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Anomalous Reimer-Tiemann Reaction from Phenol, Chloroform and Potassium Fluoride in Sulfolane.

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Abstract : Phenol reacts only at the oxygen site when opposed to chloroform in the presence of potassium fluoride and sulfolane. (Difluoromethoxy)benzene and phenyl orthoformate are formed. This leads to questions about the mechanism of the Reimer-Tiemann reaction.

Aryl difluoromethyl ethers and thioethers are usually obtained from chlorodifluoromethane, sodium hydroxide and phenols or thiophenols, either in homogeneous liquid media[1-3] or under solid-liquid phase-transfer conditions[4]. The carbenic nature of this reaction has been proved unambiguously by using deuterated water as solvent[5] and is consistent with the formation, sometimes to a large extent, of aryl orthoformates as by-products[4] :

$$CHF_2Cl + HO^- \rightleftharpoons H_2O + [\overset{-}{C}F_2Cl]\ (\rightleftharpoons :CF_2 + Cl^-)$$

$$Ar\text{-}O^- + :CF_2 \rightleftharpoons Ar\text{-}O\text{-}\overset{-}{C}F_2 \xrightleftharpoons{Z\text{-}OH\ (Z=H,\ Ar)} Ar\text{-}O\text{-}CF_2H$$

$$Ar\text{-}O\text{-}\overset{-}{C}F_2 \xrightleftharpoons{-F^-} Ar\text{-}O\text{-}\overset{\cdot\cdot}{C}\text{-}F \xrightleftharpoons{+Ar\text{-}O^-} (Ar\text{-}O)_2\overset{-}{C}\text{-}F \xrightleftharpoons{-F^-} (Ar\text{-}O)_2C:$$

$$\xrightleftharpoons{+Ar\text{-}O^-} (Ar\text{-}O)_3C^- \xrightarrow{+Z\text{-}OH\ (Z=H,\ Ar)} (Ar\text{-}O)_3C\text{-}H$$

Scheme I

According to this scheme, it could be expected that the addition of fluoride anions to the medium would prevent the decomposition of the intermediate $ArOCF_2^-$. On the other hand, fluoride is also known to act, in aprotic solvents, as a strong base[6], able to deprotonate phenols[7] and chloroform[8-10], as well as an efficient nucleophile.

The conjunction of these three remarks led us to examine the behaviour of phenol and chloroform in the presence of potassium fluoride and an aprotic solvent.

Thus, phenol (1 eq.), chloroform (1 eq.), calcined potassium fluoride (6 eq.) and dry sulfolane (800 ml/eq.) were mixed in a glass vessel fitted with a mechanical stirrer and a large and very efficient dry-ice condenser, in order to prevent any loss of chloroform. The temperature was held from 140 to 180°C over 4 hrs. After an usual work-up, a high conversion of both organic substrates was observed (85 and 87 %, resp.). (Difluoromethoxy)benzene and phenyl orthoformate were formed in amounts which increased with the temperature. The yield of the former product, relative to converted phenol, was low (16 %) and could not be improved by changing the molar ratios or the phenol concentration, or by performing the reaction under pressure. Though its yield was difficult to define precisely because of its instability under the GPC or work-up conditions, phenyl orthoformate was the major product in any case. Nevertheless, one point was noteworthy : none of the expected Reimer-Tiemann products like (dichloromethyl)- or (difluoromethyl)- phenol and hydroxybenzaldehyde were detected during the course of the experiment or after hydrolysis of the medium :

$$\text{Ph-OH} + \text{HCCl}_3 \xrightarrow[\text{sulfolane}]{\text{KF}} \text{Ph-O-CF}_2\text{H} + (\text{PhO})_3\text{CH}$$

Though the above reaction is not useful from a synthetic point of view, interesting questions can be asked concerning the mechanism of formation of (difluoromethoxy)benzene under these conditions.

