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MIGRATION OF THE FERROCENYLMETHYL GROUP FROM NITROGEN TO AROMATIC CARBON

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We wish to report readily occurring rearrangements involving migration of the ferrocenylmethyl group ($FcCH_2$-, where Fc = ferrocenyl) from an N attached to an aromatic ring to a C of the ring.

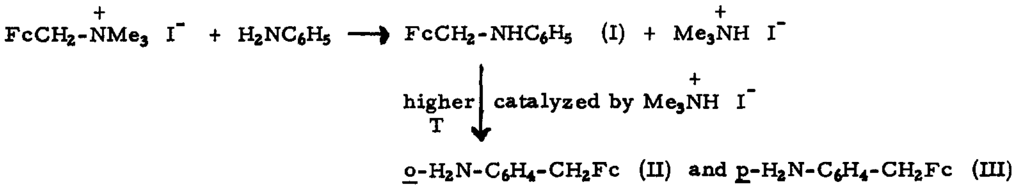
We discovered these rearrangements while engaged in a study of the ferrocenylmethylation of aromatic compounds. In the initial phase [2] of this study we had found that strongly nucleophilic aromatic compounds (like phenol, resorcinol, anisole, mesitylene, thiophene, thianaphthene, N-methylpyrrole, indole, ferrocene) are ring-C ferrocenylmethylated by $FcCH_2^+$ produced from $FcCH_2\text{-}\overset{+}{N}Me_3\ I^-$ according to equation

$$FcCH_2\text{-}\overset{+}{N}Me_3 \rightleftharpoons FcCH_2^+ + :NMe_3$$

in a solvent favoring such dissociation (e.g. in dimethylformamide), or from $FcCH_2OH$ or $(FcCH_2)_2O$ in the presence of an organic acid. We then extended our study to the ferrocenylmethylation of aniline and of some of its derivatives, even though aniline had been reported by others to be N-ferrocenylmethylated. According to the literature, N-(ferrocenylmethyl)aniline (I), m.p. 85°, results from ferrocenylmethylation of aniline with $FcCH_2\text{-}\overset{+}{N}Me_3\ I^-$ (henceforth to be referred to as methiodide) in boiling aqueous solution [3] or with $FcCH_2OH$ in hot aqueous solution [4]. I has also been synthesized by reduction of ferrocenecarboxaldehyde anil with $NaBH_4$ [5] and of ferrocenecarboxanilide with $LiAlH_4$ [6].

We do indeed find that I is produced by the action of methiodide on aniline in boiling water. The same product is obtained if the reaction is carried out in boiling triethylamine (90°) or in excess aniline near or below 130°. If, however, methiodide and excess aniline are heated to higher temperatures, increasing amounts of two new substances, namely o-(ferrocenylmethyl)aniline (II), m.p. 106-107°, and p-(ferrocenylmethyl)aniline (III), m.p. 115-116°, are formed at the expense of I. After one hour at 186° II and III are obtained to the exclusion of I in 82% total yield. Separation of II and III is achieved by column chromatography over alumina. The ratio of II to III (o/p ratio) is 1.6/1 (analysis by high-temperature gas chromatography).

We furthermore find that previously isolated I does not rearrange to II and III in refluxing aniline *unless* an acid catalyst, such as N-methylmorpholine hydrochloride or aniline hydrochloride, is present. When the more acidic aniline hydrochloride is used, the rearrangement occurs more rapidly. Thus with aniline hydrochloride catalysis I is completely rearranged after 1/2 hr at 150° (o/p ratio 1.9/1, total yield 85%), whereas with N-methylmorpholine hydrochloride catalysis the rearrangement is only 40% complete after 4 hrs at 155°. The rate at which I rearranges in the presence of N-methylmorpholine hydrochloride is similar to that at which it rearranges (without prior isolation) in the methiodide-aniline reaction mixture. We conclude that the acid catalyst responsible for the rearrangement of I in that mixture is the trimethylamine hydroiodide produced along with I in the initial phase of the reaction.



$$\mathrm{FcCH_2\text{-}\overset{+}{N}Me_3\ I^- + H_2NC_6H_5 \longrightarrow FcCH_2\text{-}NHC_6H_5\ (I) + Me_3\overset{+}{N}H\ I^-}$$

$$\Big\downarrow\ \text{higher } T;\ \text{catalyzed by } \mathrm{Me_3\overset{+}{N}H\ I^-}$$

$$\text{o-}\mathrm{H_2N\text{-}C_6H_4\text{-}CH_2Fc}\ \text{(II) and p-}\mathrm{H_2N\text{-}C_6H_4\text{-}CH_2Fc}\ \text{(III)}$$

Obviously, one may obtain II and III more rapidly and at more moderate temperatures by the simple expedient of adding some aniline hydrochloride to the methiodide-aniline reaction mixture.

The role of the acid catalyst in the rearrangement of I must be that of protonating the N of I, conferring a positive charge on this atom and thereby causing it to release the ferrocenylmethyl group as $FcCH_2^+$. The latter then attacks an ortho or para position, displacing a proton and yielding II or III.

