

Alkylation of Some β -Ketosulfones by the Ion Pair Extraction Technique

BENNY SAMUELSSON and BO LAMM*

Chemical Research Laboratory, AB Hässle, Fack, S-402 20 Göteborg 5, Sweden

Sixteen alkylated β -ketosulfones have been prepared using ion pair extraction techniques. Two different modifications have been used, one involving isolation of a salt between tetrabutylammonium ion and the conjugate base of the substrate, the other involving a one-step reaction in a two-phase system. The methods are simple and efficient, and the yields of alkylated products are in the range of 65–90 %.

Preparative applications of ion pair extraction have been summarized recently by Brändström.¹ Since β -ketosulfones, that were of interest to us as precursors to ketones *via* alkylation and electrolytic reductive cleavage,^{2,3} have acidities comparable to those of β -dicarbonyl compounds,⁴ it was assumed that they might be successfully alkylated using the ion pair extraction technique.

Conventional alkylation methods have previously been applied to β -ketosulfoxides and β -ketosulfones by other workers.⁵⁻⁹ Hydroxylic or polar aprotic solvents (DMSO or DMF, for example) have been used, but these solvents suffer from some disadvantages that have been pointed out in a communication by Brändström and co-workers,¹⁰ and in consequence, the yields using the classical alkylation methods are sometimes far from quantitative.

The ion pair extraction method is based upon the possibility of using salts soluble as ion pairs in water-immiscible organic solvents, for example chloroform and methylene chloride. Since anions are very poorly solvated in these media, the reactivity in nucleophilic substitutions is high, resulting in short reaction times and high yields. Besides, the work-up is very simple. As the cationic part, the tetrabutylammonium ion has predominantly been used.

In this connection, it is of interest to mention that Bergmann and Diller⁹ have used benzyl trimethylammonium hydroxide (Triton B) as base in the

* Present address: Department of Organic Chemistry, University of Göteborg and Chalmers Institute of Technology, Fack, S-402 20 Göteborg 5, Sweden.

Michael addition of ω -methylsulfinylacetophenone to acrylonitrile and ethyl acrylate. In these reactions, the carbanionic salt is probably reacting as an ion pair. In the cyanoethylation reaction, reviewed by Bruson,¹¹ Triton B is used as catalyst. The successful use of this catalyst is probably due to ion-pairing with the reactive anions.

For the alkylation of moderately acidic compounds, there is often a choice between two methods. In the first one of these, the salt between the anion of the compound to be alkylated and a suitable cation, *e.g.* a quaternary ammonium ion, is isolated after extraction with a solvent like methylene chloride and then redissolved and alkylated in a solvent that may be different from the one used for extraction. This method can only be applied if the substrate is sufficiently acidic to allow quantitative extraction as an ion pair, a condition fulfilled by, *e.g.*, β -ketosulfones. The second method, for which the expression "extractive alkylation" has been coined,¹² simply involves a heterogeneous reaction system, consisting of an aqueous phase initially containing quaternary ammonium ion and hydroxide ion, and an organic phase initially containing the substrate and the alkylating agent. Since the extraction equilibria are continually upset during the reaction, it is sufficient that a minor proportion of the substrate is present as anion in the organic phase.

The second method, though experimentally simpler, is subject to limitations that in some cases precluded its use in the present work. These limitations consist in competing reactions such as hydrolysis of the alkylating agent and alkylation by the solvent.

RESULTS AND DISCUSSION

Each one of four different β -ketosulfones was treated with four different alkylating agents, yielding sixteen compounds. The yields in all reactions are given in Table 1, together with an indication of the experimental method used in each case (extractive alkylation or isolation of the intermediate ion pair salt).

Table 1. Yields (%) in alkylation of β -ketosulfones $R^1COCH_2SO_2R^2$ by ion pair extraction technique.

