Oxidation–Reduction Reactions Involving Nitro Groups in Trifluoromethanesulfonic Acid. Part 3.[1] The Reactions of 2-Nitrobenzyl Alcohol and Related Compounds

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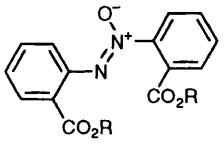
2-Nitrobenzyl alcohol reacts with trifluoromethanesulfonic acid (99%) at 90 °C to give a 66% yield of 4-amino-3-carboxyphenyl trifluoromethanesulfonate **4**. The reaction occurs through the intermediate formation of the *C*-protonated conjugate acid of anthranil *N*-oxide **7** and then probably involves the mono- and di-protonated forms of 2-nitrosobenzaldehyde. Under the same conditions, 2-nitrobenzyl chloride and 2-nitrosobenzaldehyde react to give the same product in essentially the same yield. Low temperature reactions in trifluoromethanesulfonic acid permit the conversion of *N*-phenylhydroxylamine into 4-aminophenyl trifluoromethanesulfonate in a yield of 78%.

The work described in Part 1 of the present series[2] dealt with the essentially quantitative conversion of 2-nitroethylbenzene into 3-methylanthranil in trifluoromethanesulfonic acid at 100 °C. The present work deals with the reactions, under similar conditions, of 2-nitrobenzyl alcohol and some related compounds. Neighbouring group interaction in *ortho*-substituted nitrobenzenes has been comprehensively reviewed[3] and the reactions of 2-nitrobenzyl alcohol with toluene-*p*-sulfonic acid in refluxing toluene have been studied in some detail.[4] A number of complex oxidation–reduction reactions, condensations, and rearrangements occur leading to the ester **1**, the amino acid **2** and the indazoloindazole derivative **3**. These reactions have been considered[4] to occur through the intermediate formation of 2-nitrosobenzaldehyde.



R = 2-$NO_2C_6H_5CH_2$—

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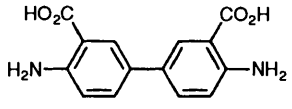

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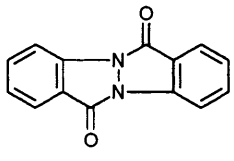

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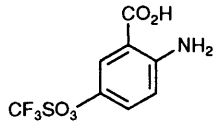
Results

Products.—When 2-nitrobenzyl alcohol (1.5 g) is heated in trifluoromethanesulfonic acid (99%) for 8 h at 90 °C, the properties of the product (yield 66%) accord with a derivative of anthranilic acid with a trifluoromethanesulfonate group in the 5-position (structure **4**). The ^{1}H NMR coupling pattern would also be consistent with the trifluoromethanesulfonate group in the 4-position but the chemical shifts accord with structure **4**. This can be seen from the δ-values for the conjugate acid of the product in trifluoromethanesulfonic acid (structure **5**) and, in particular from the δ-values for 4- and 6-H (positions equivalent with respect to the CF_3SO_2O– and $-NH_3^+$ groups). The higher chemical shift of 6-H accords with the known substituent effect of the $-CO_2H$ group.[5] A related argument for the neutral molecule is given in the Experimental section.



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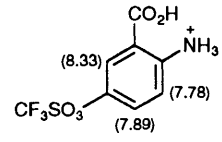
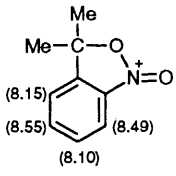
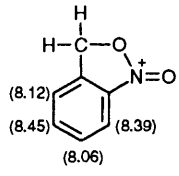


5(δ_H)



6(δ_H)



7(δ_H)

Under the above conditions, the same product in the same yield is formed from 2-nitrobenzyl chloride. The same product, in a yield of 62%, is also formed from the reaction of 2-nitrosobenzaldehyde in 99% trifluoromethanesulfonic acid at 90 °C but the reaction is then much faster, being complete in *ca.* 5 min.

The relatively high yield of the trifluoromethanesulfonate **4** led us to investigate whether a similar product could be obtained from the reactions of nitrosobenzene and *N*-phenylhydroxylamine in trifluoromethanesulfonic acid. The reaction of *N*-*tert*-butyl-*N*-phenylhydroxylamine in a mixture of trifluoromethanesulfonic acid and benzene to give a 10% yield of the corresponding trifluoromethanesulfonate has been reported.[6] Nitrosobenzene gave a mixture of products that could not be separated but *N*-phenylhydroxylamine reacted with trifluoromethanesulfonic acid at low temperatures to give a 78% yield of 4-aminophenyl trifluoromethanesulfonate.

