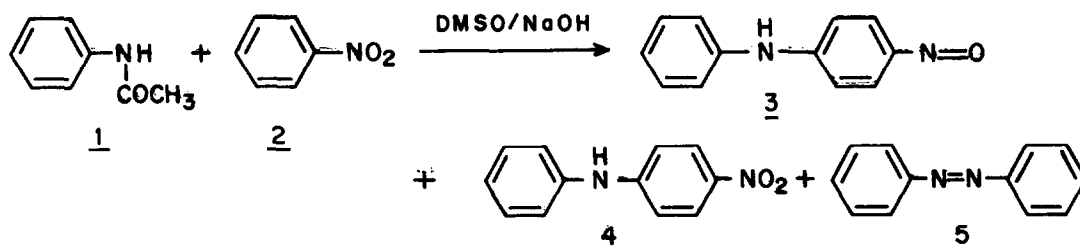


A NOVEL REACTION OF ACETANILIDE WITH NITROBENZENE IN DMSO - AN UNUSUAL SOLVENT ASSISTED REGIOSELECTIVE AROMATIC NUCLEOPHILIC SUBSTITUTION*

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Summary: The reaction of acetanilide (1) with nitrobenzene (2) in the presence of a base in DMSO yielded *p*-nitrosodiphenylamine (3) as the major product. This unusual regioselective formation of the deoxygenated product 3 has been rationalized in terms of solvent effects exerted by DMSO.

Recently, we reported a novel synthesis of unsymmetrical azo-aromatics in good yields and high selectivities by the reaction of acetanilides with nitroarene in presence of an excess of a mixture of solid sodium hydroxide and potassium carbonate.¹ Inert non-polar xylene was used as a solvent. Now we find that an aromatic nucleophilic substitution is facilitated in high selectivity when acetanilide (1) is reacted with nitrobenzene (2) in the presence of an excess of the base in the dipolar aprotic dimethyl sulphoxide as solvent instead of xylene. Thus, the reaction afforded *p*-nitrosodiphenylamine (3) as the major product together with minor amounts of *p*-nitrodiphenylamine (4) and azobenzene (5) (Scheme-1).



Scheme-1

In this communication, the unusual regioselective formation of the deoxygenated product 3 has been rationalized in terms of the solvent effects exerted by DMSO.

The reaction of acetanilide was performed under optimized conditions.² The identity of 3 was established by spectral and X-ray crystallographic analyses. Further confirmation was obtained by comparison with a standard sample.³ The feasibility of the reaction was examined in other dipolar aprotic solvents under similar conditions. The yield data are summarized in the Table.

Table: Reaction of acetanilide with nitrobenzene in dipolar aprotic solvents

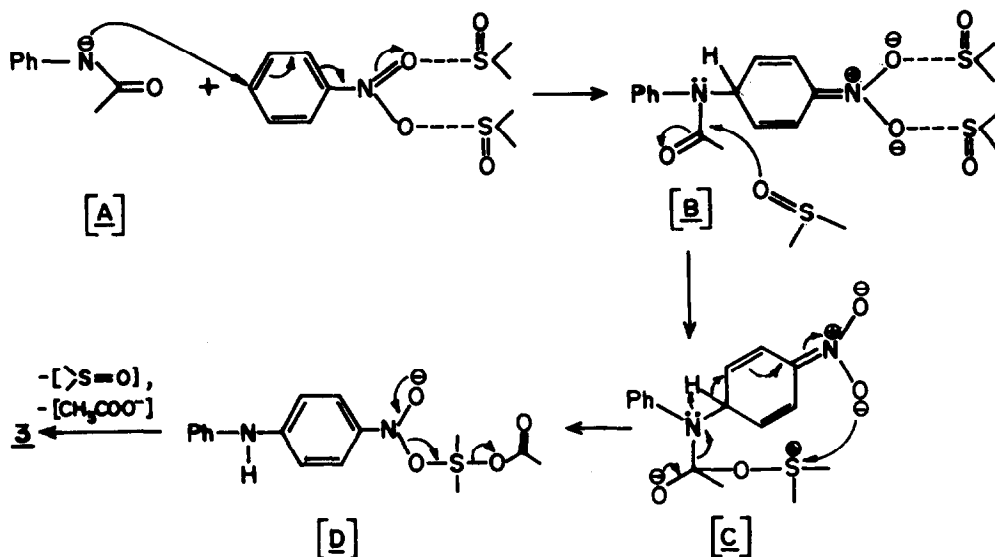
Solvent	Dielectric constant ⁶	Basicity ^a		Yield ^b (%)		
		pKa ⁷	$\Delta\delta$ ppm	3	4	5
HMPA	30	-	2.03	62	10	10
DMSO	46	-1.54	1.34	60	10	10
SulphoYane	43	-1.34	0.78	5	-	-
DMF	37	-1.60	1.30	No reaction		
THF	8	-2.32	0.80	No reaction		
Acetone	21	-2.85	0.94	No reaction		
Acetonitrile	38	-	0.31	No reaction		

^a The basicity data of the solvents are indicated in terms of both pKa and $\Delta\delta$ values. The latter values are the difference in the chemical shifts at infinite dilution of a solution of chloroform in the solvent in question (δ_{CHCl_3}) and an inert solvent such as cyclohexane(δ).

