METHYL 3-PHENYLSULPHONYL ORTHOPROPIONATE : AN EFFICIENT REAGENT FOR THE SYNTHESIS OF γ -LACTONES AND BUTENOLIDES

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<u>Summary</u> : Treatment of methyl 3-phenylsulphonyl orthopropionate with n-BuLi gives the corresponding carbanion which reacts with aldehydes or ketones to yield β -phenylsulphonyl γ -lactones. Base-catalysed elimination of sulphinic acid yields α , β or β , γ -butenolides.

We recently reported the conjugate addition of the anion derived from methyl 3-phenylsulphonyl orthopropionate 1 to enones and its application to a new method for cyclopentannulation¹. We now report the reaction of this new homoenolate reagent with aldehydes and ketones as a practical synthetic method for the preparation of γ -lactones and butenolides.²

Scheme 1



Reagent <u>1</u> was readily deprotonated with n-BuLi (1.1 equiv.) in THF at $-78\,^{\circ}$ C. Reaction of the resulting anion with aldehydes or ketones (1.1 equiv.) at $-78\,^{\circ}$ C to $-45\,^{\circ}$ C³ followed by hydrolysis with dilute sulphuric acid yielded the γ -hydroxyesters <u>2</u> together with variable amounts (20-40%) of the cyclised products <u>3</u> (Scheme 1). The crude mixtures were quantitatively converted into the lactones <u>3</u> by treatment with dry p-toluenesulphonic acid (0.2 equiv.) in 1,2-dichloroethane at 50 °C for several hours⁴. Flash chromatography gave pure lactones <u>3</u> in good overall yields (Table 1) as a mixture of diastereoisomers. The procedure is applicable to aliphatic and aromatic aldehydes and ketones. Good yields were also obtained with enolizable ketones.

These results show that homoenolate reagent <u>1</u> is more efficient in reactions with carbonyl compounds than other previously reported homoenolate reagents⁵, such as the dianions derived from 3-phenylsulphonylpropionic acid^{5a} or N-monosubstituted 3-phenylsulphonyl propionamides^{5C}.

γ -Lactones <u>3</u>	R	R	Yield (%) ^a	Isomer ratio ^b			
3a	i-Bu	Н	76	1:1			
3b	\frown	Н	80	3:2			
<u>3c</u>	Ph	Н	84	5:4			
3d	Me-CH=CH-(trans)	Н	75	3:2			
3e	n-Bu	Me	68	3:2			
3f	Ph	Me	70	3:1			
<u>3</u> g	Ph	Ph	76	·			
<u>3h</u>	-(CH ₂) ₅ -		82				
 ^a Yield of pure product after chromatography. ^b Determined by ¹H-NMR. Stereochemistry was not established. 							

Table 1 : Synthesis of β -Phenylsulphonyl- γ -Lactones (3) from Aldehydes and Ketones.

The γ -lactones 4 could be obtained in good yield from the desulphonylation of 3 following the general procedure reported by Trost and al⁶ (Scheme 2).



i : Na(Hg) 5% (3 equiv.), Na₂HPO₄ (4 equiv.), CH₃OH, -10°C, 30 min.

Basic elimination of phenylsulphinic acid from lactones 3 could be readily effected with either DBU or triethylamine in dichloromethane (Scheme 3 and Table 2). Under these conditions both lactones 3a and 3b (entries 1 and 2) exclusively gave the more stable α , β -butenolides⁷ 5a and 5b in very good yields. Excellent yields of α , β -butenolides were also obtained with lactones 3f, 3g and 3h (entries 8, 9 and 10).

In contrast, lactones <u>3c</u> and <u>3d</u> bearing a phenyl or a propenyl group at the γ -position yielded the corresponding β,γ -butenolides <u>6c</u> and <u>6d</u> under normal conditions (entries 4 and 6). However, using less than an equimolecular amount of DBU, a lower temperature and a shorter reaction time the α,β -butenolides <u>5c</u> and <u>5d</u> were obtained as the major products (entries 3 and 5). This indicates a facile isomerization of the α,β -butenolides <u>5c</u> and <u>5d</u> (kinetic products) into the more stable β,γ -butenolides <u>6c</u>⁸ and <u>6d</u>. As a result of prolonged exposure to an excess of triethylamine, compound <u>6d</u> was further converted into the fully conjugated γ -propylidene- α,β -butenolide <u>7</u> (Z:E ratio = 9:1)⁹, which could also be directly prepared from lactone <u>3d</u> (entry 7). This result suggests a potential new route to γ -ylidenebutenolides, many of which show interesting biological properties¹⁰.



Table 2	Butenolides	from lactones <u>3</u> . <u>6</u>		
Entry	Lactone <u>3</u>	Reaction Conditions ^a	Butenolide	Yield $(%)^{b}$
1	<u>3a</u>	DBU (1.1 eg), 0°C, 15 min.		(<u>5a</u>) 86
2	<u>3b</u>	Et ₃ N (10 eq), 22°C, 10 h.		(5b) 97
3	<u>3c</u>	DBU (0.6 eq), -20°C, 20 min.	Ph- (0,)=0	(<u>5</u> c) 60 [°]
4	<u>3c</u>	Et ₃ N (2eq), 22°C, 8h.	Phr 0 0	(<u>6c)</u> 82
5	<u>3d</u>	DBU (0.6 eq), -10°C, 7 min.		(<u>5d</u>) 70 ^d
6	<u>3d</u>	DBU (1.0 eq), 0°C, 15 min.		(<u>6 d</u>) 76
7	<u>3d</u>	Et ₃ N (4 eq), 22°C, 6 h.		(<u>7</u>) 71 ^e
8	<u>3f</u>	DBU (1.1 eq), 0°C, 25 min.		(<u>sf</u>) 100
9	<u>3q</u>	DBU (1.1 eq), 0°C, 15 min.	Ph 0 0	(<u>5g</u>) 100
10	<u>3h</u>	Et ₃ N (10 eq), 22°C, 30 h.		(<u>5</u> h) 98

