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Syntheses with Sulfones L : Preparation of β-Hydroxysulfones through the Combined Oxidative Desulfonylation/Condensation Reaction of Sulfonyl Anions. Application to Terpene Synthesis.

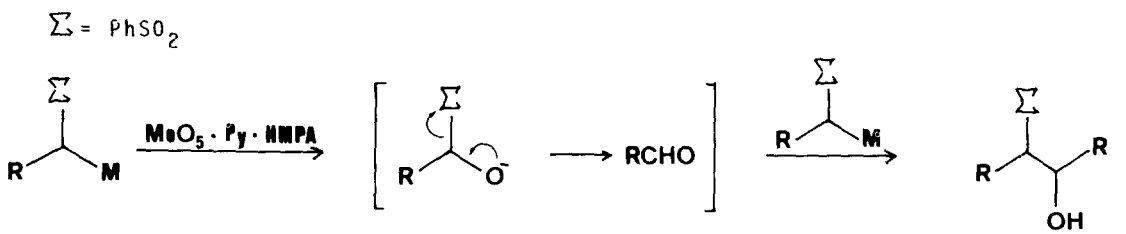
M. Capet, T. Cuvigny, C. Hervé du Penhoat, M. Julia and G. Loomis

Laboratoire de Chimie, Ecole Normale Supérieure, 24, rue Lhomond
75231 PARIS CEDEX 05 -FRANCE.

Summary : *The oxidative desulfonylation of primary sulfonyl anions with the molybdenum peroxide reagent, MoO_5.Py.HMPA, leads directly to β-hydroxysulfones through condensation of the starting α-sulfonyl anion with the aldehyde formed in situ. Symmetrical polyenes such as (Z)-12-dehydrosqualene and (Z)-16-phytoene have been obtained in three steps in > 87% stereoselectivity from the corresponding β-hydroxysulfones.*

In connection with continuing work in the sulfone field [1] we were interested in transforming primary sulfones into aldehydes. The oxidation of ketone, ester, nitrile, and lactone enolates with the molybdenum peroxide reagent MoO_5.Py.HMPA [2] has been developed by Vedejs et al. [3]. This technique has also been applied to the α-hydroxylation of chiral esters by Tamm et al. [4]. Enolates [5] and chiral imide enolates [6] have also been oxidized with oxaziridines. The use of MoO_5.Py.HMPA has been successfully extended to the oxidative desulfonylation of secondary sulfones to ketones by Little et al. [7] and this method has been applied to a trans-decalin synthesis [8]. More recently, Hwu [9] transformed primary and secondary sulfones into aldehydes and ketones respectively with bis(trimethylsilyl)peroxide. Finally, sulfonyl anions have been converted into boronic esters which have been oxidized to the corresponding aldehydes or ketones with MCPBA [10].

Treatment of [(n-pentyl)sulfonyl]benzene 1 with 1.5 equivalents of n-BuLi followed by 1.5 equivalents of MoO_5.Py.HMPA did not afford pentanal but led instead to 65% of β-hydroxysulfone 2 [11] as a 50/50 threo/erythro mixture [12], Table 1, entry 1. Similarly, [(phenylsulfonyl)methyl] benzene 3 [13] afforded 83% of a 50/50 threo/erythro mixture of compounds 4, entry 2. The in situ hydroxyalkylation of the sulfonyl anion by the aldehyde formed by oxidative desulfonylation of the substrate was not surprising.



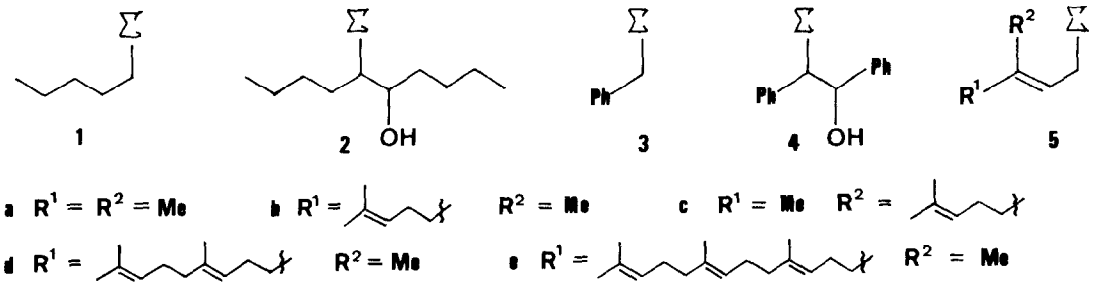


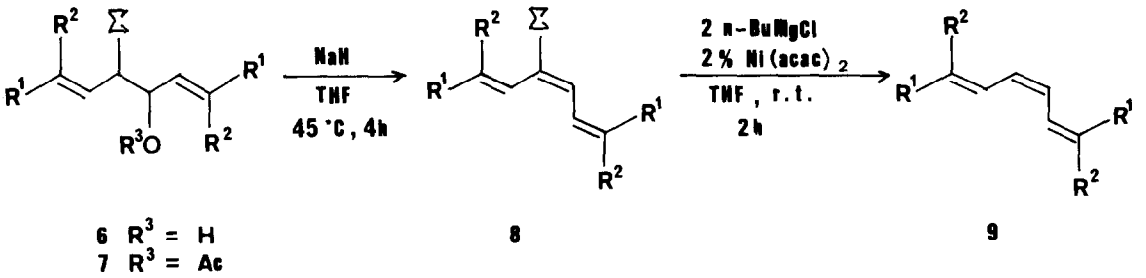
Table 1 : Oxidative desulfonylation of α-sulfonyl anions.

