

ELECTROPHILIC BROMINATION OF PHENOL ETHERS IN SUPERACID SOLUTION USING ALKALI BROMIDE

Ghassan Cherry, Jean-Christophe Culmann and Jean Sommer*
Laboratoire de Physico-Chimie des Hydrocarbures (UA CNRS 469)
Département de Chimie, Université Louis Pasteur,
1, rue Blaise Pascal, F-67000 Strasbourg, France

Summary : Electrophilic aromatic bromination of phenol ethers in superacid medium can be achieved with sodium or potassium bromide. The yield and selectivity are lower than with bromine, the oxidation of the halide to the electrophilic halogen cation is obtained by concomitant reduction of antimony pentafluoride. Selectivity is observed only in methylanisole.

The electrophilic aromatic bromination of aromatic derivatives has been achieved with bromine activated in a variety of solvent systems such as liquid SO_2 ,¹ HClO_4 ,² $\text{CF}_3\text{SO}_3\text{H}$,³ $\text{CF}_3\text{SO}_3\text{Ag}$ in CHCl_3 ⁴ and HF-SbF_5 .⁵⁻¹⁰ Bromine has also been combined with bromide ion in ammonium tribromides as mild and efficient brominating reagents.^{11 a,b}

On the basis of our recent finding of the remarkable selectivity in the superacid catalyzed C-H bond activation in the presence of bromide ions¹², we have investigated the possibility of using alkali bromides as reagents for bromination of phenol ethers. We have chosen these substrates especially because they have already been studied in detail with the $\text{Br}_2\text{-HF-SbF}_5$ system.

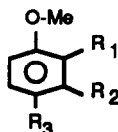
We compare here the yield and selectivities found in both systems and discuss the nature of the electrophilic species.

Experimental procedure

Bromine or the alkali bromide and the phenol ether are added in a Kel-F reactor containing HF-SbF_5 (4 - 20 mol % SbF_5) at -78°C . Generally the molar ratio was $\text{SbF}_5 : 10 / \text{eq.Br}^- : 1.4$ or $\text{eq.Br}_2 : 0.7 / \text{substrate} : 1$. The temperature of the magnetically stirred solution is then raised to -40° for 15 minutes before neutralisation and ether extraction. Identification of the products has been made on the basis of G.C. analysis (FFAP 6 m) and mass spectrometry.

Results and Discussion

Our experimental results obtained with bromine or sodium or potassium bromide in HF-SbF₅ are collected in the following table :



- I. R₁ = R₂ = R₃ = H
 II. R₁ = CH₃ R₂ = R₃ = H
 III. R₃ = CH₃ R₁ = R₂ = H

- a. 2- bromo
 b. 3- bromo
 c. 4- bromo

Exp. n°	HF/ SbF ₅ % SbF ₅	Substrate	Reagent	Conversion %	Selectivity %			Reference	
1	4.0	I	NaBr	69	Ia (3.5)	Ib (e)	Ic (56.6)	P*(39.9)	**
2	3.8	I	Br ₂	58			Ic (100)		(8)
3	4.0	II	NaBr	55	IIa (2.6)	IIb (0.6)	IIc (77.2)	P (19.4)	**
4	3.8	II	Br ₂	73			IIc (100)		(8)
5	1.3	III	Br ₂	-	IIIa (38.0)	IIIb (60.0)		P (0.2)	(8)
6	3.8	III	Br ₂	-		IIIb (88.0)		P (12.0)	(8)
7	5.5	III	Br ₂	57	IIIa (27.1)	IIIb (55.4)		P (17.5)	**
8	5.5	III	NaBr	19	IIIa (33.0)	IIIb (38.2)		P (28.8)	**
9	5.5	III	2.Br ₂	96	IIIa (10.8)	IIIb (65.4)		P (23.8)	**
10	5.5	III	2.NaBr	42	IIIa (39.0)	IIIb (25.8)		P (35.2)	**
11	5.5	III	2.Br ₂ + 4.KF	55	IIIa (42.2)	IIIb (26.6)		P (31.2)	**
12	20.0	III	2.Br ₂	91	IIIa (7.1)	IIIb (56.4)		P (36.8)	**
13	20.0	III	2.Br ₂ + 4.KF	74	IIIa (9.3)	IIIb (41.0)		P (49.7)	**

