

Aldol Reactions of Formaldehyde in Non-aqueous Media

II. Base-catalyzed Reaction of Fluorene and Nitrotoluenes with Formaldehyde in Dimethyl Sulfoxide

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Fluorene and *o*- and *p*-nitrotoluene have been shown to react in an aldol-like addition with paraformaldehyde in dimethyl sulfoxide under the influence of a strong base to give hydroxymethyl compounds.

Many anion-catalyzed reactions proceed at a high rate when performed in dimethyl sulfoxide (DMSO), which has been explained by the poor solvation of the anionic catalyst in this solvent.¹⁻³ For example, alkyl aryl ketones have been shown to react rapidly with paraformaldehyde in the presence of base in DMSO solution.⁴ The high rate of reaction may be attributed to rapid abstraction of the activated hydrogens from the ketone by the poorly solvated anionic catalyst. In the present communication it is shown that compounds with very weakly activated hydrogen atoms, such as fluorene and *o*- and *p*-nitrotoluene, react readily with paraformaldehyde in DMSO in the presence of a strong base, hydroxymethyl compounds being formed.

RESULTS AND DISCUSSION

Fluorene is known to react with aldehydes and ketones under the influence of a strong base to yield fulvenes. Ghera and Sprinzak⁵ have found that hydroxylic compounds are obtained if the reaction is performed in pyridine in the presence of benzyltrimethylammonium hydroxide (Triton B). For example, the reaction of fluorene with formaldehyde provides 9,9-bis(hydroxymethyl)fluorene (I) in a yield of 28 %.

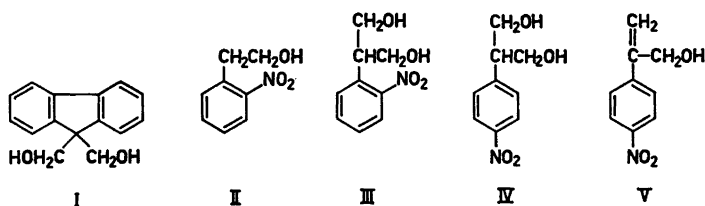
When DMSO was used as a solvent and sodium ethoxide as a catalyst, fluorene reacted with paraformaldehyde to give compound I in 70 % yield after a reaction time of 3 min at about 0°. This result suggests that the abstraction of hydrogen from fluorene and the intermediate 9-fluorenylmethanol by poorly solvated ethoxide ions proceeds very rapidly.

Nitro substituted toluenes are known to react with benzaldehydes in the presence of base. 2,4,6-Trinitrotoluene, for instance, reacts easily with benzaldehyde under the influence of piperidine to form 2,4,6-trinitrostilbene.^{6,7} The hydrogen atoms of the methyl group of 2,4-dinitrotoluene are less activated

than in the trinitrotoluene, and reaction takes place only at elevated temperature (170°) with the formation of 2,4-dinitrostilbene.⁸ It has been reported⁹ that *p*-nitrotoluene reacts with benzaldehyde in the presence of piperidine under forcing conditions (16 h at 180°) to give *p*-nitrostilbene in a moderate yield, while the less reactive *o*-nitrotoluene remains unchanged.

Russell, Becker *et al.*¹⁰ have found that in DMSO solution toluenes substituted with strongly electron attracting groups readily form carbanions under the influence of a strong base and react with benzaldehydes to give stilbenes. No hydroxylic compounds have been obtained.

The reaction of aliphatic nitro compounds with aqueous formaldehyde in the presence of base is known to yield hydroxymethyl compounds in an aldol-like addition (Henry reaction).



It has now been found that *o*-nitrotoluene reacts with paraformaldehyde in DMSO-*tert*-butyl alcohol 5:1 in the presence of potassium *tert*-butoxide. Two reaction products were isolated. By IR and NMR spectroscopy as well as elemental analysis they were found to be 2-(*o*-nitrophenyl)ethanol (II) and 2-(*o*-nitrophenyl)-1,3-propanediol (III). Compound II has previously been obtained by nitration of 2-phenylethyl acetate.¹¹ It is assumed that II and III are formed by a mechanism similar to the mechanism of the Henry reaction.¹²

The reaction of *p*-nitrotoluene with paraformaldehyde under conditions similar to the reaction of *o*-nitrotoluene afforded 2-(*p*-nitrophenyl)allyl alcohol (V), as shown by IR, NMR, and elemental analysis. It seems likely that the formation of V proceeds *via* the bis(hydroxymethyl) compound IV, formed by a reaction analogous to the formation of III. Base catalyzed elimination of water from IV yields V.

