

S0957-4166(96)00104-8

Stereoselective Synthesis of Sulfinates from Mannitol Derived Sulfites

Nadia Pelloux-Léon, Isabelle Gautier-Luneau, Silke Wendt and Yannick Vallée*

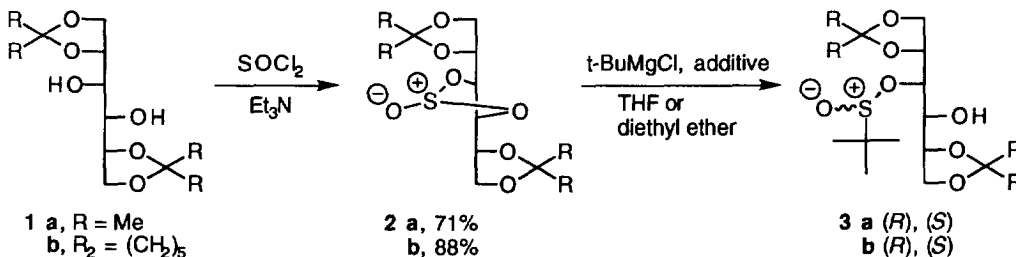
L.E.D.S.S., laboratoire associé au CNRS,
 Université Joseph Fourier, B.P. 53X, 38041 Grenoble, France

Abstract: The reaction of Grignard reagents with two mannitol derived sulfites has been studied. High diastereoselectivity (96% d.e.) was achieved with *t*-BuMgCl and a cyclohexylidene protected sulfite in THF in the presence of a Lewis acid.
 Copyright © 1996 Elsevier Science Ltd

The reaction of sulfinates with organometallic compounds, named the Andersen method when effected with menthyl sulfinates,^{1,2} is often the method of choice for the synthesis of enantiopure non-functionalized sulfoxides. It is limited only by the sometimes difficult isolation of enantiomerically pure menthyl sulfinates. Kagan *et al.* have recently extended the scope of this reaction by reacting successively two different organometallics with a cyclic sulfite.^{3,4} This method is of special interest for *t*-butyl sulfoxides.

Kagan's cyclic sulfite was obtained by reaction of thionyl chloride with (*S*)-1,1-diphenyl-propane-1,2-diol. One drawback of this sulfite is that it is obtained first as a mixture of two diastereoisomers (*trans/cis*: 90/10) which have to be separated. With a starting diol of C₂ symmetry, this problem will be overcome.⁵

With this idea in mind we choose mannitol as the starting alcohol. It is a cheap source of chirality and its two protected derivatives **1 a,b** are commercially available. They were treated with thionyl chloride to give the two sulfites **2 a,b**.^{6,7} (Scheme 1). The reaction of these sulfites with *t*-butylmagnesium chloride was studied under various conditions (temperature, solvent, additives). The results are summarized in Table 1.



