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The Gas-phase Smiles Rearrangement. The Effect of Ring Substitution. An ^{18}O Labelling Study†

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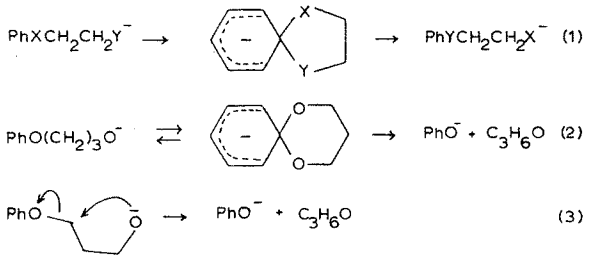
The gas-phase Smiles reaction of $RC_6H_4O(CH_2)_nO^-$ ($n = 2$ or 3) is an *ipso* rearrangement which is strongly influenced by the nature of the substituent R. Electron-withdrawing groups enhance the rearrangement. When the substituent R is halogen or MeO, and occupies the *ortho* position, *ortho* cyclization competes with the Smiles rearrangement.

INTRODUCTION

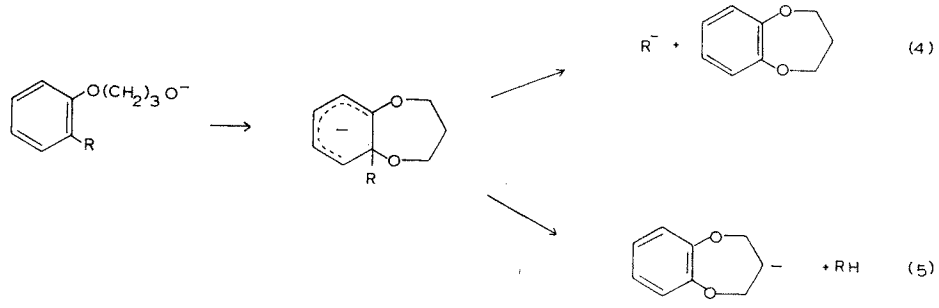
The classical condensed-phase Smiles rearrangement is summarized in Eqn (1). This *ipso* reaction normally requires an electron-withdrawing group (e.g. nitro, sulphonyl or halogen) in either the *ortho* or *para* position on the aromatic ring; generally X is a good leaving group and Y is a strong nucleophile.[1,2] The Smiles rearrangement occurs in the gas phase without the necessity for additional ring substitution.[3] For example, heavy atom (^{13}C and ^{18}O) labelling shows that the product ion PhO^- from $PhO(CH_2)_2O^-$ is formed exclusively through a Smiles intermediate. In contrast, PhO^- is formed by two processes from $PhO(CH_2)_3O^-$, viz. the Smiles process (85%, Eqn (2)), and the direct S_Ni process (15%, Eqn (3)), while the S_Ni process (cf. Eqn (3)) accounts exclusively for the formation of PhO^- from $PhO(CH_2)_4O^-$.



The Smiles rearrangement proceeds in the gas phase without the necessity for activation of the aromatic ring by electron-withdrawing groups. The first question we address in this paper is whether substituents on the aromatic ring can affect the extent of the Smiles rearrangement, e.g. does an increase in electron density at position 1 of the aromatic ring increase the activation energy of the Smiles process [Eqn (2)] with respect to that of the S_Ni reaction [Eqn (3)]? Second, if a suitable leaving group is placed in the *ortho* position of the phenyl ring, will nucleophilic attack at the *ortho* position [Eqns (4) and (5)] compete with the Smiles rearrangement?[4]‡

RESULTS AND DISCUSSION

The collisional activation mass spectra of most of the aryloxyalkanols listed in Table 1 give the $arylO^-$ ion as the sole ionic product. The exceptions are the *o*-MeO compounds (see Fig. 1) and some halo compounds (see Table 2).