Mechanism.—When 2-nitrobenzyl alcohol is placed in trifluoromethanesulfonic acid at room temp., the ^{1}H NMR spectrum of the solution [Fig. 1, spectrum (*a*)] is not as expected from the molecular structure. The methylene signal is at very low field (δ 6.55) and the aromatic spectrum indicates two protons with signals at *ca.* δ 8.1 and two with signals at *ca.* δ 8.4. The position of the methylene signal suggests the formation of a positive ion and the positions of the aromatic doublets and triplets are close to those reported[7] for the borofluoride of the ion **6**. This suggests that 2-nitrobenzyl alcohol is rapidly converted by trifluoromethanesulfonic acid into the *C*-protonated conjugate acid of anthranil *N*-oxide **7**. This is another of the

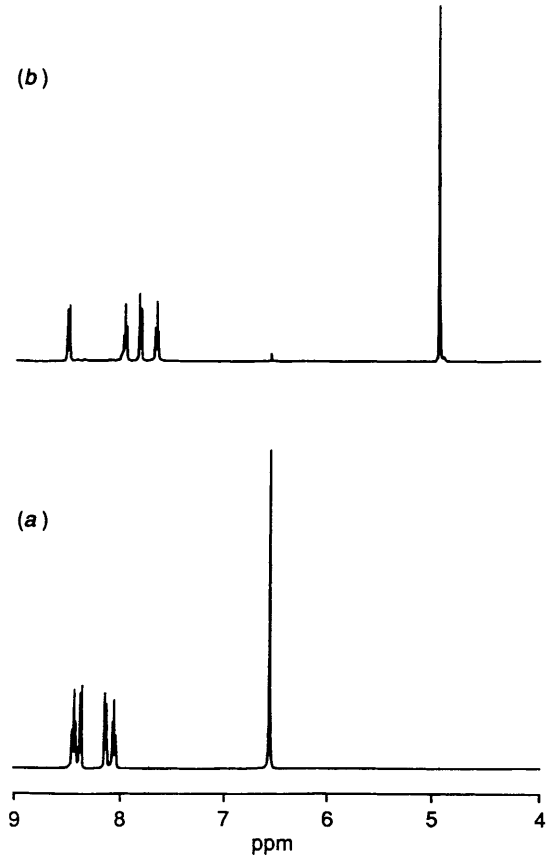


Fig. 1 ^{1}H NMR Spectra (400 MHz) at room temp. of (*a*) a solution of 2-nitrobenzyl alcohol (0.08 g) in trifluoromethanesulfonic acid (99%, 0.8 cm^3) and (*b*) a solution of 2-nitrobenzyl chloride under the same conditions. On heating the second solution to 50 °C, the spectrum changes slowly and eventually becomes identical with spectrum (*a*).

suggested intermediates in the reaction of 2-nitrobenzyl alcohol with toluene-*p*-sulfonic acid.[4]

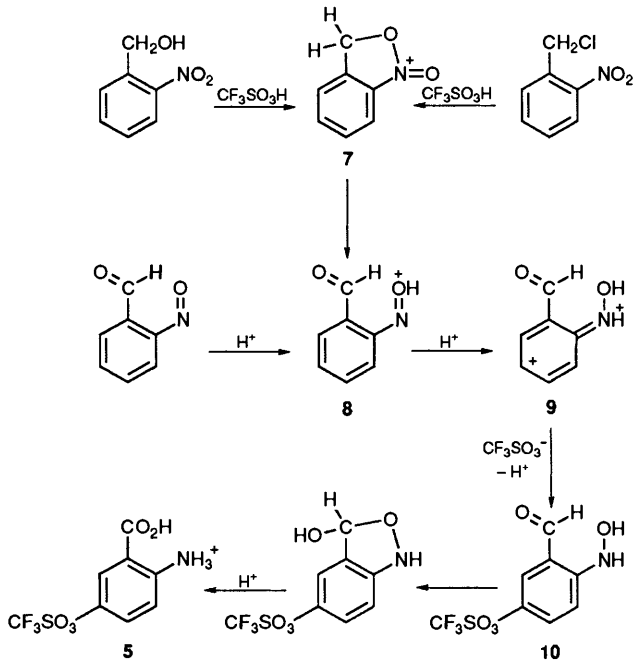
When 2-nitrobenzyl chloride is dissolved in trifluoromethanesulfonic acid at room temp., the initial spectrum [Fig. 1, spectrum (*b*)] is as expected but on heating the solution to 50 °C this spectrum changes to that given by 2-nitrobenzyl alcohol [Fig. 1(*a*)]. The first hint of this reaction is apparent from the weak signal at δ 6.55 in spectrum (*b*). The decrease in the methylene signal for 2-nitrobenzyl chloride follows good first-order kinetics with a rate coefficient of 4.6×10^{-4} s^{-1} in 98.68% trifluoromethanesulfonic acid at 50 °C. The formation of the same intermediate **7** (Scheme 1) from the two substrates supports the suggested structure for this ion. Presumably, in this highly acidic medium, –OH becomes a better leaving group than –Cl and so the reaction that is fast with 2-nitrobenzyl alcohol is slow with 2-nitrobenzyl chloride.