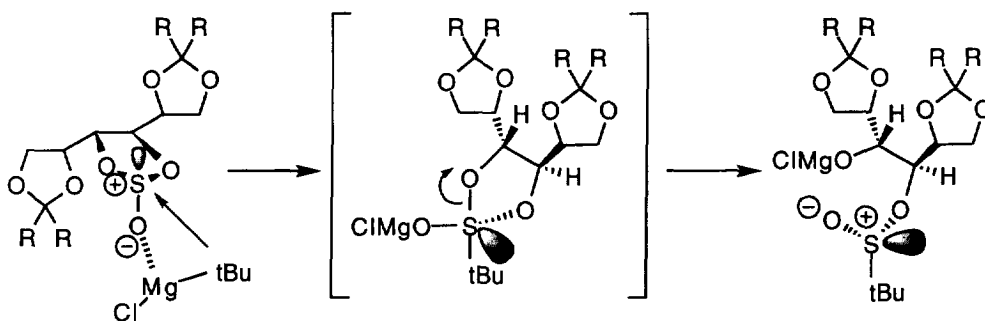
Scheme 1

Table 1 : Reactions of sulfites **2a,b** with *t*-BuMgCl⁸

Entry	Sulfite	Sulfinate	Solvent	Temperature (°C)	Additive	d.e. ⁹
1	2a	3a	THF	20	none	40
2			THF	0	none	50
3			THF	-40	none	65
4			THF	-40	Et ₂ AlCl	94
5			THF	-78	none	72
7	2b	3b	THF	0	none	73
8			THF	-40	none	90
9			ether	-40	none	74
10			THF	-40	Et ₂ AlCl	96
11			ether	-40	Et ₂ AlCl	76
12			THF	-40	EtAlCl ₂	96

As seen from Table 1, d.e.s were low at 0 °C, the bicyclohexylidene sulfite **2b** giving more selective results. Furthermore, lowering the temperature gave better selectivities, but at -78 °C the reactions were very slow (*ca.* 50% completed after 10 hours). Reactions in THF gave better results than in diethyl ether. Interestingly, addition of a Lewis acid (1 eq.) increased the stereoselectivity. This was notable in the case of the bis-isopropylidene sulfite **2a** (compare entries 3 and 4). The role of the Lewis acid is not clear yet. However, at this point, it should be noticed that without Et₂AlCl or EtAlCl₂, at least 2 equivalents of *t*-BuMgCl were needed to complete the reactions. When one equivalent of Lewis acid is present in the reaction mixture, only a slight excess of *t*-BuMgCl was needed. The sulfinate **3a**¹⁰ and **3b**¹¹ were isolated by liquid chromatography in 80% (entry 4) and 85% yield (entry 10) respectively. Compound **3b** was then recrystallized and obtained with 100% d.e.⁹

A single crystal X-ray analysis of compound **3b** was run which showed that the sulfur atom had the *R* configuration.¹² We propose that this configuration results from a chelation of the magnesium atom to the negative oxygen and attack of the *t*-Bu anion from the less hindered side (scheme 2).^{13,14}



Scheme 2

The reactions of various other Grignard reagents with **2a, b** were also tested. Representative examples are given in Table 2. The stereoselectivities were lower than with the *t*-butyl derivative but assumed to proceed to generate the same configuration. Entries 2 and 3 give an other example of the role of Et₂AlCl in these reactions.¹⁴ Interestingly, the benzyl derivative **6b** (entry 5) was obtained with 99.4% d.e.⁹ after preparative chromatography and recrystallisation (37% yield).¹⁵

Table 2 : Representative results with various Grignard reagents

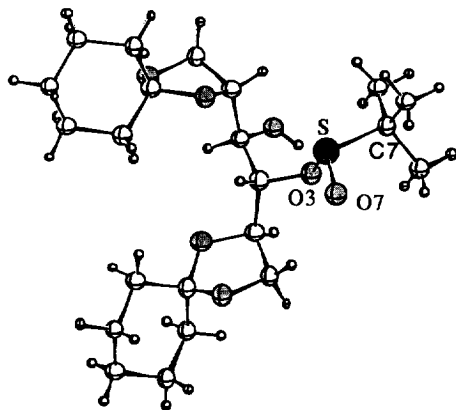
entry	Sulfite	Sulfinate	RMgX	Temperature (°C)	Additive	d.e.
1	2a	4a	MesMgCl	-78	none	54
2	2b	5b	<i>i</i> -PrMgCl	-40	none	60
3	2b	5b	<i>i</i> -PrMgCl	-40	Et ₂ AlCl	70
4	2a	6a	BnMgCl	-40	Et ₂ AlCl	70
5	2b	6b	BnMgCl	-40	Et ₂ AlCl	78
6	2b	7b	EtMgCl	-80	none	12