† This paper is dedicated to J. S. Shannon in recognition of his contributions to mass spectrometry.

‡ Although there is no direct analogy to this particular reaction in the condensed phase, various benzylic carbanions have been used to effect six-membered ring formation in anthracylinones, following nucleophilic displacement of an *o*-MeO substituent,[5] and it is possible that solvent-assistance resonance effects[6] may aid such reactions.

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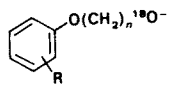
Table 1. Relative ratios of Smiles, S_Ni and *ortho* product peaks from $RC_6H_4O(CH_2)_n{}^{18}O^-$

Parent ion: 

R	n	Product peak area ratios: Smiles	S_Ni	*ortho*
H	2	100	—	
o-MeO	2	48	52	—
p-MeO	2	71	29	
H	3	85	15	
o-MeO	3	47	53	94 (−MeOH)
m-MeO	3	76	24	
p-MeO	3	51	49	
2,6-diMeO	3	35	65	200 (−MeOH)
m-Me_2N	3	58	42	
o-Me	3	67	33	—
m-Me	3	78	22	
p-Me	3	71	29	
m-*t*Bu	3	82	18	
o-F	3	60	40	400 (−HF)
m-F	3	75	25	
p-F	3	73	27	
p-Cl	3	95	5	
m-Br	3	98	2	
p-Br	3	92	8	

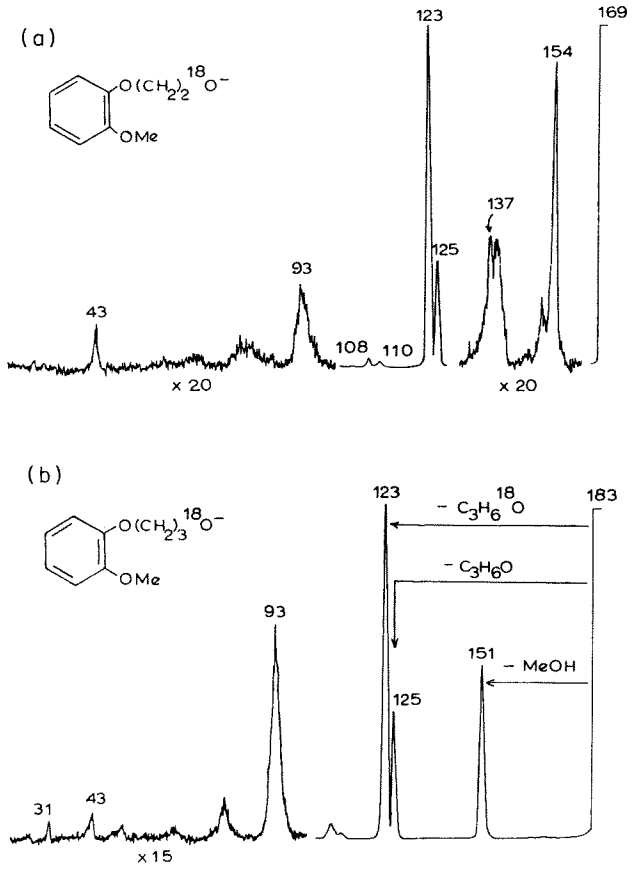


Figure 1. Collisional activation mass spectra of (a) *o*-$MeOC_6H_4O(CH_2)_2{}^{18}O^-$ and (b) *o*-$MeOC_6H_4O(CH_2)_3{}^{18}O^-$.

