ACTA CHEMICA SCANDINAVICA 21 (1967) 713–717

Aldol Reactions of Formaldehyde in Non-aqueous Media

I. Base-catalyzed Reaction of Alkyl Aryl Ketones with Formaldehyde in Dimethyl Sulfoxide

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Base-catalyzed aldol reactions between paraformaldehyde and some alkyl aryl ketones in dimethyl sulfoxide (DMSO) have been investigated. The reactions were found to yield hydroxymethyl compounds at high rates, which may be attributed to the high reactivity of the anionic catalyst in the DMSO medium.

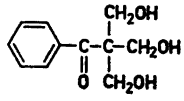
Several studies of anion-catalyzed reactions in certain polar aprotic solvents, particularly dimethyl sulfoxide (DMSO) have been reported during recent years. In such solvents, small anions, such as the hydroxyl ion and the methoxide ion, are poorly solvated and therefore much more reactive than the heavily solvated ions present in protic solvents like water and alcohols.[1] An example of the increased rates of anion catalyzed reactions in aprotic solvents is the result reported by Cram *et al.*[2] according to which the anion-catalyzed racemization of 2-methyl-3-propionitrile proceeds 10^9 times faster in DMSO than in methanol.

So far, no study concerning base-catalyzed formaldehyde reactions in DMSO seems to have been reported. Aldol reactions of formaldehyde with aliphatic aldehydes and ketones often proceed at a sufficient rate when performed in protic solvents, but alkyl aryl ketones are reported to react slowly and to give rise to complicated reaction mixtures.[3–5,7] In the present work it is shown that alkyl aryl ketones react easily and at a high rate with paraformaldehyde in DMSO solution to yield hydroxymethyl compounds.

RESULTS AND DISCUSSION

Acetophenone has been reported to react with paraformaldehyde in methanol solution in the presence of potassium carbonate at a very slow rate to yield 5-benzoyl-1,3-dioxane,[4] 1,3-dimethoxy-2-benzoylpropane and 2-

benzoyl-3-methoxypropene, in addition to considerable amounts of undistillable material.[5] When acetophenone was allowed to react in DMSO with paraformaldehyde in the presence of potassium carbonate, α,α,α-tris(hydroxymethyl)acetophenone (I) and 2-benzoylallyl alcohol (II) were obtained in yields of 4 and 13 %, respectively, after less than one hour's reaction at room temperature. In spite of the mild conditions used some polymeric material was also formed in the reaction. The use of ethanolic potassium hydroxide as a catalyst caused a rapid, exothermic reaction resulting in increased polymer formation, but when the reaction was carried out at 10—20°, I and II could be isolated in 15 and 33 % yield, respectively, after a reaction time of 45 min. No unreacted acetophenone could be detected, whereas in a similar experiment with ethanol as solvent, 83 % of the initial amount of acetophenone was found to be unreacted by vapour phase chromatography.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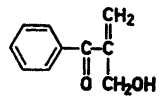
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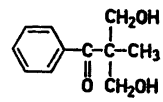
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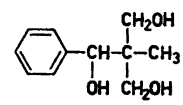
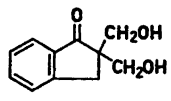

IV

The reaction of propiophenone with paraformaldehyde in DMSO, catalyzed by ethanolic potassium hydroxide, was more easily controlled and yielded less polymeric material than the reaction with acetophenone. α,α-Bis(hydroxymethyl)propiophenone (III) was obtained as the main product in a yield of 40 % after 40 min reaction at room temperature. A small amount of 1-phenyl-2,2-bis(hydroxymethyl)-1-propanol (IV) was also formed, obviously by a crossed Cannizzaro reaction between III and formaldehyde. The latter reaction was found to take place readily if III was treated in DMSO with excess of paraformaldehyde and potassium hydroxide. The alcohol IV has also been reported to be formed when the reaction of propiophenone with formaldehyde was carried out in boiling aqueous ethanol.[6]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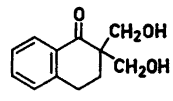
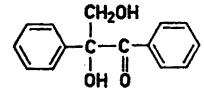

VI


VII

The cyclic aromatic ketones 1-indanone and 1-tetralone reacted rapidly with formaldehyde in DMSO in the presence of potassium hydroxide without appreciable evolution of heat and polymer formation. The reactions were complete within 7 min at room temperature, and yielded more than 70 % of 2,2-bis(hydroxymethyl)-1-indanone (V) and 2,2-bis(hydroxymethyl)-1-tetralone (VI), respectively. In a comparative experiment with ethanol as solvent, 84 % of the tetralone remained unreacted.

The α-hydroxyketone benzoin was allowed to react with paraformaldehyde under similar conditions (reaction time 15 min at room temperature), α-(hydroxymethyl)benzoin (VII) being formed in nearly quantitative yield. The formation of VII from benzoin and formaldehyde in aqueous ethanol has been reported by Kusin.[7]

As shown above, alkyl aryl ketones react rapidly with paraformaldehyde in DMSO solution under the influence of alkaline catalysts to form hydroxymethyl compounds. The high reaction rates observed may be attributed to rapid α-hydrogen abstraction by the poorly solvated anionic catalyst with the formation of the enolate anion.

