PREPARATION OF SUBSTITUTED ACETOPHENONES FROM CARBOXYLIC ACID ESTERS

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A synthesis of substituted acetophenones from carboxylic acid esters *via* β-oxo sulfones as intermediates is described. The method was also adapted for substances containing an unprotected phenolic group. For the reductive elimination of the methanesulfonyl group chromium(II) sulfate was used which was found suitable as a selective reagent also in the case of compounds containing halogen bound on aromatic nucleus.

For the synthesis of substituted acetophenones Friedel–Crafts reaction[1] or its modifications[2,3] are most commonly used. All acid catalysed acylations are limited, however, to the preparation of some positional isomers only, or to their mixtures which very often are separable only with difficulty[4,5]. Moreover, compounds sensitive to acid reagents (for example 3,5-dimethoxy-4-hydroxyacetophenone) cannot be prepared by these methods. Among base catalysed syntheses those are attractive which make use of the condensation of carboxylic acid esters with dimethylsulfinyl[6] or dimethylsulfonyl[7–10] carbanions, giving rise to α-methanesulfinyl- or α-methanesulfonylcarbonyl compounds. A broader utilisation of the dimethylsulfinyl carbanion is excluded due to its ability to generate dehydrobenzenes from halogenoaromatic compounds. We have already found earlier[11] that the dimethylsulfonyl carbanion does not cause dehydrohalogenation under analogous conditions and therefore we attempted to make use of this reaction for a general method of preparation of substituted acetophenones.

Condensation of aromatic acid esters with dimethylsulfonyl carbanion in dimethyl sulfoxide takes place in very good yield (Table I). For preparative purposes the finding is valuable that with excess reagent β-oxo sulfones may be prepared even from esters with unprotected phenolic groups. The yields are substantially the same as in the condensations of phenol esters the hydroxy group of which was protected by benzylation[11].

The hydrogenolytic cleavage of the methanesulfonyl group with aluminium amalgam[10] or zinc in acetic acid[12] gave satisfactory yields, but the isolated substituted acetophenone contained the corresponding pinacoline as an impurity, and in the case of chloroacetophenones also the dehalogenation product. The formation of by-

products could not be prevented even when the reaction conditions were changed (decrease of temperature, addition of the reagent in portions, change of solvent). Therefore, we elaborated a new method of hydrogenolysis of the C—S bond of β-oxo sulfones based on the reducing properties of bivalent chromium[13]. The methanesulfonyl group of β-oxo sulfones is cleaved by this reagent very rapidly and quantitatively, but the halogen bound to the aromatic ring remains unattacked. The stoichiometry of the hydrogenolytic reaction was checked by reduction of a model compound, *i.e.* ω-(*p*-toluenesulfonyl)acetophenone. In accordance with the reduction of benzoins with chromium(II) sulfate[13] the C—S bond cleavage of β-oxo sulfones requires two equivalents of Cr(II). In addition to acetophenone, *p*-toluenesulfinic acid was isolated from the reaction mixture. We suppose that ω-methanesulfonylacetophenones are reduced in an analogous manner.

TABLE I
Oxosulfones *I*

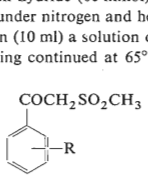
Compound	Yield, % m.p., °C	Formula (mol.w.)	Calculated/Found			
			% C	% H	% S	% Cl
Ia	65 139—140	$C_9H_{10}O_4S$ (214·2)	50·46 50·80	4·70 4·87	14·94 14·80	—
Ib	60 168—169	$C_9H_{10}O_4S$ (214·2)	50·46 50·21	4·70 4·65	14·94 14·72	—
Ic	58 173—174	$C_9H_{10}O_4S$ (214·2)	50·46 50·56	4·70 4·80	14·94 14·86	—
Id	78 77—78	$C_{10}H_{12}O_3S$ (212·2)	56·55 56·55	5·69 5·99	15·08 15·18	—
Ie	81 81—82	$C_{10}H_{12}O_3S$ (212·2)	56·55 56·39	5·69 5·78	15·08 15·08	—
If	80 114—116	$C_{10}H_{12}O_3S$ (212·2)	56·55 56·45	5·69 5·68	15·08 14·83	—
Ig	73 75—76	$C_9H_9O_3SCl$ (222·6)	46·45 46·73	3·89 3·86	13·77 13·76	15·23 15·20
Ih	75 96—98	$C_9H_9ClO_3S$ (222·6)	46·45 46·87	3·89 3·89	13·77 13·52	15·23 15·15
Ii	72 147—148	$C_9H_9ClO_3S$ (222·6)	46·45 46·54	3·89 3·81	13·77 13·82	15·23 15·26
Ij	76 157—158	$C_{10}H_{12}O_5S$ (244·2)	49·18 49·16	4·95 4·93	13·10 13·09	—
Ik	74 154—155	$C_{11}H_{14}O_6S$ (274·2)	48·17 48·65	5·14 5·33	11·66 11·67	—