Table 2. Collisional activation mass spectra (relative intensity (%)) of haloaryloxyalkoxides $RC_6H_4O(CH_2)_3O^-$

Precursor R	$H^\cdot$	Loss: C_3H_6O	RH	$(RH + C_3H_5O^\cdot)$	Formation R^-
o-F	11	26	100	2	1
m-F	8	100			
p-F	9	100			
o-Cl		100			10
p-Cl		100			
o-Br		100			18
m-Br		100			
p-Br		100			
o-I		100			68
p-I		100			5

The Smiles rearrangement: effect of substitution

In order to determine the relative extents of the Smiles and S_Ni processes [cf. Eqns (2) and (3)], we measured the spectra of all the ^{18}O-labelled ions listed in Table 1. The relative ratios of the two processes in each case are given in Table 1. The calculation of the ratios is straightforward. For example, $PhO(CH_2)_2{}^{18}O^-$ yields PhO^- and $Ph^{18}O^-$ in the ratio 1:1, hence the Smiles rearrangement occurs exclusively in this case[3]. However, in the case of the *o*-MeO derivative [Fig. 1(a)], the ratio of *m/z* 123 (*o*-$MeOC_6H_4O^-$) to 125 (*o*-$MeOC_6H_4{}^{18}O^-$) is 100:32, so the Smiles: S_Ni ratio is 48:52. Hence placing a methoxy group in the *ortho* position significantly deactivates the ring to *ipso* (Smiles) attack; a *p*-MeO group is less effective (see Table 1).

We chose to study the reactions shown in Eqns (2) and (3) in detail, because the Smiles reaction for this particular ion does not occur exclusively (Smiles: S_Ni = 85:15; see Table 1 and Ref. 3). The most effective deactivating group for the Smiles rearrangement is *o*-MeO; one *o*-MeO substituent reduces the percentage of the Smiles process from 85 to 48%, whereas two *o*-MeO substituents lower it to 35% (Table 1). The electronic effect of the substituent is best illustrated by reference to Fig 2, where the percentage of the Smiles rearrangement is plotted as a function of the Hammett σ value for *meta*- and *para*-substituted ions. The experimental values are correct to within ±3%. The trend is clear. An electron-introducing group retards the Smiles rearrangement,† whereas an electron-withdrawing substituent activates the ring and reduces the activation energy for the *ipso* rearrangement. For example, the Smiles rearrangement occurs exclusively when the substituent is *m*-Br ($\sigma = +0.39$).[7] The data in Fig. 2 (see also Table 1) show that in this system, a *m*-F group is appreciably more electron donating than indicated by

† In our earlier study,[3] we were able to authenticate the mechanism of the *ipso* rearrangement by ^{18}O and ^{13}C labelling e.g. (1 − ^{13}C-Ph) $O(CH_2)_2O^- \rightarrow$ (1-^{13}C-Ph)$O^- \xrightarrow{CID} [C_5H_5]^- + {}^{13}CO$, and $PhO(CH_2)_2{}^{18}O^- \rightarrow PhO^-$ and $Ph^{18}O^-$(1:1). The ^{13}C experiment is not applicable in these systems since the loss of CO is replaced by more facile fragmentations through the substituent, e.g. the following CID fragmentations are dominant: $FC_6H_4O^- \rightarrow C_6H_3O^- + HF$, $MeC_6H_4O^- \rightarrow C_6H_4O^{-\cdot} + Me^\cdot$ and $MeOC_6H_4O^- \rightarrow {}^\cdot OC_6H_4O^- + Me^\cdot$.