The question arises whether this rearrangement is intramolecular or intermolecular. To find the answer I was dissolved, along with aniline hydrochloride, in N,N-dimethylaniline rather than in aniline and the mixture was maintained at 130° for 35 min. II and III, which would have resulted from an intramolecular rearrangement, were not formed in detectable quantities. Instead, the result was a mixture of o-(ferrocenylmethyl)-N, N-dimethylaniline (IV), m.p. 77.5-78°, and p-(ferrocenylmethyl)-N, N-dimethylaniline (V), m.p. 139-139.5° (o/p ratio 0.3/1 by isolation, total yield 83%). Since the production of IV and V from I requires an intermolecular migration, the rearrangement of I to II and III must be intermolecular, at least predominantly so.

Mixtures of IV and V, but in somewhat different ratios than obtained above, resulted also from the direct reaction of excess N, N-dimethylaniline with methiodide (135-140° for 1/2 hr, o/p ratio 0.8/1, total yield 81%) or with $FcCH_2OH + CH_3CO_2H$ (130° for one hour, o/p ratio 0.54/1, total yield 92%).

Reaction of excess aniline with $FcCH_2OH + CH_3CO_2H$ at 130° for 3/4 hr gave I in 44% yield and N, N-di(ferrocenylmethyl)aniline)[6] (VI), m.p. 163.5-164°, in 34% yield (the combined yield accounting for 78% of the $FcCH_2OH$ used). No II and III were obtained. Thus, I does not rearrange to II and III under these experimental conditions and some of it is even further N-ferrocenylmethylated to VI.

N-methylaniline resembles aniline in its behavior towards methiodide. At relatively low temperatures, e.g. in refluxing triethylamine, N-(ferrocenylmethyl)-N-methylaniline[6] (VII), m.p. 54°, is produced (70% yield). At higher temperatures (in excess N-methylaniline at 140° for 20 min.) there results a mixture of o-(ferrocenylmethyl)-N-methylaniline (VIII), m.p. 99-100°, and p-(ferrocenylmethyl)-N-methylaniline (IX), m.p. 89.5-90° (o/p ratio 1.3/1 by isolation, total yield 86%); VII is no longer detectable. Clearly, VII undergoes a rearrangement, catalyzed by trimethylamine hydroiodide, to VIII and IX. Under comparable conditions the trimethylamine hydroiodide catalyzed rearrangement of I to II and III is much slower. That VII is more rearrangement-prone than I is ascribable to the fact that the N of VII is more basic (by virtue of the +I effect of the attached methyl group) than that of I and hence is more subject to the protonation prerequisite to the rearrangement.

N-(Ferrocenylmethyl)acetanilide (X), m.p. 115-116°, which can be prepared by acetylation of I, undergoes a partial rearrangement to o-(ferrocenylmethyl)acetanilide (XI), m.p. 182-183°, and p-(ferrocenylmethyl)acetanilide (XII), m.p. 172-173°, when heated (175°, 2 hrs) in dimethylformamide - acetanilide solution containing pyridine hydrochloride and N-methylmorpholine. The ratio of XI to XII from this rearrangement was estimated by NMR spectroscopy to be about 0.5/1, and the combined yield was 37%. Authentic specimens of XI and XII were prepared by acetylation of II and III respectively.

The rearrangement of X to XI and XII is intermolecular, a conclusion based on the fact that on heating X (150^0, 4 hrs) in a dimethylformamide - resorcinol solution containing N-methylmorpholine hydrochloride one obtains as the sole product 4-(ferrocenylmethyl)resorcinol, m.p. 164-165^0, identical with the product of the direct ferrocenylmethylation [2] of resorcinol with methiodide.

A mixture of X, XI and XII resulted from the direct reaction [7] of methiodide with excess acetanilide in dimethylformamide solution (157^0, 3 hrs). The total yield was 44%, the ratio of X to (XI + XII) was 1.1/1 and that of XI to XII was about 0.5/1 (this latter ratio closely resembling that of XI to XII obtained from the rearrangement of X). At a higher temperature (188^0, 2 hrs) the direct reaction yielded no X and gave XI and XII in a ratio of approximately 0.5/1 and in a total yield of 55%.

Structural assignments throughout this work follow from elementary analysis, IR spectroscopy and NMR spectroscopy, of which the last-mentioned is particularly useful because the chemical shift of $FcC\underline{H_2}$ is considerably further downfield when attached to N than when attached to a benzene ring.

Since the ferrocenylmethyl group promises to become popular as a labeling and/or protective group, it is important to be aware of alternate ferrocenylmethylation sites, such as N vs. aromatic ring, and to be cognizant of conditions favoring rearrangement.

Footnotes and References

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7. Generally, amides with at least one H on the N are readily N-ferrocenylmethylated by methiodide (unpublished work by G.R. Freeman and T. I. Bieber).