References and notes

- Andersen, K. K. *Tetrahedron Lett.*, **1962**, 93-95. Jacobus, J.; Mislow, K. *J. Am. Chem. Soc.*, **1967**, *89*, 5228-5234. Cherkaoui, M. Z.; Nicoud, J.-F. *New J. Chem.*, **1995**, *19*, 851-861.
- For other ways to sulfoxides, see, *inter alia* : Solladié, G. *Synthesis*, **1981**, 185-196. Walker, A. J. *Tetrahedron: Asymmetry*, **1992**, *3*, 961-998. Fernandez, I.; Khair, N.; Llera, J. M., Alcudia, F. *J. Org. Chem.*, **1992**, *57*, 6789-6796. Khair, N.; Fernandez, I.; Alcudia, F. *Tetrahedron Lett.*, **1994**, *35*, 5719-5722. Nicoud, J. F.; Cherkaoui, M. Z. *Tetrahedron: Asymmetry*, **1995**, *6*, 1941-1946. Adam, W.; Mitchell, C. M.; Saha-Möller, C. R. *Tetrahedron*, **1994**, *50*, 13121-13124 ; Bulman Page, P.C.; Heer, J. P.; Bethell, D.; Collington, E. W.; Andrews, D. M. *Tetrahedron: Asymmetry*, **1995**, *6*, 2911-2914 ; Brunel, J. M.; Diter, P.; Duetsch, M.; Kagan H. B. *J. Org. Chem.*, **1995**, *60*, 8086-8088.
- Kagan, H. B.; Rebiere, F.; Samuel, O. *Phosphorus, Sulfur, Silicon*, **1991**, *58*, 89-110.
- Rebiere, F.; Samuel, O.; Ricard, L.; Kagan, H. B. *J. Org. Chem.*, **1991**, *56*, 5991-5999.
- Kagan *et al.* indeed have tried some C2 diols (see ref.⁴), however with poor stereoselectivities.
- 2a** was previously known : J. J. Brimacombe, M. E. Evens, A. B. Foster and J. M. Weber, *J. Am. Chem. Soc.*, **1964**, 2735.
- 2b** : Treatment of **1b** with thionyl chloride in presence of triethylamine in dichloromethane gave **2b** in 88% yield after silica gel chromatography (CH₂Cl₂/Pentane : 80/20). ¹H NMR (200MHz, CDCl₃) : 1.40-1.64 (m, 20H), 3.99 (m, 1H), 4.13 (m, 4H), 4.49 (m, 2H), 4.90 (m, 1H). ¹³C NMR : 23.60, 23.90, 23.98, 24.99, 34.14, 34.32, 36.18, 36.55, 65.37, 66.46, 74.09, 75.10, 83.73, 84.89, 111.03. MS : m/z (%) = 388 (M⁺, 100), 324 (4), 308 (2), 80 (32). Anal.: calc. for C₁₈H₂₈SO₇ : C: 55.65, H: 7.26, 8.29 ; found : C: 55.95, H: 7.32, S: 8.23. [α]_D²⁰ = +83 (c 1, CH₂Cl₂).
- Typical experimental procedure : A solution of Et₂AlCl (1 eq.) in heptane was added to the sulfite (1eq.) dissolved in dry THF at -40°C. The resulting mixture was stirred at this temperature for 15 min and the Grignard reagent (1 eq.) was then added dropwise. Reaction was carried out for one hour and quenched

with water, extracted with CH_2Cl_2 , washed with water. The organic layer was dried over MgSO_4 and evaporated. The crude product was submitted to column chromatography or crystallized from ether.