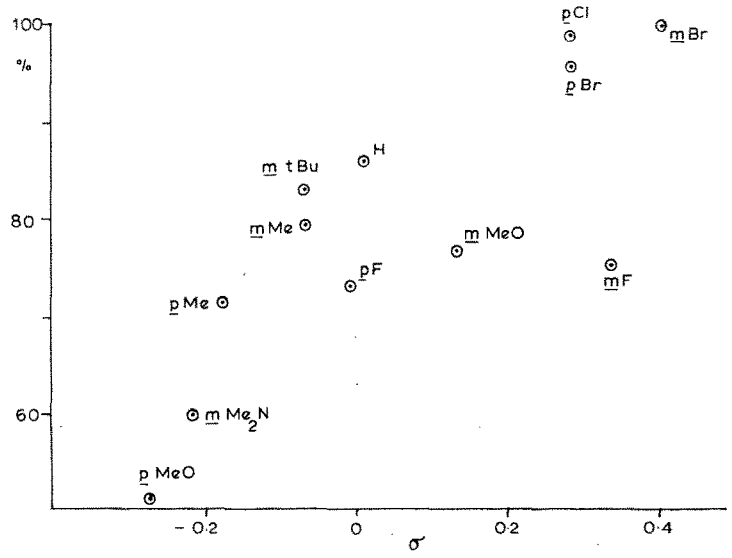
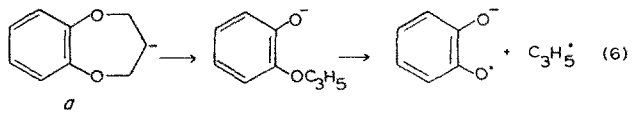


Figure 2. Comparison of the relative ratios of Smiles rearrangement and S_Ni dissociation for the various reactions $ArO(CH_2)_3O^- \rightarrow ArO^- + C_3H_6O$ for *meta*- and *para*-substituted precursors. Plot of the percentage of the Smiles rearrangement (see Table 1) against the Hammett σ value of the substituent (for σ values see Ref. 7; the value used for *p*-F is the σ^- value[7]).

the conventional σ or σ^- values (e.g. the σ value for *m*-F is +0.12).[7] Fluoro substituents are also known to give unusual effects for certain nucleophilic substitution reactions in the condensed phase.[8]

The *Ortho* cyclization process

The primary data concerning the *ortho* cyclization are contained in Tables 1 and 2 and Fig. 1. The *ortho* process [see Eqns (4) and (5)] competes with the Smiles rearrangement when R = MeO [see Fig. 1(b)], or F, Cl, Br and I (see Table 2). Displacement of R does not occur when R = Me. When R is both a good leaving group and a strong base (e.g. MeO^- and F^-; ΔH°_{acid} for MeOH and HF = 1593[9] and 1554 kJ mol^{-1} [10]), the deprotonation reaction [Eqn (5)] occurs to the virtual exclusion of nucleophilic displacement [Eqn (4)]. The most pronounced *ortho* process occurs for the *o*-F derivative, where the abundance of the peak produced by loss of HF is four times that produced by a combination of Smiles and S_Ni reactions (see Table 2). The structure of the product ion of reaction (5) is shown to be *a* [Eqn (6)] by the fragmentation data listed in Table 3. The major fragmentation of this ion is shown in Eqn (6).

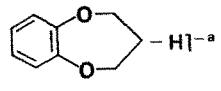


a

When R is a good leaving group but a weak base (e.g. Cl^-, Br^- and I^-, ΔH°_{acid} for HCl, HBr and HI = 1395[10], 1354[10] and 1316[11] kJ mol^{-1}), reaction (4) occurs to the exclusion of reaction (5) (see Table 2). Finally, it can be seen from Fig. 1 that whereas *ortho* cyclization to form a seven-membered ring is a facile process which competes with the Smiles process, the corresponding process to form a six-membered ring is not favoured. This is likely to be a consequence of the more facile formation of a five- than a six-membered intermediate in the Smiles rearrangement [cf. Eqns (1) and (2)], rather than a preference for seven- rather than six-membered ring formation in the *ortho* cyclization.

