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Mass spectra of halogenostyrylbenzoxazoles

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Dedicated to Professors Keith R. Jennings and Jim Scrivens on the occasion of their 80th and 60th Birthdays, respectively, in recognition of their contributions to the development and application of experimental mass spectrometry in a wide range of scientific disciplines.

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Proximity effect
Halogen atom elimination

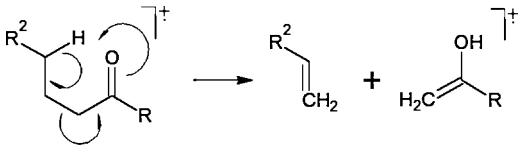
ABSTRACT

Several series of styrylbenzoxazoles of general formula $XC_6H_3(NCO)CH{=}CHC_6H_4Y$ [X = F, Cl or Br; Y = H, F, Cl, Br, CH_3 or CH_3O] have been investigated by positive ion electrospray and electron ionization mass spectrometry. These compounds, many of which are biologically active or have pharmaceutical potential, show in their electrospray spectra strong peaks for MH^+ ions, which undergo relatively little fragmentation. The electron ionization spectra are extremely clean, being dominated by the loss of an atom or radical, $Y^\bullet$, from the ortho position of the pendant ring, by a rearrangement that may be interpreted as a proximity effect. The resultant $[M-Y]^+$ ions are exceptionally stable and rarely undergo further fragmentation. The analytical value of this proximity effect, which is analogous to intramolecular aromatic substitution, in revealing the presence of a substituent in the pendant ring and determining its position, is emphasized. Elimination of a species (including $H^\bullet$ or $F^\bullet$) derived from an ortho substituent in the pendant ring occurs even when apparently more favourable alternative fragmentation is possible by direct cleavage of the C—X bond (X = Cl or Br) in the benzoxazole ring.

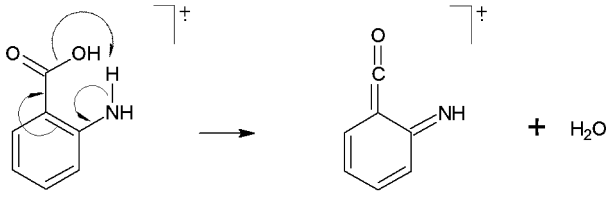
1. Introduction

Mass spectrometry has been applied in structure elucidation for at least six decades, but it is increasingly regarded in some quarters merely as a means of obtaining molecular mass or molecular formula information. Thus, even experienced organic chemists often erroneously believe that mass spectrometry can never reveal the substitution pattern of aromatic compounds. This misunderstanding is unfortunate, because it prevents maximum advantage being taken of the analytical value of mass spectrometry.

The importance of fragmentations that involve rearrangement was recognized early in the development of electron ionization (historically known as electron impact, EI) mass spectrometry. The McLafferty rearrangement [1,2] of ionized carbonyl compounds is a celebrated example (Eq. (1)). Ortho effects, as illustrated by the loss of H_2O from ionized 1,2-disubstituted benzenes such as anthranilic acid, $H_2NC_6H_4CO_2H$, and related species [3] (Eq. (2)) are another example of how rearrangements involving the interaction of separate parts of a molecular ion through space can provide extremely useful structural information by permitting orthodisubstituted aromatic compounds to be distinguished from their meta and para isomers.



McLafferty rearrangement of $[R^2CH_2CH_2CH_2COR^1]^{+\cdot}$ (1)



Loss of water by ortho effect from ionised anthranilic acid (2)

Another interesting rearrangement of this kind can arise when cyclization of the molecular ion is followed by elimination of