9. d.e. determined by HPLC. Column : Kromasil C18, 25cm; eluant : water- CH_3CN mixtures; Shimadzu UV diode array detector.
10. **3a** : ^1H NMR (200MHz, CDCl_3) : 1.2 (s, 9H), 1.35-1.45 (4s, 12H), 2.63 (d, OH), 3.86 (m, 1H), 4.0-4.2 (m, 5H), 4.38-4.42 (m, 2H). ^{13}C NMR : 21.56, 25.14, 26.81, 58.30, 65.52, 67.64, 73.78, 74.22, 78.77, 109.38, 109.82. MS : m/z (%) = 366 (M^+ , 1), 351 (100). Anal.: calc for $\text{C}_{16}\text{H}_{30}\text{SO}_7$: C: 52.44, H: 8.25, S: 8.75 ; found : C: 52.48, H: 8.36, S: 8.65.
11. **3b** : ^1H NMR (200MHz, CDCl_3) : 1.22 (s, 9H), 1.29-1.63 (m, 20H), 2.55 (d, OH), 3.85 (dd, 1H), 3.99-4.15 (m, 5H), 4.38 (m, 2H). ^{13}C NMR : 21.7, 23.7, 23.9, 25.1, 34.6, 34.7, 36.3, 36.8, 58.3, 66.9, 67.0, 72.0, 73.9, 74.0, 79.2, 110.0, 110.7. MS : m/z (%) = 446 (M^+ , 100), 389 (80), 325 (12), 292 (82), 250 (7). Anal.: calc for $\text{C}_{22}\text{H}_{38}\text{SO}_7$: C: 59.19, H: 8.58, S: 7.18 ; found : C: 59.45, H: 8.72, S: 7.10. $[\alpha]_{\text{D}}^{20} = +63.2\%$ (c 1, CH_2Cl_2).
12. Crystal structure of **3b** :



Select bond distances and angles : S-O7 : 1.472(5) Å ; S-O3 : 1.631(4) Å ; S-C7 : 1.8305(6) Å ; O3-S-C7 : 95.2(2)° ; O7-S-C7 : 105.8(3)° ; O7-S-O3 : 107.9(3)°.

Crystal data : $\text{C}_{22}\text{H}_{38}\text{O}_7\text{S}$, colourless needle , 0.10x0.15x0.30 mm, monoclinic, space group $\text{P}2_1$, a= 9.241(8) Å, b= 11.413(8) Å, c= 11.891(9) Å, $\beta = 109.84(7)^\circ$, V= 1180(2) Å³, Z=2, $\mu = 0.176 \text{ mm}^{-1}$ (λ (MoK α) = 0.71073 Å), $D_x = 1.257 \text{ g/cm}^3$. All non-hydrogen atoms were refined with anisotropic thermal parameters. Hydrogen atoms were generated in idealized positions and refined, riding on the

carrier atoms, with isotropic thermal parameters $U(\text{H}) = 1.2 U_{\text{eq}}(\text{C})$. Final cycle refinement, including 271 parameters, converged to $R(\text{F}) = 0.053$ [for 1677 $F > 4 \sigma(\text{F})$]; $wR(\text{F}^2) = 0.1226$ for all 2181 F^2 .

13. The sulfurane shown in Scheme 2 can be regarded either as an intermediate or as a transition state. Concerning possible pseudorotation in sulfurane intermediates, see : Okuyama T., *Phosporus, Sulfur, Silicon*, 1994, 95-96, 113-125.
14. In order to study the effect of the Lewis acid we have effected control experiments where the Lewis acid was added after the Grignard reagent. In agreement with a kinetic control (and not an equilibration), the observed d.e. were then the same than without Lewis acid.
15. **6b** : ^1H NMR (200MHz, CDCl_3) : 1.00-1.60 (m, 20H), 2.75 (d, OH), 3.00 (dd, 1H), 3.61-4.11 (m, 7H), 4.29 (s, 2H), 7.0-7.4 (m, 5H). ^{13}C NMR : 23.73, 23.92, 25.06, 34.66, 36.46, 36.55, 65.21, 66.48, 67.00, 71.80, 73.36, 73.47, 80.12, 110.04, 110.62, 128.34, 128.53, 128.93, 129.06, 130.09, 130.32. MS : m/z (%) = 480 (M^+ , 3), 389 (3), 91 (100) Anal.: calc for $\text{C}_{25}\text{H}_{36}\text{SO}_7$: C: 62.48, H: 7.57, S: 6.67 ; found : C: 62.47, H: 7.48, S: 7.08. $[\alpha]_{\text{D}}^{20} = +92.4$ (c 1, CH_2Cl_2).