Tetrahedron Vol. 38, No. 11, pp. 1569 to 1570, 1982.
Printed in Great Britain.

0040-4020/82/111569-02$03.00/0
Pergamon Press Ltd.

FREMY'S SALT OXIDATION OF BENZYLAMINES. AN OXIDATIVE DEAMINATION REACTION

Luis Castedo*, Ricardo Riguera and M. Jesús Rodriguez

Departamento de Química Orgánica de la Facultad de Química e Instituto de Productos Naturales Orgánicos (Sección Alcaloides) del C.S.I.C. Santiago de Compostela (Spain)

(*Received in UK 23 November* 1981)

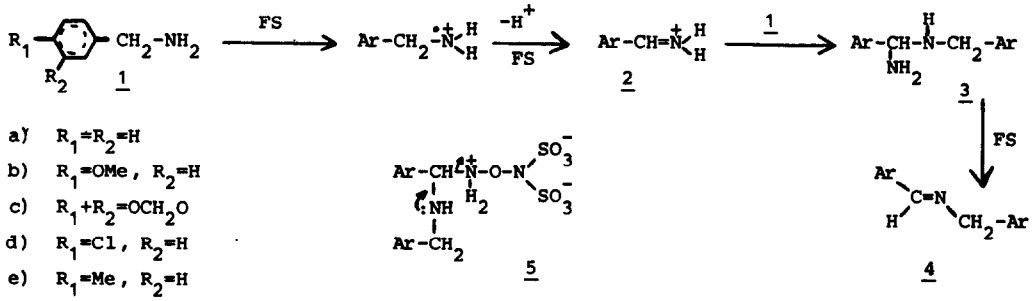
Abstract- Fremy's salt is shown to oxidize efficiently primary benzylamines to imines, benzaldehydes and nitriles.

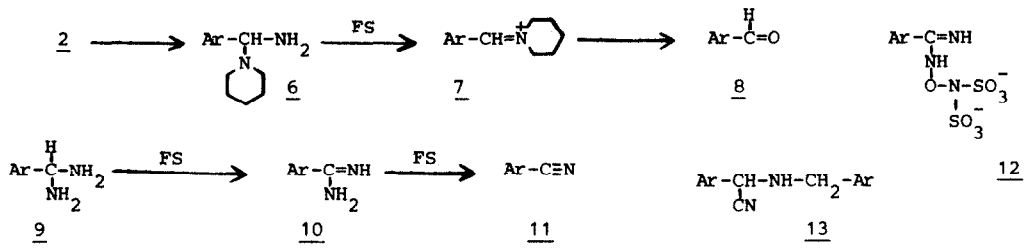
The ability of Fremy's salt (FS) to act as an oxidant towards phenols and anilines is well known[1]. It was not until quite recently that this reagent has been used to oxidize other types of amines namely tetrahydroisoquinolines and related alkaloids which were converted in this way to the corresponding aromatic and oxo compounds[2,3].

In trying to establish the general reactivity of FS with amines we here report that primary benzylamines are efficiently oxidized by this reagent, giving a variety of products depending on the reaction conditions. Thus, benzylamines 1a-e were added to an excess of FS in 5% sodium carbonate solution. After stirring for 2 hours at room temperature the reaction mixture was extracted giving a 88 to 97% yield of the corresponding imines 4a-e. This result can be explained by the known evolution[4] of the initially formed aminium radical to an immonium ion 2 which is an imine in the reaction media. This in the presence of the starting amine enters into a series of equilibria, via aminal 3, which eventually leads to 4[5a]. We attribute this to the insolubility of 4 in the reaction media. However, 4 might be the result of a further FS oxidation of 3 at its primary amino group to an adduct 5 which then suffers the cleavage of the C-N bond with assistance of the secondary nitrogen.

In the search for supplementary data we have found that when the reaction is performed in the presence of a competing nucleophile the immonium ion 2 can be trapped. A number of products are accordingly obtained depending on the position of the 2 to 3 equilibrium. Thus FS oxidation of 1 in the presence of 1 equivalent of piperidine produced a 60% yield of a (1/1) mixture of imine 4 and benzaldehyde 8, but with 4 equivalents of piperidine only 8 resulted in 50% yield[6]. The formation of 8 occurs most probably by hydrolysis of the quaternary immonium ion 7 formed along the lines of the aforementioned mechanism, the excess of piperidine being necessary to shift the equilibrium to 6. Nevertheless, the same result was obtained by using NH_4OH or pyridine instead of piperidine which indicated that aldehyde 8 could also be produced from 2.