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 % CH_2O, was supplied by Perstorp AB, Perstorp, Sweden. Other chemicals used were purum grade. IR spectra were recorded on a Beckman IR-9 spectrophotometer, and NMR spectra on a Varian A-60 instrument. Chemical shifts are reported in ppm downfield from tetramethylsilane (TMS). Melting and boiling points are uncorrected. Yields are based on the amount of ketone used.

Reaction of acetophenone with paraformaldehyde in the presence of potassium carbonate. Acetophenone (90 g, 0.75 mole) and paraformaldehyde (90 g, 3.0 moles) in DMSO (260 ml) were stirred with potassium carbonate (5 g) for 45 min at room temperature. At this time the solution had acquired a red colour and the paraformaldehyde was dissolved. The solution was filtered and the main portion of the DMSO distilled off under vacuum at 85—90°. The residue was diluted to 400 ml by the addition of water. The mixture was extracted with ether, and the extract washed with water and dried over anhydrous calcium sulfate. Evaporation of the solvent under vacuum yielded 98 g of a yellow oil. Vacuum distillation through a 40 cm Vigreux column gave 20 g of unreacted acetophenone and 15 g (12.5 %) of 2-benzoylallyl alcohol (II), b.p.$_{0.3}$ 105—114°. (Found: C 73.53; H 6.40. Calc. for $C_{10}H_{10}O_2$: C 74.05; H 6.22). The compound reduced $KMnO_4$ solution and added bromine in CCl_4 solution. IR spectrum: 3450 cm^{-1} (OH), 3090 cm^{-1} (>C = CH_2), 1652 cm^{-1} (conjugated C = O) and a shoulder at 1625 cm^{-1} (conjugated C = C). NMR spectrum: 5.82 and 6.21 ppm (>C=CH_2), 4.56 ppm (—CH_2—O—) and 3.31 ppm (—OH). A compound supposed to be II has previously been obtained by Terada [8] on treatment of 5-benzoyl-1,3-dioxane with acid.

The aqueous phase was evaporated under vacuum and the residue (54 g of a colourless oil) dissolved in acetic anhydride-pyridine 1:1 (240 ml). After the initial exothermic reaction the mixture was heated to 80° for 20 min. Water (100 ml) was added, and after 30 min the solution was extracted with chloroform. The extract was washed with dilute hydrochloric acid and saturated sodium bicarbonate solution and dried over anhydrous calcium sulfate. Evaporation of the solvent under vacuum yielded 10 g (4 %) of the triacetate of α,α,α-tris(hydroxymethyl)acetophenone (I), m.p. 105—106°. (Found: C 60.85; H 5.76. Calc for $C_{17}H_{20}O_7$: C 60.71; H 5.99). It crystallized in colourless prisms from diisopropyl ether. IR and NMR spectra were consistent with the assigned structure.

Reaction of acetophenone with paraformaldehyde in the presence of potassium hydroxide. A solution of acetophenone (6.1 g, 51 mmoles) in DMSO (25 ml) was added during 45 min to a stirred suspension of paraformaldehyde (6.3 g, 210 mmoles) in DMSO (50 ml), containing KOH (0.5 g) dissolved in ethanol (4 ml). The reaction was performed under nitrogen, and the mixture was cooled by ice water to keep the reaction temperature between 10 and 20°. The reaction mixture was diluted by water to 400 ml, neutralized by dilute hydrochloric acid and saturated with sodium chloride. It was extracted repeatedly with ethyl acetate. The extract was washed with saturated sodium chloride solution and dried over anhydrous calcium sulfate. The solvent was removed under vacuum, and 9.6 g of a yellow oil was obtained. Chromatography of 1.61 g of this oil on a silica gel

column with ethyl acetate as eluent gave 0.45 g (33 %) of 2-benzoylallyl alcohol (II) and 0.38 g of α,α,α-tris(hydroxymethyl)acetophenone (I), identified as the triacetate.

Reaction of propiophenone with paraformaldehyde. A solution of propiophenone (5.80 g, 43 mmoles) in DMSO (10 ml) was added at room temperature during 40 min to a stirred suspension of paraformaldehyde (3.0 g, 100 mmoles) in DMSO (15 ml) containing KOH (0.15 g) dissolved in ethanol (2 ml). The reaction mixture was diluted by water to 150 ml and neutralized with dilute hydrochloric acid. After saturation with sodium chloride it was extracted with ethyl acetate. The extract was washed with saturated sodium chloride solution and dried over anhydrous calcium sulfate. Evaporation of the solvent under vacuum left a residue of 7.0 g of a colourless oil. Chromatography of 1.5 g of this oil on a silica gel column with ethyl acetate as eluent gave three groups of fractions, which on evaporation yielded the following products:

1) 0.57 g of an oil, which according to its IR and NMR spectra was a mixture of about 75 % propiophenone and other products;

2) 0.70 g of colourless needles, m.p. 79—80° after recrystallization from CCl_4. The product was identified by IR and NMR spectra as α,α-bis(hydroxymethyl)propiophenone (III). (Found: C 67.97; H 7.43. Calc. for $C_{11}H_{14}O_3$: C 68.02; H 7.26). Yield 40 %;

3) 0.07 g of colourless prisms, which were recrystallized from CCl_4—$CHCl_3$, 1:1. The product was identified as 1-phenyl-2,2-bis(hydroxymethyl)-1-propanol (IV) by IR and NMR spectra. M.p. 95—97° (lit.[7] 96—97°). Yield 5 %.