^b Isolated yield

Apparently, DMSO has not only exerted a solvent effect in facilitating an aromatic nucleophilic substitution but has also brought about the deoxygenation of a nitro to a nitroso group. It was initially thought that the solvent itself may be abstracting the oxygen from the nitro group forming dimethylsulphone.⁴ However, our attempts to detect dimethylsulphone either by liquid chromatographic separation or by GC-MS of the reaction mixture did not succeed. Alternatively, the hypothesis that the *p*-nitrodiphenylamine (4) formed initially underwent deoxygenation to 3 was also ruled out, since the pure 4 did not afford 3 under identical conditions.

Based on the above observations, a probable mechanism as shown in Scheme-2 may be postulated for the formation of 3. A nitrogen anion [A] of acetanilide is easily generated under the enhanced basicity of the dipolar aprotic solvent medium which, on account of its low degree of solvation in DMSO, is highly reactive. The anion [A] reacts in a facile manner at the electron-deficient *para* carbon of nitrobenzene, giving rise to a Meisenheimer salt [B]. The enhancement of the electrophilicity at this carbon atom is due to a solvent assisted resonance effect caused by the high basicity and dielectric constant of DMSO. An evidence in support of this observation is the greater deshielding of the *para* proton of nitrobenzene in DMSO by 0.2 ppm as compared to its chemical shift in the absence of the solvent.⁵ A solvent DMSO molecule then reacts at the electron deficient carbonyl carbon generating the species (C) which undergoes deacetylation. The deacetylation enhances the electron



Scheme - 2

density at the nitrogen which then picks up the proton triggering an aromatization. The oxygen anion of the nitro group reacts with the electrophilic sulphur in a concerted fashion as shown in (C) leading to the species (D). A deoxygenation with the elimination of a solvent DMSO molecule and elements of an acetate anion leads to 3. The formation of 4 may be explained by the loss of hydrogen as a hydride ion from (B).

The results of the reaction in other dipolar aprotic solvents such as HMPA, DMF, sulpholane, THF, acetone and acetonitrile (Table) suggest that the feasibility of the reaction is determined by the basicity and dielectric constant of the medium. The solvents with higher basicities and dielectric constants have promoted the reaction. Although HMPA has a lower dielectric constant in relation to DMSO, it has given a comparable yield of 3 owing to its stronger basicity. Sulpholane which has a much lower basicity but a comparable dielectric constant has given rise to much lower yield of 3. Although DMSO and DMF are known to enhance the medium basicity to the same extent, the non-occurrence of the reaction in the latter solvent may be attributed to its lower dielectric constant and to a facile side-reaction with the hydroxide ion present liberating dimethylamine and formate ion.⁶ In THF and acetone with much lower dielectric constants, and acetonitrile with much lower basicity, no reaction was observed.

To conclude, a strongly basic dipolar aprotic solvent with a high dielectric constant viz. DMSO has facilitated a normally sluggish nucleophilic reaction at an aromatic carbon. In addition, a solvent assisted unusual deoxygenation also occurred simultaneously to yield an industrially important organic chemical viz. p-nitrosodiphenylamine in a one-step operation.

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References and Notes:

+ NCL Communication No. 4870

1. N.R. Ayyangar, S.N. Naik and K.V. Srinivasan, Tetrahedron Lett. **30**, 7253 (1989).
2. In a typical experiment, a mixture of acetanilide (0.05 mole), nitrobenzene (0.05 mole), sodium hydroxide (0.2 mole) and potassium carbonate (0.05 mole) in DMSO (75 ml) was heated at 80°C for 5 h. The reaction mixture was cooled to 28°C and drowned into ice-cold water (50 ml). It was then neutralized with dil. hydrochloric acid and extracted with ethyl acetate (5 x 50 ml). The dried extract was freed of the solvent and the residual liquid was chromatographed through a silica gel column using pet. ether: ethyl acetate (1:1) as eluant to isolate the products. Identical results were obtained when potassium carbonate was excluded from the mixture of bases. At 130°C, the reaction afforded a higher proportion of azobenzene (30%) with a decrease in formation of **3** (30%).
3. A standard sample of **3** was synthesized by the Fischer-Hepp rearrangement of N-nitroso diphenylamine as per the procedure described in Japanese Patent 78,77,025 (1978); Chem. Abstr., **90**, 6070c (1979).
4. Cf. see M. Akitoshi, N. Nobuyoshi, N. Tadahiko (Kiresuto Guken Co. Ltd.), Jpn. Kokai Tokkyo Koho 79,44,611 (1977); Chem. Abstr. **91**, 91170y (1979).
5. Chemical shift of para proton of nitrobenzene (δ ppm): $\delta_{\text{DMSO}} = 7.88$; $\delta_{\text{neat}} = 7.68$; $\Delta\delta = 0.2$.
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