β -Ketosulfone	I $R^1 = C_6H_5$ $R^2 = CH_3$	II $R^1 = p\text{-}CH_3OC_6H_4$ $R^2 = C_6H_5$	III $R^1 = CH_3(CH_2)_5$ $R^2 = C_6H_5$	IV $R^1 = C_6H_5CH_2$ $R^2 = C_6H_5$
Alk. agent				
CH_3I	81 ^a	87 ^a	78 ^a	86 ^{a,c}
C_2H_5I	73 ^a	82 ^a	81 ^a	76 ^a
$C_6H_5CH_2Cl$	65 ^b	74 ^b	67 ^b	59 ^b
$ClCH_2COOC_2H_5$	74 ^b	78 ^b	68 ^b	30 ^b
$C_6H_5CH_2Br$	—	—	—	75 ^a
$BrCH_2COOC_2H_5$	—	—	—	90 ^a

^a Extractive in methylene chloride.

^b Extraction of ion pair into methylene chloride. Evaporation. Alkylation in ethyl acetate.

^c 4 % of this amount was dimethylated.

In the runs involving redissolution of the quaternary ammonium salt, different solvents were tried for the alkylation step, namely 1,2-dimethoxyethane, toluene, and ethyl acetate. The last one of these gave superior yields of easily purified products.

Apart from the alkylating agents listed in Table 1, isopropyl iodide and methyl chloroformate were tried. Both these halides gave, however, too much *O*-alkylated (59 %) and *O*-acylated (100 %) products, respectively, to be preparatively interesting (the percentages refer to experiments with p - $\text{CH}_3\text{OC}_6\text{H}_4\text{COCH}_2\text{SO}_2\text{C}_6\text{H}_5$).

Dialkylated products, which are presumably always formed to a certain extent, could not, except in one case, be detected in the recrystallized products. In that particular case (see Table 1), the pure monomethylated compound had to be synthesized directly from ethyl phenyl sulfone and ethyl phenylacetate.

Compound IV (Table 1) gave low yields with benzyl chloride and ethyl chloroacetate. Since it has two acidic methylene groups, considerable amounts of by-products were formed, presumably from aldol condensation reactions, during the relatively long reaction times necessary with the chlorine compounds. By using the corresponding bromine compounds instead, extractive alkylation could be used because of their much increased reactivity. Satisfactory yields were thus obtained.

For completeness, it should be added that the extractive alkylation technique would most probably have been successful with compounds I–III in their reactions with benzyl bromide and ethyl bromoacetate. Since the yields obtained by using the redissolution technique were satisfactory, the extractive alkylations were omitted in these cases.

Table 2. Melting points of β -ketosulfones $\text{R}^1\text{COCH}(\text{R}^2)\text{SO}_2\text{R}^3$.

Substituents			Melting point, °C	
R^1	R^2	R^3	Obs.	Lit.
C_6H_5	CH_3	CH_3	60	56–57.5 ⁷
»	»	C_2H_5	113	— ^a
»	»	$\text{CH}_2\text{C}_6\text{H}_5$	139	137–138 ⁸
»	»	$\text{CH}_2\text{COOC}_2\text{H}_5$	123	— ^a
p - $\text{CH}_3\text{OC}_6\text{H}_4$	C_6H_5	CH_3	80	— ^a
»	»	C_2H_5	90	— ^a
»	»	$\text{CH}_2\text{C}_6\text{H}_5$	136	— ^a
»	»	$\text{CH}_2\text{COOC}_2\text{H}_5$	77	— ^a
n - C_6H_{13}	»	CH_3	36	— ^a
»	»	C_2H_5	48	— ^a
»	»	$\text{CH}_2\text{C}_6\text{H}_5$	73	— ^a
»	»	$\text{CH}_2\text{COOC}_2\text{H}_5$	44	— ^a
$\text{C}_6\text{H}_5\text{CH}_2$	»	CH_3	95	— ^a
»	»	C_2H_5	89	— ^a
»	»	$\text{CH}_2\text{C}_6\text{H}_5$	126	— ^a
»	»	$\text{CH}_2\text{COOC}_2\text{H}_5$	75	— ^a

^a This compound is believed to be new.

