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STUDIES ON ORGANOPHOSPHORUS COMPOUNDS—IV[a]

HMPA AS PRECURSOR FOR DIMETHYLAMINE IN NUCLEOPHILIC AROMATIC SUBSTITUTION REACTIONS

E. B. PEDERSEN,* J. PERREGÅRD and S.-O. LAWESSON
Department of Organic Chemistry, Chemical Institute, University of Aarhus,
DK-8000 Aarhus C, Denmark

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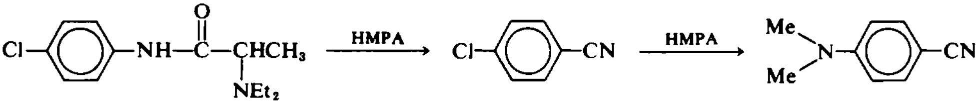
Abstract—The potential leaving groups (NO_2, Cl, Br, OH, OMe) in nucleophilic aromatic substitution reactions are replaced by a dimethylamino group simply by heating the aromatic compounds (activated by cyano- or nitro-groups) in HMPA at elevated temperature.

INTRODUCTION

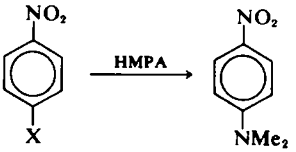
Hexamethylphosphoric triamide (HMPA) has been used to convert chloronitrobenzenes to dimethylaminonitrobenzenes.[1,2] In a previous paper[3] it was postulated that the formation of *p*-dimethylamino-benzonitrile from a *p*-chloro-propioanilide occurred according to the following sequence:



To get the scope of such reactions and evidence of the mechanism, an investigation of other possible leaving groups than the Cl atom and of other activating groups than the nitro group has been made. The results are presented in this paper.

DISCUSSION

p-Substituted nitrobenzenes (Fig 1) are heated for ½–1½ hr at 210–230° in HMPA giving the corresponding N,N-dimethyl-*p*-nitr-aniline. However, if X = SMe or NH_2, no replacement with the dimethylamino group could be found. The leaving groups, X, are also well known as such in the bimolecular nucleophilic aromatic substitution reactions. The resemblance is even more striking, as SMe and NH_2 are known to be poorer leaving[4] groups in nucleophilic aromatic substitution than those with which we succeeeded in replacement with a dimethylamino group.



X: NO_2, Cl, Br, OH, OMe

Fig 1

As should be predicted from the similarity with nucleophilic aromatic substitution, *o*-chloro-nitrobenzene and *o*-nitro-phenol (by treatment with HMPA at elevated temperature) are converted to N,N-dimethyl-anthranilo-nitrile, whereas *m*-chloro-nitrobenzene gave only a minor yield of N,N-dimethyl-*m*-nitr-aniline.

For *o*- and *p*-chloro-benzonitrile considerably longer reaction time (16–22 hr) than for the corresponding chloronitrobenzenes was needed to get a replacement of the chlorine with a dimethylamino group. The same trend was also found for *p*-hydroxy-benzonitrile. This is also in accordance with the postulated similarity for these reactions with nucleophilic aromatic substitution reactions, which are accelerated by electron-withdrawing groups.[5]

A nucleophilic aromatic substitution mechanism is suggested in Fig 2. It is assumed that one of the N atoms in HMPA attacks the aromatic ring giving a Meisenheimer complex. Rearrangement of the bis-(N,N-dimethylamido)-phosphono group from nitrogen to X is supposed to produce a new Meisenheimer complex and the leaving group $[-X-PO(NMe_2)_2]^+$ formed in this way is then easily

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[a] Part III, Ref 3.

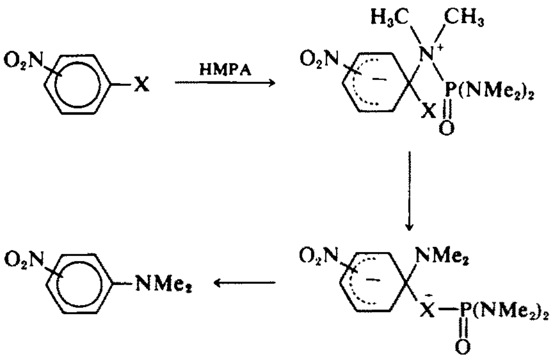

Fig 2

split off and the N,N-dimethylaniline is formed. That it is claimed that HMPA acts as an electron donor in the first step of this reaction is supported by the fact that the donor properties of HMPA have been established in complexes between HMPA and metal ions.[13] If X = OH, the corresponding bis-(dimethylamino)-arylphosphate is possibly a reaction intermediate, as it is known that phenol reacts with an excess of HMPA to give bis-(N,N-dimethylamido)-phenylphosphate.[12] Other evidence for the arylphosphate as an intermediate is that **1** (Fig. 3) could be thermally decomposed to N,N-dimethyl-*p*-butro-anilin. Furthermore *bis*-(N,N-dimethylamido)-*p*-cyanophenyl phosphate was isolated in small amount in the reaction of *p*-hydroxybenzonitrile with HMPA.

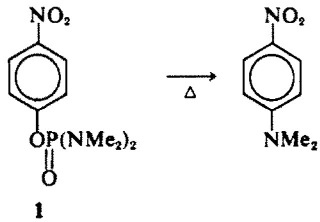

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Fig 3

CONCLUSION

When dimethylamine is the nucleophile in nucleophilic aromatic substitution reactions, the reactions are normally performed at high pressure. However, as shown in this paper, substitution by a dimethylamino group can be performed on activated aromatic rings at normal pressure by heating in HMPA.