EXPERIMENTAL

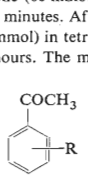
The melting points were determined on a Kofler block and they are not corrected. Samples for analysis were dried at room temperature and at 0·1 Torr for 8 hours.

Oxosulfones *Ia—Ic, Ij, Ik*

A mixture of sodium hydride (60 mmol) and dimethyl sulfone (60 mmol) in dimethyl sulfoxide (30 ml) was stirred under nitrogen and heated at 65°C for 45 minutes. After cooling and dilution with tetrahydrofuran (10 ml) a solution of methyl ester (10 mmol) in tetrahydrofuran (5 ml) was added and the heating continued at 65°C for another 2·5 hours. The mixture was poured into



I



II

Ia, IIa; R = 2-OH
Ib, IIb; R = 3-OH
Ic, IIc; R = 4-OH
Ig, IIg; R = 2-Cl
Ih, IIh; R = 3-Cl
Ii, IIi; R = 4-Cl

Id, IId; R = 2-CH_3
Ie, IIe; R = 3-CH_3
If, IIf; R = 4-CH_3
Ij, IIj; R = 3-OCH_3-4-OH
Ik, IIk; R = 3,5-$(OCH_3)_2$-4-OH

a saturated sodium chloride solution and 0·5M-HCl, cooled with ice, and extracted with chloroform (5 × 50 ml). The combined extracts were worked up in the conventional manner. Oxo sulfones *Ig—If* were prepared by a procedure described recently[10]. The crude oxo sulfones were crystallised from a mixture of ethyl acetate and light petroleum. The yields, melting points and analyses of all substances prepared are listed in Table I.

Reduction of Oxo Sulfones *I*

A) A solution of oxo sulfone (1 mmol) in a mixture of ethyl acetate (3 ml), ethanol (1 ml), and acetic acid (1 ml) was refluxed in the presence of zinc dust. The reaction course was followed by thin-layer chromatography in ether–light petroleum. When the reaction was terminated the solution was filtered and worked up in the usual maner. Crude ketones were purified by crystallisation from a mixture of ether and light petroleum (*IIb,c,j,k*) or by vacuum distillation (*IIa,d—l*). The yields of aryl methyl ketones were in the 85—90% range.

B) To a solution of oxo sulfone (1 mmol) in dimethylformamide (7 ml) 0·5M-$CrSO_4$ (4 ml) was added under argon and the mixture was allowed to stand at room temperature overnight (under exclusion of air). It was diluted with water (14 ml), extracted with light petroleum (3 × 10 ml) and worked up in the usual manner. The yields of aryl methyl ketones were quantitative. The physical constants of all products obtained agreed with those from the literature.

Reduction of ω-(*p*-Toluenesulfonyl)acetophenone

To a solution of ω-(*p*-toluenesulfonyl)acetophenone (274 mg, 1 mmol) in dimethylformamide (7 ml) a solution was added under argon, which contained the required molar amount of chromous

sulfate (determined iodometrically). The mixture was allowed to stand at room temperature overnight, diluted with water (14 ml), and acetophenone was eliminated by extraction with light petroleum (3 × 10 ml). The remaining reaction mixture was acidified with citric acid and extracted with ether (4 × 10 ml). The extract was washed with water and worked up in the usual manner. The *p*-toluenesulfonic acid obtained had m.p. 85—86°C. The results were the following

Ratio of Cr(II)/oxo sulfone	1	1·5	2·0	2·5
Sulfinic acid, mol	0·45	0·70	0·93	0·90

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