All compounds prepared in the present work are listed in Table 2, together with their melting points. The NMR spectra of all compounds were in complete agreement with the proposed structures. No further analyses were therefore considered necessary.

EXPERIMENTAL

Melting points were determined on a Kofler Heizbank or, for substances melting below 60°C, on a Mettler FP 1 melting point apparatus. NMR spectra were recorded on a Varian T 60 instrument.

Extractive alkylation. To a stirred solution of 0.1 mol of β -ketosulfone and 0.2 mol of alkyl iodide (0.11 mol of benzyl bromide and ethyl bromoacetate) in 100 ml of methylene chloride, a solution of 34 g (0.1 mol) of tetrabutylammonium hydrogen sulfate and 8 g (0.2 mol) of sodium hydroxide in 100 ml of water was added. In case of methyl iodide, a reflux condenser was necessary. The mixture was stirred until neutral reaction (5–30 min) as determined with moist indicator paper. The layers were separated, the methylene chloride evaporated and the tetrabutylammonium iodide (or bromide) precipitated by adding ether to the residue. Since the products were poorly soluble in ether, the crystallized residue was transferred to a Soxhlet extractor, and was continually extracted with ether overnight. The ether was evaporated and the alkylated β -ketosulfone was recrystallized from 95 % ethanol.

Redissolution alkylation. 0.1 mol of β -ketosulfone was dissolved in approximately 100 ml of 2 M sodium hydroxide aqueous solution. To this solution, 34 g (0.1 mol) of tetrabutylammonium hydrogen sulfate was added with stirring. The stirring was continued for 5 min and the mixture was transferred to a separatory funnel and extracted with two 50 ml portions of methylene chloride. The organic phase was dried over magnesium sulfate and vacuum evaporated thoroughly at room temperature. The crude ion pair compound was immediately dissolved in 150 ml of ethyl acetate, and 0.11 mol of benzyl chloride or 0.15 mol of ethyl chloroacetate was added. The solution was refluxed until neutral reaction (30 min for ethyl chloroacetate, 1–2 h for benzyl chloride). The ethyl acetate was evaporated leaving an oily residue behind, consisting of a mixture of product and tetrabutylammonium chloride. Dissolving the latter in water (which was facilitated by adding ether) caused the main part of the β -ketosulfone to crystallize. This was filtered off and the aqueous part of the filtrate was extracted with two portions of ether. The combined ether phases were evaporated and the residue was recrystallized together with the main crop from 95 % ethanol. The melting points are collected in Table 2.

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REFERENCES

1. Brändström, A. *Kem. Tidskr.* **82** (1970) 32.
2. Lamm, B. and Samuelsson, B. *Acta Chem. Scand.* **24** (1970) 561.
3. Samuelsson, B. and Lamm, B. *Acta Chem. Scand.* **24** (1970) 3070.
4. Truce, W. E., Bannister, W. W. and Knospe, R. H. *J. Org. Chem.* **27** (1962) 2821.
5. Gassman, P. G. and Richmond, G. D. *J. Org. Chem.* **31** (1966) 2355.
6. Russell, G. A. and Mikol, G. J. *J. Am. Chem. Soc.* **88** (1966) 5498.
7. House, H. O. and Larson, J. K. *J. Org. Chem.* **33** (1968) 61.
8. Carroll, N. M. and O'Sullivan, W. I. *J. Org. Chem.* **30** (1965) 2830.
9. Bergmann, F. and Diller, D. *Israel J. Chem.* **7** (1969) 57.
10. Brändström, A. *et al.* *Acta Chem. Scand.* **23** (1969) 2202.
11. Bruson, H. A. In Adams, R. *Organic Reactions*, Wiley, New York 1949, Vol. V, p. 79.
12. Brändström, A. and Junggren, U. *Acta Chem. Scand.* **23** (1969) 2204.

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