There is no doubt that phenol was deprotonated by fluoride[7]. On the other hand, according to the recent observation that thoroughly dried Me_4NF undergoes a fast halogen exchange with chloroform at room temperature ($CHCl_2F/CHClF_2/CHF_3$= 2/3/1)[11], it could be imagined that chloroform reacted primarily with potassium fluoride to produce mainly chlorodifluoromethane (gaseous fluoroform, a possible by-product, would escape from the medium). This haloform, more acidic than $CHCl_3$, would be deprotonated by fluoride more rapidly than chloroform, to deliver difluorocarbene and chloride. Further reactions would follow Scheme I. This hypothesis, where the $CHClF_2$ yield (v.s. converted $CHCl_3$) cannot excess 50%, is consistent with the low yield of $PhOCF_2H$ we observed.

However, as Christe himself wrote about halogen exchange upon chloroform[11], "the mild conditions under which the reaction proceeds are surprising". As very dry fluoride ("naked" fluoride) must behave as a very strong base rather than a nucleophile[12], we suggest that this formal substitution involves more probably successive addition and elimination processes on dichlorocarbene rather than a S_N2 process :

$$2\ F^- + H\text{-}CCl_3 \rightleftharpoons HF_2^- + [^-CCl_3]\ (\rightleftharpoons Cl^- + :CCl_2)$$

$$:CCl_2 \xrightleftharpoons{+F^-} {}^-CCl_2F \xrightleftharpoons{-Cl^-} :CClF \xrightleftharpoons{+F^-} {}^-CClF_2 \xrightleftharpoons{-Cl^-} :CF_2$$

In the absence of any nucleophile other than fluoride, the above trihalomethyl anions are reprotonated by HF_2^- but, in the presence of phenoxide, phenoxydihalocarbanions could occur :

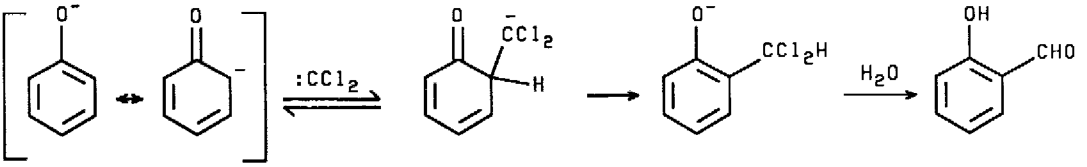
$$\text{Ph-O}^- + :\text{CX}_2 \rightleftharpoons \text{Ph-O-}\overset{-}{\text{C}}\text{X}_2 \quad (\text{I})$$

Because of the carbon-halogens bond energies, the more stable (I) (X_2= F_2) would be rather protonated by HF_2^- whereas less stable (I) (X_2= Cl_2 or ClF) would rather collapse into phenoxylated carbenes and finally provide phenyl orthoformate, in a similar way as the one postulated in Scheme I. It can be suggested that the formation of phenyl orthoformate was favoured (v.s. the protonation of Ph-O-CX_2^-) by the aprotic character of the medium.

This explanation would seem to disagree with the formation of dichloronorcarane, free of any difluoro analog, from cyclohexene, chloroform and tetraethylammonium fluoride[9]. However, it is well known, now, that Et_4NF, prepared according to [9], cannot be obtained anhydrous, even after a long drying under vacuum[13], and is decomposed, when heated at 100°C under vacuum, with formation of HF_2^- [14]. It can be suspected that F^-, nH_2O and HF_2^-, able to deprotonate chloroform, are not nucleophilic enough to compete with cyclohexene in the reaction with dichlorocarbene (it is noteworthy that the yield of dichloronorcarane produced in this reaction, 20 %, is of the same order of magnitude as the yield of $PhOCHF_2$ we obtained).