No further change was observed when these solutions were left at 50 °C but, on heating to 90 °C, a slow reaction occurred to give the protonated trifluoromethanesulfonate **5**.

Discussion

Since the first stage of these reactions is clear from the ^{1}H NMR spectrum [Fig. 1(*a*)], this discussion is restricted to the mechanism of formation of the product **5** from the ion **7** and to the reason for the different reaction paths found in trifluoromethanesulfonic acid and toluene-*p*-sulfonic acid.

The analogy with the arylation of nitrosobenzene in trifluoromethanesulfonic acid[6] suggests that the present reaction occurs through the monoprotonated **8** and diprotonated **9** forms of 2-nitrosobenzaldehyde (Scheme 1). 2-



Scheme 1

Nitrosobenzaldehyde would be formed by an β-elimination from the ion **7** but, since this reaction would be facilitated by protonation of the leaving group, the immediate product has been shown in Scheme 1 as the *O*-conjugate acid of 2-nitrosobenzaldehyde **8**. This reaction path accords with the fact that, under the same conditions, 2-nitrosobenzaldehyde gives rise to the same product as 2-nitrobenzyl alcohol and in essentially the same yield. Some substituted nitroso compounds are known to undergo diprotonation in super acids[8] and the resulting species (*e.g.*, **9**) have been termed 'iminium–benzenium ions'.[6] The substituted hydroxylamine **10** resulting from substitution in the ion **9** could undergo a further ring substitution *via* a nitrenium ion or protonated nitrenium ion[6] but, with the present substrate, the presence of the aldehyde group apparently leads to cyclisation and a further β-elimination to form the conjugate acid of the final product **5**. The much greater reactivity of 2-nitrosobenzaldehyde compared with 2-nitrobenzyl alcohol suggests that the rate-determining step in the overall reaction of 2-nitrobenzyl alcohol is the β-elimination **7** ⟶ **8**.

Reaction through the imminium–benzenium ion **9** receives some support from theoretical calculations. The position of nucleophilic attack on aryl nitrenium ions has been shown to accord with the results of semiempirical MO calculations of the LUMO coefficients and charge distributions[9] but no attention appears to have been given to iminium–benzenium ions such as **9** and related species. Since the trifluoromethanesulfonate ion is an oxygen nucleophile with a single negative charge, it should be considered as a 'hard' nucleophile[10] and so the position of substitution on the ring should depend more on the overall charge distribution than on the LUMO coefficients.[11] The calculated properties of some possible intermediates in this reaction are compared in Table 1.

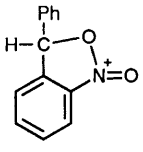
The ring chlorination of 2-nitrobenzyhydrol during the reaction with thionyl chloride to give 5-chloro-3-phenylanthranil has been considered[12] to occur by direct nucleophilic substitution on the ion **11** (analogous to **7**). However, neither the LUMO coefficients nor the charge distribution for the ion **7** (Table 1) suggest any preference for nucleophilic attack at the 5-position. The nitrenium ion **12** could be formed following *O*-protonation at the carbonyl group of 2-nitrosobenzaldehyde but the calculations suggest that the preferred structure is **13**

Table 1 Semiempirical calculations (AM1) of the LUMO coefficients (c_{p_z}) and atomic charges (ζ) at the carbon, nitrogen and oxygen atoms in some of the structures shown in Scheme 1. The asterisks show the positions of greatest $|c_{p_z}|$ and greatest positive charge.