a 0.3 - 1.0 mmole scale.
 b Yield of pure product after silica gel chromatography.
 c 35% of <u>6c</u> was also isolated.
 d 22% of <u>6d</u> was also isolated.
 e Z:E ratio = 9:1.

It is clear from the above results that the reaction of homoenolate reagent $\underline{1}$ with aldehydes and ketones provides one of the most efficient and practical entries for the synthesis of γ -lactones and butenolides.

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References and notes

- 1) S. De Lombaert, I. Nemery, B. Roekens, J.C. Carretero, T. Kimmel and L. Ghosez, Tetrahedron Lett., 1986, 27, 5099.
- 2) Recent reviews : a) Y.S. Rao, <u>Chem. Rev.</u>, 1976, 76, 625; b) S. Kano, S. Shibuya and T. Ebata, <u>Heterocycles</u>, 1980, 14, 661; c) R.S. Ward, <u>Chem. Soc. Rev.</u>, 1982, 11, 75. See also : d) P. Canonne, M. Akssira and G. Lemay, <u>Tetrahedron Lett.</u>, 1981, 22, 2611; e) P. Brownbridge, E. Egert, P.G. Hunt, O. Kennard and S. Warren, J. Chem. Soc., <u>PerkinTrans.1</u>, 1981, 2751; f) D. Goldsmith, D. Liotta, M. Saindene, L. Waykole and P. Browen, <u>Tetrahedron Lett.</u>, 1983, 24, 5835; g) S. Hanessian, P.J. Hodges, P.J. Murray and S.P. <u>Sahoo</u>, <u>J. Chem. Soc.</u>, Chem. Commun., 1986, 754.
- 3) We have observed that the addition of the α -sulphonylcarbanion of 1 to ketones is a reversible process at temperatures above -40°C. See also : M. Julia and J.M. Paris, Tetrahedron Lett., 1973, 4833.
- 4) General procedure for the preparation of 3 : To a solution of 548 mg (2.0 mmol) of 1 in $\overline{6 \text{ ml}}$ of dry THF was slowly added a solution of n-BuLi 2.3 M in hexane (0.96 ml, 2.2 mmol) at -78°C under argon. The resulting pale yelow solution was stirred for 20 min and then, freshly distilled aldehyde or ketone was added (2.2 mmol). The reaction was stirred for 2h at -78°C and then slowly warmed to -45°C (ketones) or -20°C (aldehydes) over a period of 1h. After addition of 1.2 ml of HpS0₄ 2M (2.4 mmol) the mixture was brought to room temperature. After 30 min the biphasic system was diluted with water (25 ml), extracted with CH₂Cl₂(3X20 ml) and the organic layers were dried (MgS0₄) and evaporated. The residue (mixtures of 2 and 3) was dissolved in 5 ml of dry 1,2-dichloroethane and 69 mg (0.4 mmol) of dry p-TsOH were added. The homogeneous solution was stirred and warmed to 50°C for 4-24h, until the lactonization was complete. The reactions were monitored by tlc or i.r. ($_{\odot}$ (co) 2 = 1740 cm and $_{\odot}$ (co) 3 = 1790 cm ⁻¹). The solvent was evaporated and the residue was chromatographed on siTica gel (CH₂Cl₂ or C₆H₁₂-AcOEt 5:1 as eluant). 64-84% of pure lactones <u>3</u> were obtained.
- 5) a) T. Iwai, H. Kosugi, A. Miyazaki and H. Uda; <u>Synth. Commun</u>, 1976, 6, 357; b) D. Caine and A. S. Frobese, Tetrahedron Lett., 1978, 5167; c) K. Tanaka, H. Wakita, H. Ioda and A. Kuji, <u>Chem. Lett.</u>, 1984, 1359; d) A.J. Meyers, and R.F. Spohn, <u>J. Org. Chem.</u>, 1985, 50, 4872.
- 6) B.H. Trost, H.C. Arndt, P.E. Strege and T.R. Verhoeven, Tetrahedron Lett., 1970, 3477.
- For the stability of α,β and β,γ-butenolides see : a) A.B. Hornfeldt, Ark.Kemi, 1967, 29, 229; b) N. Bodor, M.J.S. Dewar and A.J. Harget, J. Am. Chem. Soc., 1970, 92, 2929.
- 8) Isomerization of 5c to 6c has been previously reported : A.W. Nineham and R.A. Raphael, J. Chem. Soc., 1949, 118. We also found that this isomerization takes place quantitatively on silica gel in refluxing toluene.
- 9) E:Z ratio determined by ^IH-NMR. For stereochemical assignment rules in γ-ylidenebutenolides see : P.J. Babidge and R.A. Massy-Westropp, Aust. J. Chem., 1981, 34, 1745.
- 10) G. Pattenden, Fortschr. Chem. Org. Naturst., 1978, <u>35</u>, 133.

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