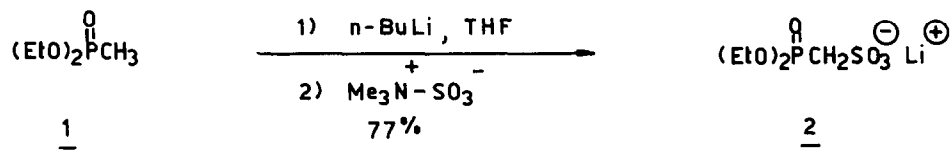
Tetrahedron Letters,Vol.28,No.10,pp 1101-1104,1987 0040-4039/87 $3.00 + .00
Printed in Great Britain Pergamon Journals Ltd.

A NEW SYNTHESIS OF α,β-UNSATURATED SULPHONATES AND THEIR STEREOSELECTIVE CONVERSION INTO trans-α,β-EPOXYSULPHONATES.

Juan Carlos Carretero and Léon Ghosez*
Laboratoire de Chimie Organique de Synthèse, Université Catholique de Louvain
Place L. Pasteur, 1, B-1348 LOUVAIN-LA-NEUVE, BELGIUM

Summary : Diethylphosphoryl methanesulphonates 2 and 4 were readily converted into α,β-unsaturated sulphonates by successive treatment with n-BuLi and aldehydes or ketones. Epoxidation of esters 5 with t-butyl hydroperoxide in the presence of Triton B yielded stereoselectively salts of trans-α,β-epoxysulphonic acids.

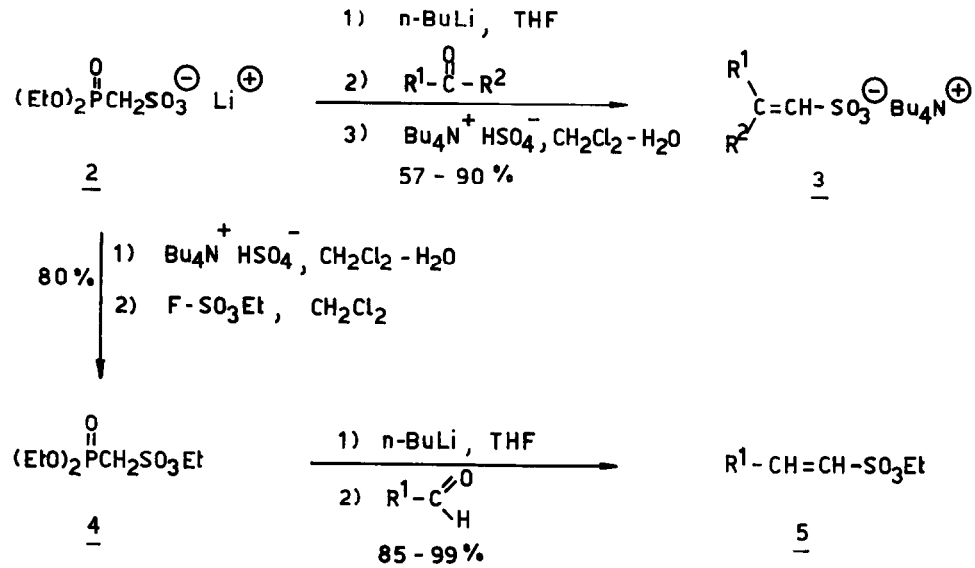
In connection with our current search for new types of inhibitors of serine-proteases, we required an efficient method for the preparation of α,β-epoxysulphonic acid derivatives which would be compatible with the presence of sensitive functional groups[1]. We expected the epoxidation of α,β-unsaturated sulphonic acids to fulfill this goal. However the few available methods[2] for the synthesis of these compounds were not readily applicable to the preparation of compounds bearing sensitive groups. In this communication we describe a practical and general synthetic method for α,β-unsaturated sulphonates based on the Wittig-Horner reaction [3] and their stereoselective transformation into salts of trans-α,β-epoxysulphonic acids.



1 2

Commercially available diethyl methanephosphonate 1 was treated with n-BuLi (1.1 equiv., THF, -78°C) and the resulting anion was sulphonated (0.5 equiv. Me_3N^+-SO_3^-, 4hrs, -78°C to -10°C), then HCO_2H (1.5 equiv., -10°C, filtration, flash chromatography, CH_2Cl_2:CH_3OH 7:1) to give compound 2 in 77% yield[4].

Deprotonation of 2 with n-BuLi (-15°C, THF) and treatment with a carbonyl compound (1.4 equiv., -78°C to 20°C, overnight) gave the corresponding unsaturated lithium sulphonates together with lithium diethyl phosphate. The separation of the two salts was readily effected by ion-pair extraction[5] (Bu_4N^+ HSO_4^- + LiOH, 1 equiv., H_2O-CH_2Cl_2). This yielded α,β-unsaturated tetrabutylammonium sulphonates 3 with a purity greater than 95 %[6].