	7		**8**		**9**	
Atom	c_{p_z}	ζ	c_{p_z}	ζ	c_{p_z}	ζ
C-1	0.291	−0.066	0.371	−0.088	0.364	−0.050
C-2	−0.108	−0.171	−0.071	−0.204	0.258	0.002
C-3	0.326	0.014	0.397	0.066	0.398	0.031
C-4	0.036	−0.120	0.091	−0.152	−0.072	−0.150
C-5	−0.315	−0.020	−0.403	0.029	−0.503*	0.229
C-6	−0.001	−0.080	−0.101	−0.105	−0.148	−0.120
C-7 (CHO)[a]	−0.024	0.009	−0.106	0.234	0.044	0.235*
N	−0.586*	0.500*	−0.565*	0.280*	−0.474	0.207
O (CHO)[a]	0.238	−0.150	−0.143	−0.285	−0.118	−0.221
O (NO)[a]	0.530	−0.055	0.361	−0.015	0.261	−0.068

[a] Defined with respect to 2-nitrosobenzaldehyde.

with the plane of the aldehyde group *ca.* perpendicular to that of the ring. The LUMO of this ion is essentially an antibonding carbonyl orbital with very little contribution from the p_z orbitals of the ring. The results for structures **8** and **9** are included in Table 1 and show that only for structure **9** do the LUMO coefficients indicate a clear preference for attack at the 5-position. For this structure, the charge at the 5-position is second only to that at the carbonyl carbon. For the orientation of ring substitution, the calculations are therefore consistent with the mechanism put forward in Scheme 1.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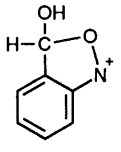
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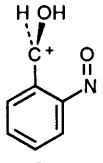
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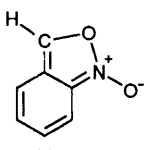
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The products from the reaction of 2-nitrobenzyl alcohol in toluene-*p*-sulfonic acid (**1**–**3**) appear to derive from an initial coupling of two substrate molecules at the nitrogen atoms followed (for compound **3**) by a benzidine rearrangement.[4] If one of the substrate molecules concerned is acting as a nucleophile the greater degree of protonation in trifluoromethanesulfonic acid should decrease the rate of these reactions and favour reaction with the solvent. The ratio of *C*-substitution to *N*-substitution in the phenylation of *N*-arylhydroxylamines and nitrobenzene also increases with acidity and this has been attributed to the greater importance of reaction through iminium–benzenium ions in the more acidic medium.[6] This change in the orientation accords with the calculations in Table 1.

The above work provides further examples of the way in which reactions in trifluoromethanesulfonic acid can often give high yields of single products in spite of the complexity of the reaction paths. In the present work, the nitro group is acting as a nucleophile; in the earlier studies[1,2] the protonated nitro group was acting as a hydride ion acceptor.

Experimental

Materials.—Nitrobenzene, 2-nitrobenzaldehyde, 2-nitrobenzyl alcohol, 2-nitrobenzyl chloride and trifluoromethanesulfonic acid were obtained from Aldrich and were used without further purification.

2-Nitrosobenzaldehyde was prepared as described by Bamberger:[13] the product had mp 113 °C (lit.,[14] 111–112 °C); $\delta_H(CDCl_3)$ 12.06 (1 H, s), 8.21 (1 H, d, *J* 8 Hz), 7.9 (1 H, t, *J* 8 Hz), 7.68 (1 H, t, *J* 9 Hz) and 6.44 (1 H, d, *J* 8 Hz); $\delta_C(CDCl_3)$ 193.7, 162.1, 136.4, 134.1, 132.8, 127.8 and 106.3. The strong carbonyl absorption[14] (1700 cm^{-1}) shows that the molecule exists as the nitroso–carbonyl structure (Scheme 1) and not as anthranil *N*-oxide **14**.

N-Phenylhydroxylamine was prepared by the reduction of nitrobenzene:[15] the product had mp 81 °C (lit.[12] 81 °C).