Reduction of III by paraformaldehyde. A mixture of III (51 mg, 0.26 mmole), excess paraformaldehyde and potassium hydroxide in DMSO (3 ml) was kept overnight at room temperature. The solution was diluted to 20 ml by the addition of water, neutralized by dilute sulfuric acid and saturated with sodium chloride. Extraction of the mixture with ethyl acetate yielded 40 mg of a colourless oil, which crystallized on standing. The product was identified as IV by m.p., thin layer chromatography, and IR spectrum.

2,2-Bis(hydroxymethyl)-1-indanone (V). A solution of 1-indanone (1.30 g, 9.8 mmoles) in DMSO (5 ml) was added during 3 min to a stirred suspension of paraformaldehyde (0.65 g, 22 mmoles) in DMSO (10 ml) containing KOH (50 mg) dissolved in ethanol (0.5 ml). The reaction was carried out under nitrogen at room temperature. After 2 more min the solution was neutralized by dilute hydrochloric acid and after the addition of 100 ml of water the mixture was saturated with sodium chloride. It was extracted with ethyl acetate, and the extract was washed with water and dried over anhydrous calcium sulfate. Evaporation of the solvent under vacuum yielded 1.42 g of a crystalline product, prisms with m.p. 92—93° after recrystallization from diisopropyl ether. IR and NMR spectra were consistent with structure V. (Found: C 68.58; H 6.34. Calc. for $C_{11}H_{12}O_3$: C 68.73; H 6.30). Yield of crude product 70 %.

2,2-Bis(hydroxymethyl)-1-tetralone (VI). A solution of 1-tetralone (8.0 g, 55 mmoles) in DMSO (10 ml) was added during 6 min to a stirred suspension of paraformaldehyde (4.0 g, 134 mmoles) in DMSO (25 ml) containing KOH (0.28 g) dissolved in ethanol (1 ml). The reaction was carried out under nitrogen at room temperature. The solution was neutralized by dilute hydrochloric acid, diluted to 200 ml by the addition of water and saturated with sodium chloride. Extraction with ethyl acetate and evaporation of the solvent under vacuum yielded a yellow oil, which crystallized on the addition of carbon tetrachloride. Recrystallization from $CHCl_3$—CCl_4, 1:4, gave 8.53 g (76 %) of VI, colourless needles, m.p. 93—94°, from diisopropyl ether. (Found: C 69.89; H 7.10. Calc. for $C_{12}H_{14}O_3$: C 69.88; H 6.84). IR and NMR spectra were consistent with the assigned structure.

α-(Hydroxymethyl)benzoin (VII). A solution of benzoin (5.9 g, 28 mmoles) in DMSO (15 ml) was added during 10 min to a stirred suspension of paraformaldehyde (1.0 g, 33 mmoles) in DMSO (35 ml) containing KOH (80 mg) dissolved in ethanol (1 ml). The reaction was performed under nitrogen at room temperature. After 5 more min the reaction mixture was neutralized by dilute hydrochloric acid, diluted to 250 ml by the addition of water and saturated with sodium chloride. The mixture was extracted with ethyl acetate, and the extract was washed with saturated sodium chloride solution and dried over anhydrous calcium sulfate. The solvent was removed under vacuum, which yielded 6.6 g (98 %) of slightly yellow crystals of VII. The compound crystallized from CCl_4 as colourless plates, m.p. 85—86° (lit.[8] 85—86°). The NMR spectrum of the product confirmed structure VII.

Acknowledgements. Financial support from Perstorp AB, Perstorp, Sweden, is gratefully acknowledged. The author also wishes to express his thanks to Professor Erich Adler for his kind interest in this work.

REFERENCES

1. Parker, A. J. *Quart. Rev.* **16** (1962) 163.
2. Cram, D. J., Rickborn, B. and Knox, G. R. *J. Am. Chem. Soc.* **82** (1960) 6412; Cram, D. J., Rickborn, B., Kingsbury, C. A. and Haberfield, P. *Ibid.* **83** (1961) 3678.
3. Van Marle, C. M. and Tollens, B. *Ber.* **36** (1903) 1351; Tollens, B. *Ibid.* **37** (1904) 1435.
4. Fuson, R. C., Ross, W. E. and McKeever, C. H. *J. Am. Chem. Soc.* **60** (1938) 2935.
5. Heeringa, L. G. and Beets, M. G. J. *Rec. Trav. Chim.* **76** (1957) 213.
6. Manta, J. *J. prakt. Chem.* **142** (1935) 11.
7. Kusin, A. *Ber.* **68** (1935) 2169.
8. Terada, A. *Nippon Kagaku Zasshi* **81** (1960) 612.

Received December 8, 1966.