The method is quite general (Table 1). Yields are good even in the case of enolizable or hindered carbonyl compounds. Poor stereoselectivities were observed except with aromatic (3d-3f) or hindered (3c) carbonyl coumpounds which gave predominantly the (E) isomer. Addition of HMPA (5 equiv.) or TMEDA (2 equiv.) as cosolvent did not modify significantly the E:Z ratio. However a significant improvement of stereoselectivity in favour of the (E) isomer was observed when the ionic reagent 2 was replaced by the neutral sulphonic ester 4[7] (compare 5a-d with 3a-d).

All attempts to epoxidize α,β-unsaturated tetrabutylammonium salts 3 with powerful epoxidizing reagents[8] were unsatisfactory : unchanged starting material was recovered with Na_2WO_4-H_2O_2 (pH=6)[8a], oxone (water-acetone, pH=7.5)[8b], CCl_3CN-H_2O_2(pH=6.8)[8c], H_2O_2 (pH=13.5)[8d] or t-BuOOH in the presence of Triton B[8e]. A slow reaction was observed with m-CPBA in refluxing CH_2Cl_2 but the method was unpractical owing to low yields and difficulties experienced isolating the epoxide from the reaction mixture.

The corresponding ethyl sulphonates 5 were inert toward m-CPBA even in refluxing dichloroethane but reacted smoothly with hydroperoxides under basic conditions. The reaction of 5 with t-butyl hydroperoxide (2.5 equiv.) and Triton B (1.3 equiv.) in THF at 30°C for 2 hrs resulted in the epoxidation of the double bond followed by hydrolysis of the ethyl sulphonate. Ion-pair extraction gave trans-α,β-epoxy tetrabutylammonium sulphonates 6 in good yields[9] (Table 1). In all cases both cis and trans-α,β-unsaturated sulphonates 5 exclusively yielded trans-epoxides indicating a high stereoselectivity but no stereospecificity. Thus the stereochemical course of these epoxidation parallels that of α,β-unsaturated sulphones[10].

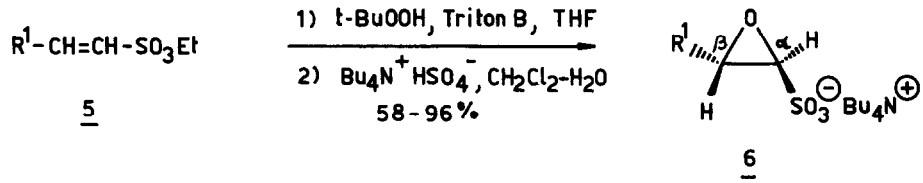


Table 1 : α,β-Unsaturated Sulphonates 3 and 5 ($R^1R^2C=CH-SO_3X$) and trans-α,β-Epoxy-Tetrabutylammonium Sulphonates 6.

α,β-Unsaturated Sulphonates 3 and 5						trans-α,β-Epoxysulfonates 6		
Compound	R^1	R^2	X	Yield (%)[a]	E:Z[b]	Compound	Yield(%)[c]	$J_{H\alpha-H\beta}$(Hz)[d]
3a	Et	H	n-Bu_4N	57	44:56			
3b	i-Pr	H	n-Bu_4N	80	45:55			
3c	t-Bu	H	n-Bu_4N	90	92:8			
3d	p-ClC_6H_4	H	n-Bu_4N	77	80:20			
3e	i-Pr	Me	n-Bu_4N	68	48:52			
3f	Ph	Me	n-Bu_4N	69	88:12			
5a	Et	H	Et	85	74:26	6a	89	2.0
5b	i-Pr	H	Et	96	85:15	6b	79	2.0
5c	t-Bu	H	Et	94	>98:<2	6c	58	2.0
5d	p-ClC_6H_4	H	Et	99	98:2	6d	96	1.8
5e	m-$NO_2C_6H_4$	H	Et	93	94:6	6e	72	1.8

[a] All reactions have been carried out at 0.4-0.6 mmole scale. Isolated yields after ion-pair extraction (X=n-Bu_4N, purity >95%) or flash chromatography (X=Et).
[b] Determined by ^{1}H-NMR (200 MHz). The ratios were unchanged after ion-pair extraction.
[c] Yield of 6 calculated after ion-pair extraction and corrected after determination of the purity by ^{1}H-NMR of the crude product [11].
[d] These values are in accordance with those previously observed for trans-α,β-epoxysulphoxides[12], sulphones[10] and sulphonates.[1a]

The experimental convenience of the methods described above and their amenability to many structural variations combine to make them very practical for laboratory synthesis of the title compounds.

Acknowledgments : This work has been generously supported by the Ministère de la "Région Wallonne" contract 6-141-36.