Reactions.—A mixture of 2-nitrobenzyl alcohol (1.5 g) and trifluoromethanesulfonic acid (99%, 15 cm^3) was heated in a sealed tube under dry argon for 8 h at 90 °C. The contents were then poured into iced water (200 cm^3) and the solution extracted with dichloromethane (8 × 50 cm^3). The extracts were dried ($MgSO_4$), and the solvent was removed. The resulting red solid was dissolved in chloroform (100 cm^3), boiled with activated charcoal, and then recrystallised from chloroform to give 4-amino-3-carboxyphenyl trifluoromethanesulfonate **4** (1.82 g, 65.5%) mp 162 °C (Found C, 33.4; H, 1.9; N, 4.8. $C_8H_6F_3NO_5S$ requires C, 33.7; H, 2.1; N, 4.9%); $\delta_H(Me_2SO)$ 8.6 (br s), 7.61 (1 H, d, *J* 3 Hz), 7.34 (1 H, dd, *J* 3, 9 Hz) and 6.85 (1 H, d, *J* 9 Hz); $\delta_C(Me_2SO)$ 168.2, 151.4, 137.6, 127.1, 123.1, 118.3 (q, $^1J_{C-F}$ 321 Hz), 117.9 and 109.1; ν_{max}(KBr)/cm^{-1} 3493 (NH_2), 3379 (NH_2), 2965 (OH) and 1682 (CO).

The low chemical shift (δ 6.85) of one signal in the ^1H NMR spectrum indicates a proton *ortho* to an amino group; this indicates that the molecule does not exist as the zwitterion in dimethylsulfoxide and also confirms the given structure since this signal shows only *ortho* coupling.

The reaction of 2-nitrobenzyl chloride (0.6 g) in trifluoromethanesulfonic acid (99%, 15 cm^3) was carried out in the same way and gave the product **4** (0.61 g, 66.9%). The reaction of 2-nitrosobenzaldehyde (0.3 g) with trifluoromethanesulfonic acid (99%, 4.0 cm^3) was carried out in the same way but the reaction mixture was heated to 90 °C for only 1 h before extraction. The product **4** (0.39 g, 61.6%) was again obtained. A subsequent experiment followed by ^1H NMR spectroscopy showed that the reaction was effectively complete after only 5 min at 90 °C.

The vigour of the reaction of *N*-phenylhydroxylamine with trifluoromethanesulfonic acid led to the use of low temperatures in these studies. Two methods were used but gave identical products. In one trifluoromethanesulfonic acid (99%, 2 cm^3) was added to a solution of *N*-phenylhydroxylamine (0.15 g) in dry dichloromethane (10 cm^3) at 0 °C under argon. The solution was stirred for 2 h before being poured into iced water (150 cm^3) and extracted with dichloromethane (5 × 50 cm^3). The extracts were dried ($MgSO_4$) and the solvent removed to give 4-aminophenyl trifluoromethanesulfonate as a yellow oil (0.26 g, 78%). In the other, *N*-phenylhydroxylamine (0.08 g) was added in small portions to trifluoromethanesulfonic acid (99%, 4 cm^3) at *ca.* −78 °C. The solvent was allowed to melt to dissolve each sample but was refrozen after each addition. The reaction mixture was then allowed to stand at room temp. for

1 h before being poured into iced water (50 cm^3). The solution was neutralised ($NaHCO_3$) and extracted with dichloromethane (4 × 50 cm^3); the extracts were dried ($MgSO_4$) and the solvent removed to give 4-aminophenyl trifluoromethanesulfonate (0.138 g, 78%) (Found C, 35.2; H, 2.4; N, 5.7. Calc. for $C_7H_6F_3NO_3S$: C, 34.9; H, 2.5; N, 5.8%); $\delta_H(CDCl_3)$ 7.06–6.63 (4 H, q) and 3.79 (2 H, br s); $\delta_C(CDCl_3)$ 146.5, 141.6, 122.3, 118.8 (q, $^1J_{C-F}$ 321 Hz) and 115.5.

Molecular Orbital Calculations.—The calculations listed in Table 1 were carried out by the restricted Hartree–Fock approach using the semiempirical AM1 method in the MOPAC 6.0 program[16] implemented on 386 PC computer. The calculations were carried out by full optimisation using the keyword PRECISE. In calculating the c_{p_z} values, the x,y plane is defined by atoms 1, 2 and 6 of the benzene ring; small contributions to the LUMO coefficients from other orbitals have been ignored.

Acknowledgements

One of us (R. P. A.) thanks the SERC for a studentship.

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Paper 4/01810I
Received 25*th March* 1994
Accepted 12*th April* 1994