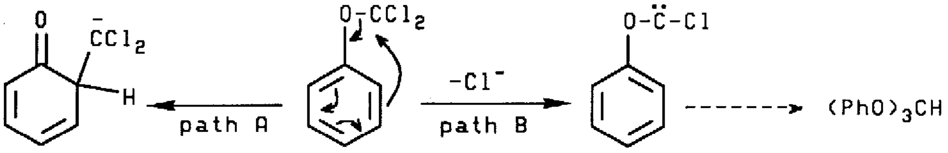
Though completely different from the mechanism we propose here, the interpretation generally accepted for the Reimer-Tiemann reaction (Scheme II) seems to us to be a rather simplifying one, because:

- it does not account for the occurrence of phenyl orthoformate which is always detected during this reaction and has been already noted by Tiemann himself[15],
- though the different behaviours of dichloro- and difluoro- carbenes towards phenoxide could be rationalized in terms of the HSAB theory (the harder electrophile $:CF_2$ is attacked by the harder site of phenoxide (oxygen) whereas the softer $:CCl_2$ reacts with the softer carbon), the difference in hardness of these two carbenes does not seem important enough to account for such opposite regioselectivities.



Scheme II

Consequently, we are led to wonder whether the Reimer-Tiemann reaction does not imply, as its first step, the condensation of dichlorocarbene with the oxygen atom of phenoxide, followed by a migration of the dichloromethyl moiety. This proposal would be in agreement with the fact that ortho compounds are usually predominant in such a reaction :



Scheme III

The question was already raised by Miller and Thanassi[1] who explained in that way the low apparent conversion of phenoxide, compared to that of chloroform, in the "classical" Reimer-Tiemann reaction: (dichloromethoxy)benzene, when formed, is hydrolysed to phenoxide and sodium formate by the aqueous base. This argument, which is ambiguous when sodium hydroxide is used as base (since sodium formate could also result from the direct hydrolysis of dichlorocarbene), would be corroborated by the experiments in an anhydrous medium we describe here, where equal conversions of phenol and chloroform were observed.

We are aware that these explanations are, at the moment, rather speculative. A deeper mechanistic reinvestigation of the Reimer-Tiemann reaction would be necessary to support them.

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References

1. Miller, T.G.; Thanassi, J.W. *J. Org. Chem.*, 1960, **25**, 2009.
2. De Cat, A.; Van Poucke, R.; Pollet, P.; Schots, P. *Bull. Soc. Chim. Belges,* 1965, **74**, 270.
3. Hine, J.; Porter, J.J. *J. Am. Chem. Soc.*, 1957, **79**, 5493.
4. Langlois, B.R. *J. Fluorine Chem.*, 1988, **41**, 247.
5. Moore, G.G.I. *J. Org. Chem.*, 1979, **44**, 1708.
6. Yakobson, G.G.; Akhmetova, N.E. *Synthesis*, 1983 (3), 169 (review).
   Clark, J.H. *Chem. Rev.*, 1980, **80**, 429 (review).
7. Rozhkov, I.N.; Knunyants, I.L. *Doklady Chem. USSR*, 1971, **199**, 622.
8. Dyatkin, B.L.; Delyagina, N.I.; Mysov, E.I.; Knunyants, I.L. *Tetrahedron*, 1974, **30**, 4031.
9. Hayami, J.I.; Ono, N.; Kaji, A. *Tetrahedron Lett.*, 1968, 1385.
10. Nesmeyanov, A.N.; Pecherskaya, K.A.; Uretskaya, G.Ya. *Izv. Akad. Nauk SSSR*, OKhN, 1948, 240.
11. Christe, K.O.; Wilson, W.W. *J. Fluorine Chem.*, 1990, **47**, 117.
12. Rieux, C.; Langlois, B.R.; Gallo, R. *C.R. Acad. Sci. Paris*, Série II, 1990, **310**, 25.
13. Fujiwara, F.Y.; Martin, J.S. *J. Am. Chem. Soc.*, 1974, **96**, 7625.
14. Rieux, C. *PhD Thesis*, Univ. of Aix-Marseille III, December 16th, 1989.
15. Tiemann, F. *Ber.*, 1882, **15**, 2686.

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