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ASYMMETRIC SYNTHESIS OF OPTICALLY PURE *tert*- BUTYL SULFOXIDES USING THE "*DAG METHODOLOGY*"

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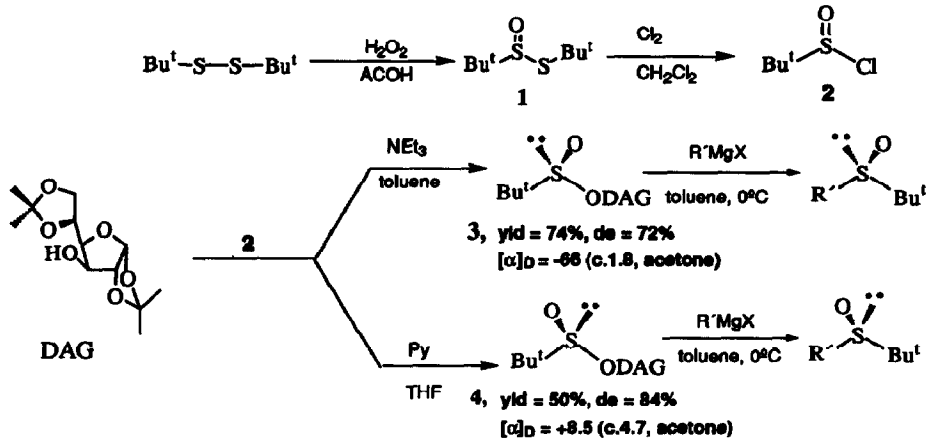
Abstract : Diacetone-*D*-glucose (DAG) reacts with *t*-BuSOCl in the presence of NEt_3 and Py to give(-)-(*S*)- and (+)-(*R*)-*tert*-butanesulfinate respectively, in high diastereomeric excess. These sulfinates were transformed into various enantiomerically pure *tert*-butyl sulfoxides by reaction with different Grignard reagents. Additionally, the reaction of tert-butylmagnesium chloride with (+)-(*R*)- and (-)-(*S*)-methanesulfinates of DAG has been found to occur with complete inversion of configuration and not with retention as previously reported.

Chiral sulfoxides are one of the most powerful chiral controlers in asymmetric C-C bond formation.[2] In particular, it has been demonstrated recently that optically active alkyl *tert*-butyl sulfoxides react with acyclic α,β-unsaturated esters[3] and aldehydes[4] with high selectivity. However, *tert*-butyl sulfoxides have scarcely been used as chiral inducers because until recently there was no satisfactory route for their preparation in optically pure form.[5]

In connection with our interest in the synthesis of optically pure (o.p.) sulfoxides with synthetical and biological interest,[6] we have recently developed a cheap and efficient method for the synthesis of both epimers of various dialkyl and aryl alkyl sulfoxides in high optical purity (100% ee),[7] most of them cannot be obtained by the classical Andersen's methodology.[8] This method uses diaceton-*D*-glucose (DAG) as unique inducer of chirality, and by a simple change of the base used from pyridine to *i*-Pr_2NEt, (*S*)-sulfinates are obtained instead of (*R*)-sulfinates, with very high diastereomeric excess in both cases. In this communication we report the generalisation of this method to the synthesis of both o.p. (+)-(*R*)- and (-)-(*S*)-*tert*-butanesulfinates of DAG , important chiral intermediates for the preparation of both epimers of various (alkyl and aryl) *tert*-butyl sulfoxides in high enantiomeric excess (up to 100%). Additionaly, the reaction of *tert*-butylmagnesium chloride with the methanesulfinates of DAG has been reexamined and different results from those previously reported[7] have been obtained.

The oxidation of *tert*-butyl disulfide with hydrogen peroxide in acetic acid gives *tert*-butyl thiosulfinate **1** in quantitative yield, which upon treatment with chlorine gives the desired *tert*-butanesulfinyl chloride **2**[9] (scheme 1). The reactivity of **2** with DAG has been checked in the two optimal conditions determined before, that is, using a hindered base in one case and a non-hindered base in the other (Scheme 1). Treatment of DAG with *tert*-butanesulfinyl chloride **2** in the presence of Et_3N, from -78ºC to room temperature, gives the *tert*-butanesulfinate (-)-**3**[10] in 74% yield and 72% d.e.. When pyridine was used as base, *tert*-butanesulfinate (+)-**4**, which is epimer of (-)-**3** at sulfur, was predominately obtained in 50% yield and 84% d.e. Also in this case the base used acts as chiral discriminator, and a simple change of the base gives the same result than the change of the inducer of chirality from the cheap diaceton-*D*-glucose to the diacetone derivative of the expensive, nonnatural (-)-*L*-glucose.