The importance of the equilibrium imine- aminal in controlling the reaction products is remarkable. Thus, when the FS oxidation of 1b was conducted in conc. ammonium hydroxide instead of carbonate solution (equilibria strongly shifted to aminal 9) a mixture of benzaldehyde 8b, benzamidine 10b and benzonitrile 11b (4/ 1/ 2 ratio) resulted in 50% yield. The presence of benzamidine can be explained as the FS oxidation product of aminal 9b followed by the loss of an alpha proton. In the literature[5b] a similar reaction has been found, consisting of the treatment of imine 2 with iodine in liq. ammonia which gives a low yield of amidine 10b. On the other hand, the formation of benzonitrile 11b, considering the reaction temperature, should not be the result of an amidine elimination[5c]. It can be interpreted as the FS oxidation product of





benzamidine 10b through the intermediate 12 by a similar mechanism to that put foward previously for the conversion of 3 to 4. It is worth noting that imines such as 2 are oxidized by oxygen in the presence of methoxide to the corresponding nitriles 11[5b], which should occur by a similar process. Finally, when the above FS oxidation was carried out in the presence of other nucleophiles such as AcO^- and N_3^- a mixture of imine 4 and aldehyde 8 was obtained in 60% yield. The same result was found when the reaction was performed in the presence of EtOH as cosolvent, while in the presence of CN^- the aminonitrile 13 resulted in a quantitative yield.

The conversion of primary benzylamines to imines, benzaldehydes, amidines and nitriles illustrates the potential of FS as a reagent in Organic Chemistry. It also serves to stress that a number of biogenetic transformations which involve the oxidative deamination of a primary amino group could be due to a series of one electron oxidations performed by the biological equivalent of FS, which by analogy with the metabolic oxidations of alpha aminoacids and amines might be of the flavin type[7,8].

EXPERIMENTAL

NMR spectra were determined at 80 MHz on a Varian CFT-20 spectrometer in $CDCl_3$ with TMS as internal standard. Mass spectra were run on a KRATOS MS-25 instrument (direct insertion, 70 eV). IR spectra were run on a PYE UNICAM 1100 spectrometer and UV spectra on a PYE UNICAM 1700 spectrometer. Tlc was carried out on silicagel GF-254 (type 60) and CH_2Cl_2 as eluent. The tlc slides were visualized with UV light. Glc was performed on a Hewlett-Packard 5710A instrument. The packing used was 3% OV-17 on chromosorb W (mesh size 85/100). The column was 0.125 in. inner diam. and 2.3m long. The carrier gas (Nitrogen) flow rate was 15 ml/min. and oven temperature was programed from 120°C to 160°C. Peak areas were used to estimate the relative proportions of compounds in mixtures.

All reactions were carried out with Fremy's salt obtained according to a literature procedure (1) and used without further purification. The starting benzylamines were purchased from Aldrich Co. All reaction products have already been described in the literature.

General procedure

To the violet solution obtained by dissolving FS (aprox. 10 equivalents) in 40-60 ml. of 5% Na_2CO_3 aqueous solution was added the benzylamine 1 (100 mg.) neat or dissolved in a small amount (5 ml.) of THF or EtOH. The reaction mixture was stirred for about two hours at room temperature until disappearance of the starting benzylamine (by tlc). (When the FS oxidation was carried out in conc. NH_4OH (60 ml.), the reaction mixture was stirred for three days at room temperature). The reaction mixture was extracted with ether and the combined extracts were dried (Na_2SO_4) and concentrated in vacuo to dryness. The residue was distilled to give the imine 4, identified by direct comparison (UV, IR, NMR and MS) with authentic samples. When the FS oxidation was conducted in conc. NH_4OH the reaction mixture was extracted with $CHCl_3$ and the combined extracts were dried (Na_2SO_4) and concentrated in vacuo to give an oil which upon addition of Et_2O produced a small amount of a precipitate which was centrifugated and identified as the amidine 10b. The Et_2O solution was shown to contain a mixture of benzaldehyde 8b and benzonitrile 11b by direct comparison with authentic samples (tlc, glc and NMR).

AKCNOWLEDGEMENT. To the Comisión Asesora (Spain) for its financial support.

REFERENCES

1. H.Zimmer, D.C.Lankin and S.W.Horgan, Chem. Rev., 229 (1971).
2. P.A.Wehrli and B.Schaer, Synthesis, 288 (1974).
3. L.Castedo, A.Puga, J.M.Saá and R.Suau, Tet. Lett., 2233 (1981).
4. Y.L.Chow, W.C.Danen, S.F.Nelsen and D.H. Rosenblatt, Chem. Rev., 243 (1978).
5. a) P.A.S.Smith "Open Chain Nitrogen compounds", W.A.Benjamin Inc., N.Y., vol.1, p.301 (1965); b) ibid, p.311; c) ibid, p.179.
6. A second compound isolated from this reaction was shown to be N-nitrosopiperidine.
7. T.C.Bruice, Acc. Chem. Res., 13, 256 (1980).
8. J.Staunton "Primary Metabolism, a Mechanistic Approach", Clarendon Press, Oxford 1978.