In conclusion, we have shown that the extent of the gas-phase Smiles rearrangement is dependent on the electronic effect of any substituents attached to the aromatic ring, and the presence of a methoxyl or halogen

Table 3. Collisional activation mass spectra of *m/z* 149 product ions resulting from *ortho* cyclization

Precursor ion (*m/z*)	Product ion (*m/z*)	Spectrum: *m/z* (loss) relative intensity (%)
o-$MeOC_6H_4O(CH_2)_3O^-$(179)	(−MeOH)(149)	148($H^\cdot$)18, 134($Me^\cdot$)2, 119(CH_2O)3, 108($C_3H_5^\cdot$)100, 92(C_3H_6O)1, 79(70)0.5, 51(98)0.2
o-$FC_6H_4O(CH_2)_3O^-$(169)	(−HF)(149)	148($H^\cdot$)16, 134($Me^\cdot$)1, 119(CH_2O)3, 108($C_3H_5^\cdot$)100, 92(C_3H_6O)1.5, 79(70)0.4, 51(98)0.1
 (149)		148($H^\cdot$)15, 134($Me^\cdot$)0.5, 119(CH_2O)2, 108($C_3H_5^\cdot$)100, 92(C_3H_6O)1, 79(70)0.5, 51(98)0.2

[a] Prepared by deprotonation of the neutral species.

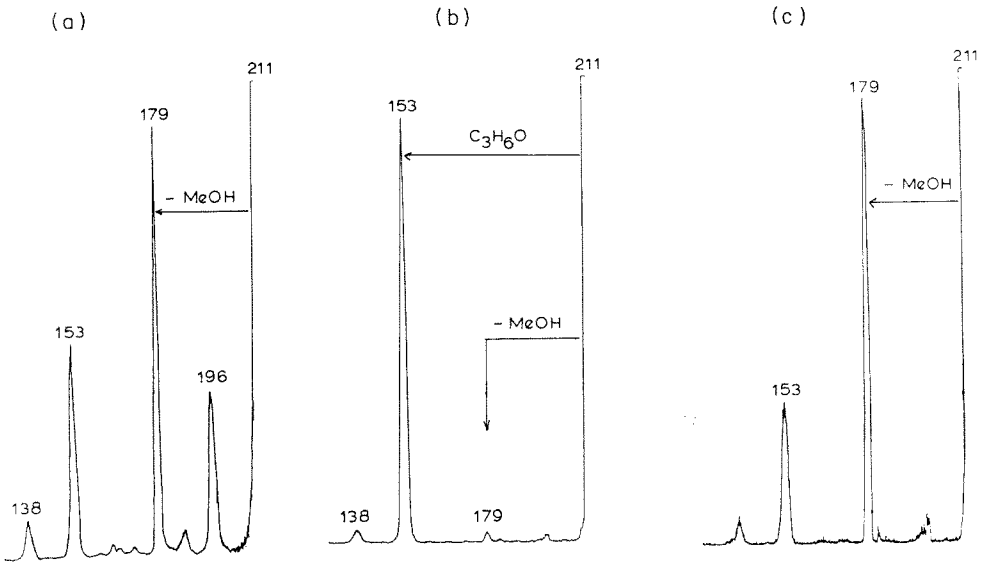


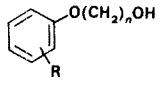
Figure 3. Collisional activation mass spectra of (a) 2,4-diMeO$C_6H_4O(CH_2)_3O^-$, (b) 2,5-diMeO$C_6H_4O(CH_2)_3O^-$ and (c) 2,6-diMeO$C_6H_4O(CH_2)_3O^-$.

group *ortho* to the alkoxide residue induces an *ortho* cyclization process which competes with the Smiles rearrangement. The sensitivity of the competitive reactions to the position of substituents can be readily seen in Fig. 3, i.e. the 2,4-dimethoxy substituents both deactivate the ring to *ipso* attack, thus the *ortho* effect is pronounced [Fig. 3(a)], the 5-methoxy substituent (of the 2,5-isomer) is electron withdrawing towards position 1 but electron introducing at position 2, hence the *ortho* effect is retarded [Fig. 3(b)], and for the 2,6-isomer [Fig. 3(c)], the presence of the two *ortho* groups enhances the probability of the *ortho* process.