Entry	Starting Sulfone	n-BuLi Equiv.	β-Hydroxy-Sulfone (Yield %)	iPr_2NLi Equiv.	β-Hydroxy Sulfone [b] (Yield %)
1	1	1.05	2 (65)	2	2 (69)
2	3	"	4 (83)	-	-
3	5a	"	6a (47)	-	-
4	"	2	" (70)	2	6a (82)
5	5b	1.05	6b (49)	"	6b (76)
6	5c	"	6c (49)	"	6c (65)
7	5d [a]	-	-	"	6d [a] (63)
8	5e	-	-	"	6e (68)

[a] Paratolylsulfone [b] a 55/45 threo/erythro mixture according to ^1H NMR at 250 MHz (±5%).

Typical Procedure : A solution of 278mg (1mmol) of geranylsulfone 5b in 5 ml of THF was added to a stirred solution of 2 mmol of LDA in 3 ml of THF at -78°C. After stirring for 15 minutes at -78°C, the reaction vessel was allowed to warm up to room temperature (15 min), cooled to -35°C and 650mg (1.5 mmol) of MoO_5.Py.HMPA were added rapidly. The solution, initially red, turned a dark bluish green. Stirring was maintained at -35°C for 2h and then the reaction mixture was hydrolyzed at this temperature with 5 ml of an aqueous solution of NH_4Cl. After stirring for 1h at room temperature, the usual workup and flash chromatography [23] afforded 344 mg (76%) of β-hydroxysulfone 6b ~95% pure according to ^1H NMR at 250 MHz.

Similar mixtures of diastereoisomers were obtained in a new preparation of Z olefins [14] in which the condensation of lithiated sulfones with aldehydes was conducted under analogous conditions (-35°C, THF). The resulting β-hydroxysulfones were then converted into β-acetoxysulfones and elimination of acetic acid afforded E vinylsulfones which were stereospecifically reduced to Z alkenes either with sodium dithionite [14b] (> 99% Z) or Grignard reagents under transition metal catalysis [14c] (> 98% Z). As the oxidative desulfonylation/condensation sequence would be an efficient approach to the synthesis of symmetrical polyenes several substrates 5a-e, were investigated. β-Hydroxysulfones 6a-e [15] were obtai-



6 R^3 = H
7 R^3 = Ac

8

9

ned in good yields, 63-82%, provided 2 equivalents of base were used, as previously noted for chiral ester enolates [4]. Slightly better results were obtained with LDA as compared with n-BuLi, entries 4 to 6. β-Hydroxysulfones 6b-e were then readily converted into trienesulfones 8b-e upon treatment with acetic anhydride/DMAP/Et_3N (20°C, 4h) [16] followed by elimination of acetic acid with sodium hydride (THF, 65°C, 1h) [17], Table 2. Sulfones 8b-e contained only the E isomer according to ^1H NMR (±5%) [18]. HPLC analysis (±1%) of a sample of 8b indicated a 1/95/4 mixture of isomers (increasing R_f). The stereospecific reduction of the sulfonyl moiety with 2 equivalents of n-BuMgCl in the presence of 2% of $Ni(acac)_2$ proceeded smoothly to furnish trienes 9b-e in 78-85 % yield. The newly produced double bond was > 88 % Z according to ^1H [19] and ^{13}C NMR [20] in comparison with literature data. In the case of 9b Glc analysis indicated a 82/4/14 mixture (increasing T_r) of the EZE/?/EEE isomers confirming 87 % stereospecificity for the reduction step.

Table 2 : Transformation of β-hydroxysulfones 6 into polyenes 9.

Entry	6	7 (Yield) %	Trienesulfone 8 (Yield) %	%E	Polyene 9 (Yield %)	Isomer Ratio
9	6b [a]	65	71	95.2 [b]	78	82/4/14 [cde]
10	6c	62	85.6	> 95 [c]	88	88/12 [ce]
11	6d	86	85.1	"	85.4	"
12	6e	76.5	84	"	80	"

[a] Prepared according to ref.14 [b] HPLC-Du Pont B 1500 Zorbax Sil. (4.6mmx25cm) column (eluent : 2,2,4-trimethylpentane/AcOEt-97/3) 3 isomers in a 1/95/4 ratio [c] ^1H NMR at 250MHz [d] Glc-CPSil S 7470 Chrompack (25M, 0.2μ) [e] ^{13}C NMR at 100MHz.

Trienes 9 have been prepared previously by several techniques with widely varying stereoselectivity as regards the central C-12 double bond : the Wittig [21ab] (9b, 9c, and 9e)

and Wittig-Horner [21c] (9b) routes, or from sulfonyl anions (9b, 9c, and 9e) [21d] and (9b) [21ef].

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15. The spectral data were identical with that of a sample of 6b prepared from geranyl sulfonyl benzene and E citral according to ref. 14a (65%). ^{1}H NMR at 250MHz (δ $CHCl_3$ 7.27ppm) : 1.01(d,1.2,1.5H), 1.06(d,1.2,1.5H), 1.39 to 1.60(m,15H), 1.74 to 2.00(m,8H), 3.63(dd,J_1=11, J_2=1, 0.5H), 3.84(m,0.5H), 3.70(br d, 11,0.5H), 3.86 to 5.0(m,5H), 5.06(br d, J_1=8.5, J_2=1, 0.5H), 5.21(br d, 9, 0.5H), 5.40(br d, 11, 0.5H), 7.41 to 7.50(m,2H), 7.52 to 7.61(m,1H), 7.75 to 7.82(m,2H).
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