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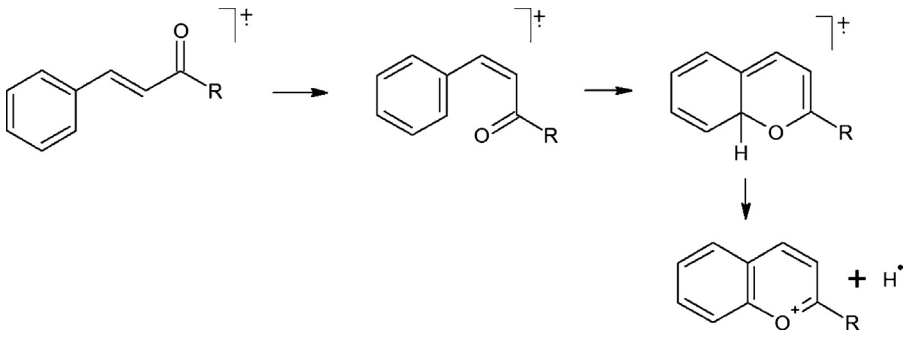
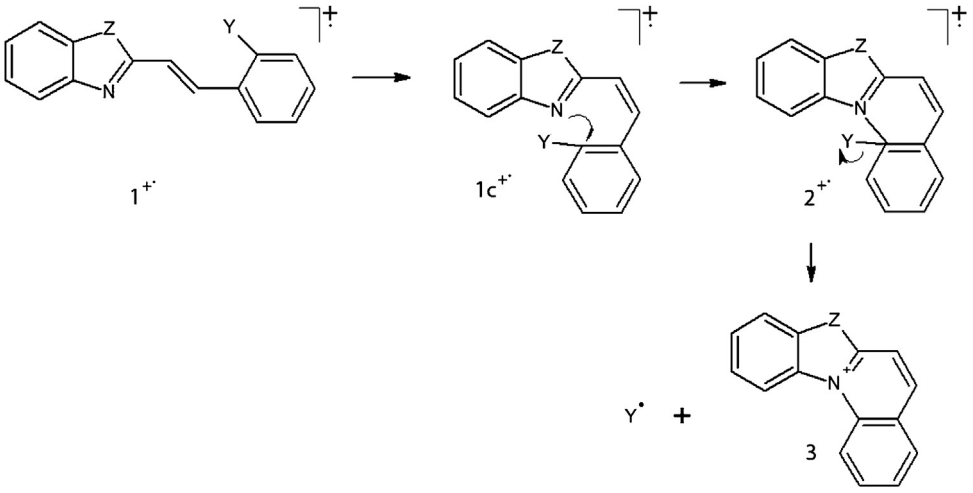


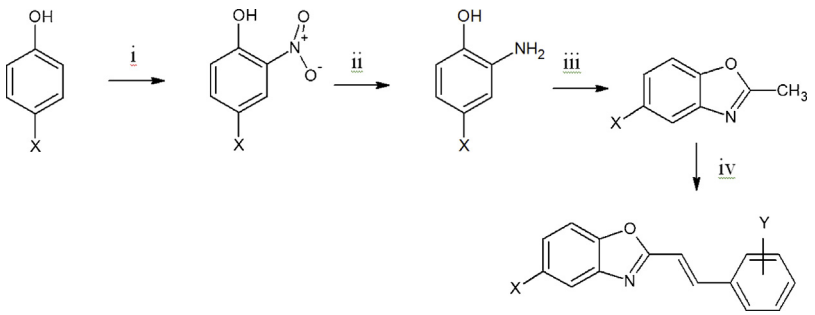
Scheme 1. Loss of H• from PhCH=CHCOR•+ species.

a substituent from an existing ring, with the production of an especially stable product ion in which a new ring has been formed. The archetypal example was discovered through the observation [4] of unexpectedly strong $[M-H]^+$ signals in the EI of cinnamic acid, $C_6H_5CH{=}CHCO_2H$, and several other compounds containing the $C_6H_5CH{=}CHC(R)O$ subunit (R = H, OH, CH_3 or C_6H_5). Deuterium labelling revealed that the eliminated hydrogen atom originated from the ortho position of the aromatic ring. The rearrangement is readily interpreted as shown in Scheme 1. Subsequently, further support for this mechanism was provided by establishing that the structure of the fragment ion formed from ionized benzylacetones (R = CH_3) was the 2-methylbenzylpyrillium cation [5].

This class of rearrangement, which can be described as an intramolecular aromatic substitution [6], is sometimes referred to as a proximity effect. Its analytical value is by no means restricted to cinnamyl derivatives. Thus, aurones [7] and other natural products show $[M-R]^+$ ions in their EI mass spectra when the R group is suitably located in an ortho position. Polycyclic compounds containing an ArCH=CH side chain also tend to show signals in their mass spectra that may be attributed to a proximity effect. For example, prominent $[M-H]^+$ and $[M-Y]^+$ signals are seen in the spectra of a wide range of styrylbenzazoles, **1**, of general formula $C_6H_4(NCZ)CH{=}CHC_6H_4Y$ [Z = NH, O or S; Y = H, F, Cl, Br, CH_3, CH_3O or NO_2] when the substituent, Y, is in the ortho position of the pendant ring (Scheme 2) [8]. Following isomerization of the trans C=C bond



Scheme 2. Loss of Y• from $C_6H_4(NCZ)CH{=}CHC_6H_4Y^+$ species grnerated under electron ionization conditions.



Scheme 3. Synthetic routes to 5XYSBOs (with reagents and conditions). (i) HNO_3, 16 °C, 2 min (X = F); 2 h (X = Br). (ii) H_2/Pd (X = F); $SnCl_2$/HCl 4.5 h (X = Br). (iii) Ac_2O/Δ (X = F/Cl); $CH_3C(OCH_3)_3$/reflux, 1.5 h (X = Br). (iv) YC_6H_4CHO (Y = H, F, Cl, Br, CH_3, CH_3O), $C_6H_5CH_2N(C_2H_5)_3{}^+Cl^-$/NaOH(aq)/DCM.