References and Notes

1. The preparation of α,β-epoxysulphonates and sulphonamides by the Darzens reaction has been reported: a) M.H.H. Nkunya and B. Zwarenburg, Recl. Trav. Chim. Pays-Bas, 1983, 102, 461; b) ibid, 1985, 104, 253.
However this method was not applicable to the synthesis of some of our target molecules.
2. a)E.E. Gilbert, Synthesis, 1969, 3; b) B.M. Culberton and S. Dietz, J. Chem. Soc. (C), 1968, 992; c) Organic Syntheses, vol.1, P. 846; d) M. Ali, J. Bangladesh Acad. Sci., 1979, 3, 97 (C.A., 1981, 94, 30834h); d) P. Bourgeois, G. Herault, N. Duffant and R. Callas, J. Organometallic Chem.; 1973, 59, 145 ; f) H. Distler, Angew. Chem. Int. Ed. Engl., 1965, 4, 300.
3. An earlier paper describes the preparation of β-aryl-α,β-unsaturated sulphonic esters and amides by the Wittig-Horner reaction : M. Fild and H.P. Rieck, Chem. Ber., 1980, 113, 142.
4. Rf= 0.2 in CH_2Cl_2/MeOH (7/1). ^{1}H-NMR (CD_3OD) δ (ppm) : 1.42 (t, J=7.0Hz, $-OCH_2CH_3$), 3.68 (d, J = 17Hz, $-CH_2-P$) and 4.28 (pseudo quintuplet, J=7.0 Hz, $-O-CH_2CH_3$). I.R. (KBr) ν : 2985, 2920, 1250, 1235, 1200, 1020-1040, 975 and 820 cm^{-1}.
5. S. Brandstrom P. Berntsson, S. Carlsson, A. Djurhuus, K Gustavii, V. Junggren, B. Lamm and B. Samuelsson; Acta Chem. Scand., 1969, 23,2202.
6. General Procedure for the preparation of 3 :
A solution of ^{n}BuLi 2.3 M (0.50 mmol, 1.2 eq) was added at -40° under an argon atmosphere to a suspension of dry powdered lithium diethylphosphoryl methanesulfonate (2, 100 mg, 0.42 mmol) in 2 ml of dry THF. The resulting mixture was stirred at -15° for 60 min, cooled to -78° and then freshly distilled aldehyde or ketone (1.4 eq) was added. The mixture was stirred at -78° for 30 min and then slowly warmed to room temperature. Stirring was continued overnight in the case of aldehydes and for 40h in the case of Ketones. After removal of tne solvent the residue was treated with water (10 ml) and extracted with CH_2Cl_2 (2x6ml). Then n-$Bu_4N^+HSO_4^-$ (142 mg, 0.42 mmol, 1.0 eq) and $LiOH.H_2O$ (18 mg, 0.42 mmol, 1.0 eq) were added to the aqueous phase which was extracted with CH_2Cl_2 (5x10 ml). The organic phase was dried ($MgSO_4$) and evaporated to yield the crude sulphonate 3.
7. Sulphonate 4 has been previously prepared by a less practical method; see ref. 3.
8. a) K.S. Kirshenbaum and K.B. Sharpless, J. Org. Chem., 1985, 50, 1979; b) R. Curci, M. Fiorentino, L. Troisi, J.O. Edwards and R.H. Pater, J. Org. Chem., 1980, 45, 4758; c) L. A. Arias, S. Adkins, C.J. Nagel and R.D. Bach, J. Org. Chem., 1983, 48, 888, d) H.O.House, Modern Synthetic Reactions, W.A. Benjamin Inc. (1965), p. 117-118 and references cited therein. c) N.C. Yang and R.A. Finnegan, J. Am. Chem. Soc., 1958, 80,5845.
9. General procedure for the preparation of 6 :
To a solution of 5 (0.40 mmol) and 140 μl (1.00 mmol, 2.5 eq) of ^{t}BuOOH (commercial 70% solution in water) in 3 ml of THF was slowly added at 30°C 240 μl (0.52 mmol, 1.3 eq) of Triton B (commercial 40% solution in methanol). After 2h, the reaction mixture was diluted with distilled water (10 ml) and extracted with AcOEt (3x6 ml). Then n-$Bu_4N^+HSO_4^-$ (142 mg, 0.42 mmol, 1.05 eq) and $LiOH.H_2O$ (18 mg, 0.42 mmol, 1.05 eq) were added to the aqueus phase followed by extraction with CH_2Cl_2 (4x10 ml). The combined dichloromethane extracts were dried ($MgSO_4$) and evaporated to afford crude epoxides 6.
10. a) B. Zwanenburg and J. ter Wiel; Tetrahedron Lett., 1970, 935; b) R. Curci and F. Difuria, Tetrahedron Lett., 1974, 4085.
11. The products were contaminated by a small amount of salts derived from the saponification of unreacted 5 (less than 8% with the exception of 6c which contained 36% of this by-product). If a higher purity is required, 6 can be readily converted back to the corresponding esters which can be readily purified.
12. a) V. Rentrakul and W. Kanghae, Tetrahedron Lett., 1977, 1377; b) D.F. Tavares, R.E. Estep and M. Blezard, Tetrahedron Lett., 1970, 2373.

(Received in France 12 December 1986)