* : poly brominated or heavy material

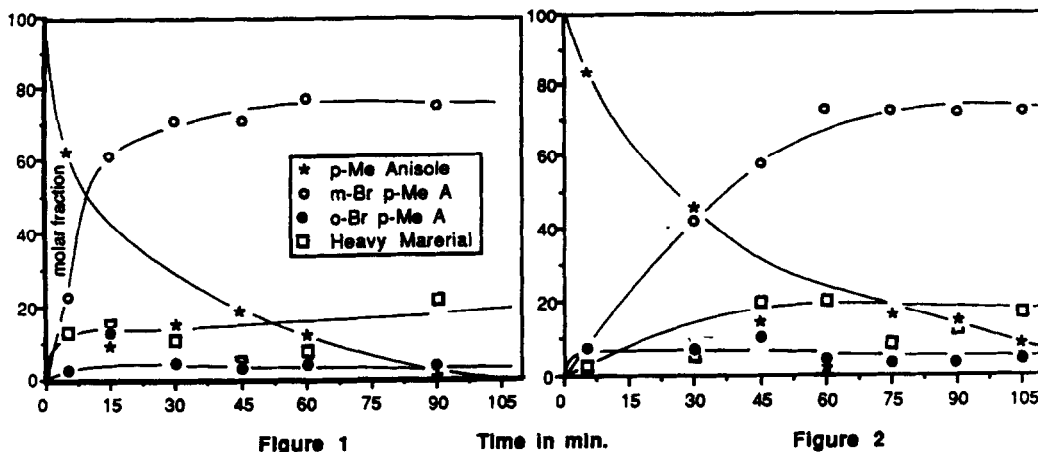
** : this work

Anisole¹ and ortho-methylanisole¹¹ as shown earlier are predominantly para brominated independently of the nature of the reagent. The suggested meta orienting effect due to rapid O-protonation of the phenol ether⁶ is only noticed when the 4-position is methyl substituted. The hypothesis of an initial para-bromination followed by a 1,2 shift as supposed by Fischer and Henderson³ can not be repeated on our experiment basis.

The selectivity in meta-bromo para-methylanisole seems somewhat better when bromine is used instead of the bromide ion (Exp. 7 and 8). As the bromide ion needs one more oxidation step than bromine to reach "Br⁺", this means also that the acidity level of the superacid will be more affected.

The meta-selectivity is even increased when the amount of bromine is doubled (Exp. 9). The opposite effect observed with sodium bromide is probably due to the strong neutralising effect of the bromide ion on the acidity level of the superacid. This could be checked by adding a stoichiometric amount of KF in the experiment with bromine (Exp. 11). When the experiments are run at higher SbF₅ concentrations (Exp. 12 and 13), the acidity level is well enough buffered by the Lewis acid.¹³

On the other hand we have also conducted two comparative kinetic experiments by measuring the product distribution versus time over the first two hours of reaction when Br₂ (Figure 1) or NaBr (Figure 2) is used in HF-SbF₅ (11 mol % SbF₅).

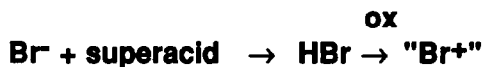


Beside the fact that the reaction is faster when bromine is used, the product distribution is the same. After one hour at -45°C the equilibrium distribution between the ortho and meta brominated methylanisoles is attained as observed in other superacid media.^{8,10}

Despite the low temperature conditions of the reaction it was not possible in these experiments to prove the bromination sequence as both the ortho- and meta-isomers are present at the start. The nature of the brominating electrophile "Br⁺" is not clear. The suggestion by Jacquesy that bromine is protonated in the superacid :



with subsequent oxidation of HBr could be extended to the bromide ion as

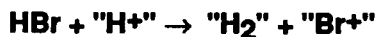


This leaves however open two main questions : the nature of the electrophile and the nature of the oxidant.

Our experiments can answer in part these questions :

1. When sodium or potassium bromide are dissolved in HF-SbF₅ a strong red colour develops, which disappears during reaction with the aromatic. This colour is difficult to observe when bromine (itself coloured) is used. We suppose that the light red colour observed here is due to the Br₂⁺ cation described by Gillespie and Morton.¹⁴

2. When the alkali bromide is dissolved in the HF-SbF₅ solution no hydrogen evolution can be detected in the reactor. This point should eliminate the hypothesis of the bromide oxidation by the proton as suggested earlier following :



The oxidant in this case is certainly SbF₅ itself, as antimony trifluoride could be observed as a precipitate and characterized by X Ray powder diffraction.

Our observation should be related with the electrophilic bromination reaction which has been observed earlier in the alkylation reaction of aromatic compounds with ethylbromide in superacid media¹⁵ : both alkylated and brominated compounds were obtained.



On the other hand our attempts to use chloride and iodide salts as starting materials failed. Whereas chlorine has been used in superacid media for electrophilic chlorination of alkanes,¹⁶ the chloride ion could not be oxidized in these media even at 0°C. When iodide salts were used, a complex mixture of unidentified heavier compounds was obtained.

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