Scheme 1

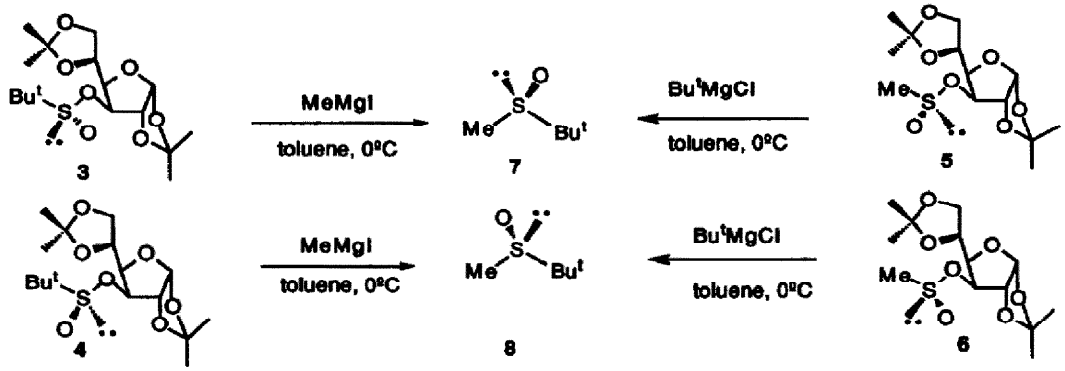
The d.e. was easily determined by ^{1}H-NMR and the two sulfinates 3 and 4 were well resolved on TLC, which has permitted their obtention in optically pure form by column chromatography separation. After purification, o.p. *tert*-butanesulfinates 3 and 4 were treated with various Grignard reagents to give the corresponding alkyl and aryl *tert*-butyl sulfoxides of valuable synthetical interest with high ee (table 1).

Table-I : Syntesis of optically active *tert*-butyl sulfoxides, *t*-BuS(O)R', from DAG alkanesulfinates, RS(O)ODAG, and Grignard reagents, R'MgX.

Sulfinate				Sulfoxide				
Comp	R	*Config* at S	R'	*Comp*	*Yield, %*	$[\alpha]_D$	*Confign* (ee %)	Lit. $[\alpha]_D$
3	*t*-Bu	*S*	Ph	9	85	-155(c.1.3,$CHCl_3$)	*S*(90)[a]	-175[5a, 14]
3	*t*-Bu	*S*	*p*-Tol	10	87	-178(c.0.7, EtOH)	*S*(93)[a]	-185[5d]
4	*t*-Bu	*R*	Me	8	60	+8.7(c.1.6, $CHCl_3$)	*S*(100)[b]	+7.8[5d]
5	Me	*R*	*t*-Bu	7	>95	-7.6(c.7.2, $CHCl_3$)	*R*(100)[b]	-7.8[5d]
6	Me	*S*	*t*-Bu	8	>95	+7.8(c.7.4, $CHCl_3$)	*S*(100)[b]	+7.8[5d]
7	Me	*S*	*t*-Bu	8	>95	+19.2(c.1.4;MeOH)	*S*(100)[b]	+22[5c]

[a]Determined by comparison of the optical rotation to the maximum rotation in the literature. [b]Enantioselectivity determined by chiral shift studies with (*R*)-(-)-N-(3,5-dinitrobenzoyl)(1-phenylethyl)amine.[13]

The absolute configurations of the final sulfoxides are known which has permited the determination of the absolute configuration of the sulfinate intermediates **3** and **4**. By assuming that the displacement step occurs with complete inversion of configuration at sulfur, as it is usual in the Andersen synthesis, one can conclude that sulfinate **3**, predominately obtained with Et_3N as the base, has the (*S*) configuration at sulfur, while sulfinate **4**, predominant with Py as base, has the (*R*) configuration, which is in complete agreement with our previous finding.[7]