EXPERIMENTAL

In all experiments commercial HMPA dried over molecular sieves (3 A) was used.

p-*Chloro-nitrobenzene* (10 g) was heated in HMPA (50 ml) at 220° for 1 hr. The mixture was allowed to cool to room temp and was then poured into water (400 ml) and extracted 4 times with 200 ml ether. The combined ether-phases were washed twice with 100 ml water, dried over $CaSO_4$, the ether was stripped off and by recrystallization from EtOH yielded 6·9 g (65%) of N,N-dimethyl-*p*-nitr-aniline m.p. 165°, litt.[6] m.p. 165°.

o-*Chloro-nitrobenzene* (10 g) was heated in HMPA (50 ml) at 220° for 1 hr. The mixture was allowed to cool to room temp and was then poured into water (400 ml) and extracted 4 times with 200 ml ether. The combined ether phases were extracted 3 times with 25 ml 4 N HCl. To the combined water phases 30% NaOH was added until basic and they were then extracted 3 times with 100 ml ether. The ether extract was dried and distillation 130–131/9 mm gave 7·1 g (67%) of N,N-dimethyl-*o*-nitr-aniline, n_D^{22} = 1·6083, litt.[7] n_D^{22} = 1·6120, litt.[7] b.p. = 154/24 mm.

m-*Chloro-nitrobenzene* (10 g) was heated in HMPA (50 ml) at 235° for 3 hr and worked up as for *o*-chloronitrobenzene. Instead of distillation, the raw material was subjected to preparative TLC (silica gel as supporting material and elution twice with ether–light petroleum ether (1:4)), and yielded 0·3 g (3%) of N,N-dimethyl-*m*-nitroaniline, R_f = 0·33, recrystallization from EtOH m.p. 56°, litt.[8] m.p. 59–60°.

p-*Nitrophenol* (10 g) was heated in HMPA (50 ml) at 230° for 1 hr under N_2. The mixture was allowed to cool to room temp and poured into 400 ml water. Filtration and recrystallization gave 6·5 g (54%) of N,N-dimethyl-*p*-nitr-aniline.

p-*Methoxynitrobenzene* (10 g) was heated in HMPA (50 ml) at 235° for 2 hr, worked up as for *p*-nitrophenol and 3·6 g (33%) of N,N-dimethyl-*p*-nitr-aniline was obtained.

p-*Bromonitrobenzene* (10 g) was heated in HMPA (50 ml) at 210° for 1 hr, worked up as for *p*-nitro-phenol and 4·1 g (50%) of N,N-dimethyl-*p*-nitr-aniline was obtained.

p-*Dinitrobenzene* (2 g) was heated in HMPA (10 ml) at 230° for 1½ hr. The cooled mixture was poured into 100 ml water and filtration followed by sublimation at 150°/0·2 mm gave 0·8 g (40%) of N,N-trimethyl-*p*-nitr-aniline.

o-*Nitrophenol* (10 g) and HMPA (50 ml) were heated so that the temp was allowed to rise from 215° to 235° during 20 min. The mixture was then worked up as for *o*-chloronitrobenzene and 1·0 g of N,N-dimethyl-*o*-nitraniline was obtained.

o-*Chloro-benzonitrile* (10 g) and HMPA (50 ml) were heated at 235° for 22 hr, worked up as for *o*-chloronitrobenzene and distillation 122–124/8 mm, litt.[9] b.p. 137–138/14 mm gave 2·5 g (23%) of N,N-dimethyl-anthranilo-nitrile.

p-*Chlorobenzonitrile* (5 g) and HMPA (25 ml) were heated at 220 for 16 hr, worked up as for *o*-chloronitrobenzene and recrystallization from light petroleum benzene gave 3·2 g (60%) of *p*-dimethylaminobenzonitrile; m.p. 73° litt.[10] m.p. 76°.

p-*Hydroxybenzonitrile* (11·9 g) and HMPA (50 ml) were heated at 227–230° for 22½ hr. HMPA was distilled off at 112–134°/10 mm. Further distillation gave:

(a) A fraction, b.p. 148–162°/1·0 mm was poured into water (150 ml). The water phase was extracted 4 times with ether (100 ml), washed twice with water (50 ml), dried over $CaSO_4$ and ether stripped off. Recrystallization from light petroleum—benzene (3:1) gave 7·6 g (52%) of *p*-dimethylamino-benzonitrile.

(b) A fraction, b.p. 163–210°/1 mm, was chromatographed on a silica gel column. Eluation with ether gave further 0·6 g of the benzonitrile. Eluation with MeOH gave a fraction which, when the MeOH was stripped off, was poured into 100 ml water (saturated with NaCl). The water phase was extracted twice with 75 ml ether, the combined ether phases were washed twice with 25 ml water (saturated with NaCl) dried over $CaSO_4$ and the ether eaporated. Distillation gave 0·8 g (3%) of bis-(N,N-dimethylamido)-*p*-cyanophenyl phosphate, b.p. 153–154/0·2 mm, $n_D^{24} = 1{\cdot}5209$, litt.[14] $n_D^{25} = 1{\cdot}5196$.

Bis(dimethylamido)-p-nitro-phenylphosphate[11] (1 g) was heated at 220° for $\frac{1}{2}$ hr and sublimation gave N,N-dimethyl-*p*-nitr-aniline.

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