentiate among the various possibilities and to explain the absence of VIIa among the reaction products.

To our knowledge the initial abnormal nucleophilic displacement observed for II and IV is the first to be noted in the pyrazine series. As the principal, if not sole reaction path for these compounds it represents a potentially useful synthetic method. Currently we are studying the reactions of a variety of nucleophiles in an attempt to prepare substituted pyrazines hitherto not available or available only by more circuitous routes. A full report of these investigations will appear in the future.

## REFERENCES


1. The term "abnormal nucleophilic substitution" has been used to indicate a process of substitution with rearrangement. On the basis of our present data we are unable to differentiate between a concerted displacement (Sn2') or an addition-elimination process.

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3. All new compounds gave correct elemental analyses. Ir, uv, nmr and mass spectral data were in accord with proposed structures. Nmr spectra were taken in carbon tetrachloride solution using TMS as an internal standard.

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5. All alkoxy pyrazines were separated on a 1/4" x 15' 20% PDEAS column at 195° with a helium flow of 200 ml/min. SE 30, DC 200 and Carbowax 20M columns were also used.

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9. Vpc analysis on two separate columns, previously used to separate a variety of chloropyrazines, established a purity of 99+% for the 2-trichloromethylpyrazine. The trace impurity (<1%) was 2-chloro-3-dichloromethylpyrazine (IV) which gave a trace (<1%) of 3,5-dimethoxy-2-methoxymethylpyrazine (VIIa) in the reaction mixture.

10. R. H. Cox and A. A. Bothner-By, J. Phys. Chem., 72, 1642, 1646 (1968).