EXPERIMENTAL

Collisional activation tandem mass spectra were recorded with a Vacuum Generators ZAB 2HF mass spectrometer; full operating procedures have been reported earlier.[3] In summary, the chemical ionization mode was used, ionizing energy 70 eV, ion source temperature 150 °C and accelerating voltage 7 kV. Deprotonation was effected by NH_2^- (from NH_3); source pressure of NH_3, 5×10^{-4} Torr (measured) (1 Torr = 133.3 Pa), substrate (introduced through the direct probe with no

Table 4. Details of new aryloxyalkanols



R	n	B.p. (°C)/mm Hg	Formula	$M^{+\cdot}$ Found	$M^{+\cdot}$ Calculated
o-MeO	2	110–112/0.05	$C_9H_{12}O_3$	168.0793	168.0787
p-MeO	2	115–117/0.05	$C_9H_{12}O_3$	168.0790	168.0787
o-MeO	3	110–115/0.015	$C_{10}H_{14}O_3$	182.0939	182.0943
m-MeO	3	110–115/0.015	$C_{10}H_{14}O_3$	182.0948	182.0943
p-MeO	3	100–102/0.02	$C_{10}H_{14}O_3$	182.0945	182.0943
m-Me_2N	3	145–147/0.0.5	$C_{11}H_{17}NO_2$	195.1253	195.1259
o-Me	3	220–222/25	$C_{10}H_{14}O_2$	166.0977	166.0994
m-Me	3	220–224/25	$C_{10}H_{14}O_2$	166.1000	166.0994
p-Me	3	225–227/30	$C_{10}H_{14}O_2$	166.0997	166.0994
m-*t*Bu	3	105–107/12	$C_{13}H_{20}O_2$	208.1469	208.1463
o-F	3	123–125/15	$C_9H_{11}O_2F$	170.0739	170.0743
m-F	3	130–135/13	$C_9H_{11}O_2F$	170.0744	170.0743
p-F	3	123–125/7	$C_9H_{11}O_2F$	170.0748	170.0743
o-Br	3	125–127/0.2	$C_9H_{11}O_2Br$	229.9948	229.9942
m-Br	3	130–132/0.2	$C_9H_{11}O_2Br$	229.9937	229.9942
p-Br	3	130–132/0.18	$C_9H_{11}O_2Br$	229.9944	229.9942
o-Cl	3	165–167/12	$C_9H_{11}O_2Cl$	186.0446	186.0447
p-Cl	3	170–172/12	$C_9H_{11}O_2Cl$	186.0453	186.0447
o-I	3	158–161/0.02	$C_9H_{11}O_2I$	277.9795	277.9804
p-I	3	160–165/0.02	$C_9H_{11}O_2I$	277.9806	277.9804
2,4-diMeO	3	130–135/0.02	$C_{11}H_{16}O_4$	212.1054	212.1049
2,5-diMeO	3	124–127/0.02	$C_{11}H_{16}O_4$	212.1044	212.1049
2,6-diMeO	3	128–130/0.02	$C_{11}H_{16}O_4$	212.1046	212.1049

heating), 5×10^{-7} Torr. The estimated total source pressure was 0.1 Torr. Helium was used as the collision gas in the second cell; the pressure of gas was measured as 2×10^{-7} Torr outside the cell, producing a decrease in the main beam of *ca* 10%.

All the substituted aryloxyalkanols used in this study are new compounds. They were all prepared by a standard method[12] from the appropriate potassium alkoxide and the required chloroalkanol. All products were purified by distillation. Yields were typically 60–80%. Many of the compounds colour immediately on exposure to the atmosphere. Their purity (when freshly prepared) was established by ^{1}H NMR and positive-ion mass spectrometry. Boiling points, formulae and mass measurements of molecular ions are given in Table 4.

All of the ^{18}O-labelled compounds (listed in Table 1) were prepared by the standard method[12] using the required potassium phenoxide and the appropriate [^{18}O]chloroalkanol (^{18}O = 91%).

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