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TRICARBONYLCYCLOHEXADIENONEIRON: A NEW PHENYLATING AGENT FOR AMINES

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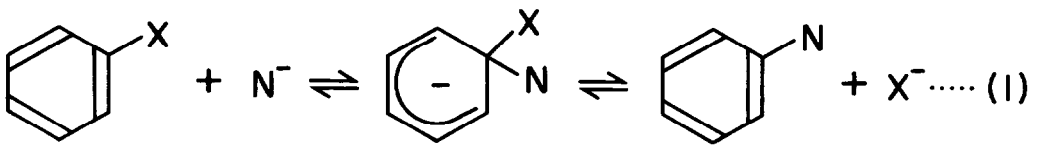
The arylation of amines is a difficult reaction and takes place only under rather severe conditions. For example, the copper catalysed arylation of amines (Ullmann reaction) is carried out at 200° for between several hours and several days.[1] Some milder reagents such as diaryliodonium salts[2] and triaryloxonium salts[3] have been used but apart from the unsubstituted (phenyl) compounds, these are not readily available. Triaryloxonium salts are fairly sluggish arylating agents and usually require several hours refluxing at 100°.[3]

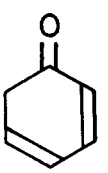
The lithium salts of secondary amines reacted with bromobenzene in HMPT at room temperature to give the phenylated amines in good yields, but much lower yields were obtained with primary amines.[4] These reactions may go via a benzyne intermediate.

Most of these arylation reactions probably take place via an addition-elimination sequence (Equation 1) and the severe conditions required reflect the amount of energy required to destroy the aromaticity.



..... (1)

If one could start with a hypothetical reagent (1) where the aromaticity has been destroyed beforehand, then obviously arylation could proceed under much milder conditions.



(1)

Tricarbonylcyclohexa-2,4-dien-1-oneiron derivatives,[5] e.g. (2) have normal if rather low carbonyl reactivity,[5,6] leading to the hope that they might constitute such arylating agents by nucleophilic attack on the carbonyl, and aromatisation by removal of the iron. A possible example is shown in Scheme 1. Hitherto, however, the hope has not been realised with the usual carbon nucleophiles for two major reasons: ready enolisation by basic reagents leads to loss of iron and formation of phenol (it has not even been possible to exchange the CH_2 with deuterium using sodium methoxide in deuteromethanol and decomposition is therefore as fast as formation of enolate anion) and the ready reducibility of the carbonyl, even by Grignard reagents, leads often chiefly to dimeric pinacols. The one success,[6] of a Reformatsky reaction, may be due to the low basicity and low reducing effect of the zinc reagent.

Under the correct conditions, we now find that the complex (2, R,R' = H) acts as an efficient phenylating agent for primary aromatic amines. The reaction of (2, R,R' = H) with aniline requires glacial acetic acid as solvent, and then gives diphenylamine (4, R = Ph) (90%). Similarly (2, R,R' = Me) gives 3,5-dimethyldiphenylamine (4, R = 3,5-dimethylphenyl)(95%). Hydroxylamine hydrochloride and sodium acetate under similar conditions, using (2, R,R' = H), give diphenylamine (65%). In this instance a reduction step, possibly by Fe(0), is required.

The success or failure of the reaction depends on the acidity of the medium and the pK_a of the amine. Without the acetic acid the reaction is very slow and it fails with trifluoroacetic acid. *p*-Nitroaniline reacts more slowly than aniline, presumably because of its lower nucleophilicity, and the product is a mixture of N-*p*-nitrophenylaniline and N,N'-diphenyl-*p*-phenylenediamine, due to reduction and further reaction of the former. *p*-Anisidine reacts to form N-phenyl-*p*-anisidine (85%).

By contrast, cyclohexylamine failed to react under a variety of conditions, as did the phosphinimine (3). With basic amines such as these, the preferred reaction with (2, R,R' = H) appeared to be on the tricarbonyliron group, forming a deep red solution from which only phenol could be isolated. On the mechanism in Scheme 1, failure of reaction may reflect the non-availability of the free amine under conditions required to protonate (2). An appropriate cation can be generated in a different manner by alkylation of (2) with triethyloxonium tetrafluoroborate giving (5). The salt is also obtained by hydride abstraction from (6). It is an effective phenylating agent for basic amines under essentially neutral and mild conditions (2 minutes at room temperature).

Reaction of (5) with cyclohexylamine (2 equivalents) in methylene chloride gives

N-phenylcyclohexylamine (70% based on 5). The first equivalent appears to react with the tricarbonyliron group to give a deep red complex, and the second equivalent is necessary to bring about the substitution. This behaviour has not been noted[7] in the alkylation of amines by acyclic tricarbonyldieneiron cations. The secondary amine diethylamine similarly gives N,N-diethylaniline (50%), but diphenylamine failed to react.

The more general use of reagents such as (2) and (5) as mild phenylating agents is under further investigation.

Procedures :

(i) Tricarbonylcyclohexadienoneiron (0.5 g, 2.14 mmole) and aniline (180 µl, 2.0 mmole) in glacial acetic acid (1.0 ml) were kept at 75° overnight under nitrogen. The product was partitioned between ether and dilute KOH solution, and the ether-soluble product purified on silica to give pure diphenylamine (290 mg, 90%), m.p. 52-54° undepressed by authentic material.

(ii) Tricarbonylcyclohexadienoneiron (0.4 g, 1.7 mmole) and triethyloxonium tetrafluoroborate (0.33 g, 1.73 mmole) in methylene chloride were stirred overnight under nitrogen. Cyclohexylamine (390 µl, 3.4 mmole) was then added. Work-up of the deep red solution as above gave N-cyclohexylaniline as an oil (207 mg, 70%) identified by comparison with an authentic sample of t.l.c. behaviour and mass spectrum, and by the hydrobromide m.p. 189-190° undepressed by the authentic compound.

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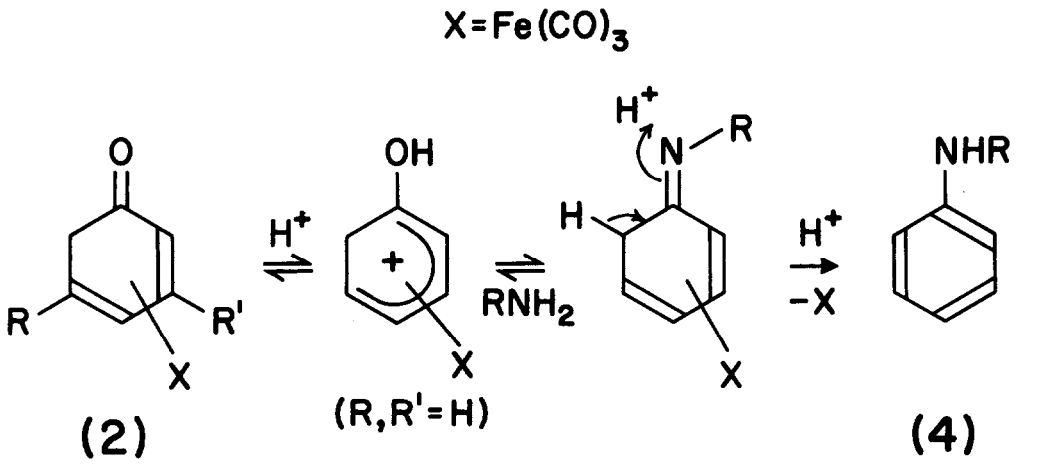

Scheme I

$Ph_3P=N-CH_2Ph$

(3)