Scheme 2

Using the "*DAG methodology* ", both epimers of a given *tert*-butyl sulfoxide can also be obtained in good yield and high ee by the "inverse reaction" between the *tert*-butyl Grignard reagent and the corresponding (*R*)- and (*S*)-sulfinates of DAG, as ilustrated in scheme 2 for the synthesis of o.p. (*R*)- **7** and (*S*)- **8** methyl *tert*-butyl sulfoxides. This reaction has been reported to occur with retention of configuration at the sulfinyl sulfur based on the the specific rotation of a purified sample recorded in acetone as solvent[7]. However, when the specific rotations of the hygroscopic and slightly volatil **7** and **8** were checked in the other solvents reported in the literature for this compound (chloroform and methanol) we found that the addition of *tert*-butylmagnesium chloride over (*R*)- and (*S*)-methanesulfinates of DAG (**5** and **6**) gave (*R*)- and (*S*)-methyl *tert*-butyl sulfoxides (**7** and **8**) respectively, in quantitative yields and 100% ee (Table 1 entry 5, 6 and 7). These results implie that the reaction between the sterically demanding tert-butyl Grignard and DAG methanesulfinates occurs with complete inversion of configuration at sulfur, and not with retention as previously reported.

The absolute configurations of the sulfoxides **7** and **8** have been determined by comparing our specific rotation values with those reported in the literature in chloroform and methanol (Table 1 entry 5, 6 and 7). We have also observed that the rotation of methyl tert-butyl sulfoxide in acetone is strikingly dependant on concentration[12], which can lead to erroneous interpretations.

In conclusion, *DAG methodology* is a simple, general and efficient way of access to o.p. DAG (*R*)- and (*S*)-sulfinates, important chiral intermediates in the synthesis of o.p. compounds bearing a chiral sulfinyl sulfur such as the chiral *tert*-butyl sulfoxides reported in this communication. Some of these sulfoxides are now being used in those processes where the commonly used *p*-tolyl derivative gives low diastereomeric excess.

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10. (-)-3: ^{1}H NMR (200 MHz, $CDCl_3$) δ 5.89 (d, *J* = 3.7 Hz, 1H, H-1), 4.72 (d, *J* = 2.4 Hz, 1H, H-3), 4.58 (d, *J* = 3.7, 1H, H-2), 4.37-4.26 (m, 2H, H-6), 4.13-3.94 (m, 2H, H-4, H-5), 1.50, 1.42, 1.33, 1.31 (4s, 12H, $OCMe_2O$). 1.20 (s, 9H, Me_3C-SO-). ^{13}C NMR (50 MHZ, $CDCl_3$) δ 112.40, 109.11, 104.84, 83.06, 80.55, 80.41, 72.49, 66.60, 58.11, 26.69, 26.58, 26.23, 25.08, 21.61. HRMS calcd for $C_{16}H_{28}SO_7$ (M^+ - CH_3) 349.1321, found 349.1341 (5.9 ppm).

11. (+)-4: ^{1}H NMR (200 MHz, $CDCl_3$) δ 5.87 (d, *J* = 3.5 Hz, 1H, H-1), 4.79 (d, *J* = 3.5 Hz, 1H, H-3), 4.67 (d, *J* = 1.8 Hz, 1H, H-2), 4.12-4.07 (m, 3H, H-4, H-6, H-6´), 3.95-3.88 (m, 1H, H-5), 1.47, 1.38 (2*s*, 6H, $OCMe_2O$), 1.27 (s, 6H, $OCMe_2O$), 1.19 (s, 9H, Me_3C-SO-). ^{13}C NMR (50 MHz, $CDCl_3$) δ 112.17, 109.29, 105.18, 83.53, 82.59, 81.16, 71.69, 67.87, 58.45, 26.64, 26.06, 25.08, 21.45,. HRMS calcd for $C_{16}H_{28}SO_7$ (M^+ - CH_3) 349.1321, found 349.1311 (2.8ppm).

12. Ilustrative values of the $[\alpha]_D$ at 25ºC of compound **8** in acetone are -1.14 at c. 2.1, -0.66 at c. 3.0 and +0.77 at c. 5.6. For a similar behaviour see Krow and Hill, *Chem. Comm* **1968**, 430.

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