EXPERIMENTAL

Dimethyl sulfoxide (purum) was dried over calcium hydride and distilled at 2 mm Hg through a 60 cm Vigreux column. Paraformaldehyde, containing 99.5 % CH₂O, was supplied by Perstorp AB, Perstorp, Sweden. Other chemicals used were purum grade. The IR spectra were recorded on a Beckman IR-9 spectrophotometer. NMR spectra were recorded in deuteriochloroform solution using a Varian A-60 instrument. Melting points are uncorrected.

9,9-Bis(hydroxymethyl)fluorene (I). Paraformaldehyde (4.0 g, 0.13 mole) was suspended in DMSO (50 ml), and sodium ethoxide (0.57 g, 8.4 mmoles) dissolved in ethanol (3 ml) was added. To the stirred mixture, which was cooled in an ice bath, a solution of fluorene (8.0 g, 0.05 mole) in DMSO (50 ml) was added during 30 sec. Most of the solid paraformaldehyde dissolved instantly. After a total reaction time of 3 min the solution was neutralized with hydrochloric acid, and diluted with 200 ml of water. The mixture was saturated with sodium chloride, and extracted with ethyl acetate. The

extract was washed with water and dried over anhydrous sodium sulfate, and the solvent was removed under vacuum. Slightly yellow crystals of I were obtained (8.4 g, 74 %). The compound crystallized from benzene in colourless needles, m.p. 144–145° (lit.⁵ 145.5–146.5°).

Reaction of paraformaldehyde with o-nitrotoluene. *o*-Nitrotoluene (6.1 g, 49.5 mmoles) was dissolved in DMSO (25 ml), and paraformaldehyde (4.1 g, 137 mmoles) was suspended in the solution. The mixture was stirred under nitrogen. Potassium *tert*-butoxide (0.9 g, 8 mmoles), dissolved in 5 ml *tert*-butanol, was added to the mixture, which acquired a strong reddish brown colour. After a reaction time of 5 min at room temperature the solution was heated to 70° for 5 min. After neutralizing with hydrochloric acid the solution was diluted with water (150 ml). Sodium chloride was added to saturation, and the mixture was extracted with ethyl acetate. The extract was washed with sodium chloride solution and dried over anhydrous calcium sulfate. Evaporation of the solvent under vacuum yielded 8.1 g of a yellow oil. Chromatography of this oil on a silica gel column with ethyl acetate as eluent gave three groups of fractions, which on evaporation of the solvent yielded the following products:

- 1) 0.13 g of an oil, which according to its IR spectrum consisted of *o*-nitrotoluene;
- 2) 0.23 g of 2-(*o*-nitrophenyl)ethanol (II). Yield 11 %. (Found: C 57.78; H 5.38. Calc. for C₈H₉O₃N: C 57.48; H 5.43);
- 3) 1.17 g of an oil, which was identified as 2-(*o*-nitrophenyl)-1,3-propanediol (III) by IR and NMR spectra. Yield 49 %. (Found: C 54.94; H 5.52. Calc. for C₉H₁₁O₄N: C 54.82; H 5.52).

Reaction of paraformaldehyde with p-nitrotoluene. *p*-Nitrotoluene (6.1 g, 49.5 mmoles) was dissolved in DMSO (25 ml), and paraformaldehyde (4.1 g, 137 mmoles) was suspended in the solution. Potassium *tert*-butoxide (0.9 g, 8 mmoles) dissolved in *tert*-butyl alcohol (5 ml) was added to the stirred mixture, which became strongly coloured (wine red). The reaction was performed under nitrogen. After 5 min reaction at room temperature, the reaction mixture was heated to 70° for 20 min. After neutralizing with hydrochloric acid the solution was diluted with water (150 ml), and the reaction mixture was worked up as in the reaction of *o*-nitrotoluene. A red oil (8 g) was obtained, and chromatography of 2.0 g of this oil on a silica gel column with ethyl acetate as eluent yielded 380 mg 2-(*p*-nitrophenyl)allyl alcohol (V). Yield 23 %. Further purification by repeated preparative thin layer chromatography yielded a slightly yellow crystalline product, m.p. 38–40°. (Found: C 60.67; H 4.88; N 8.04. Calc. for C₉H₉O₃N: C 60.29; H 5.06; N 7.87.) IR and NMR spectra were consistent with the assigned structure.

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