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Andersen chemistry with an α,β-unsaturated sulfinyl chloride: synthesis and Grignard reactions of homochiral cholesteryl $(R)_S$-(*E*)-*t*-butylethenesulfinate

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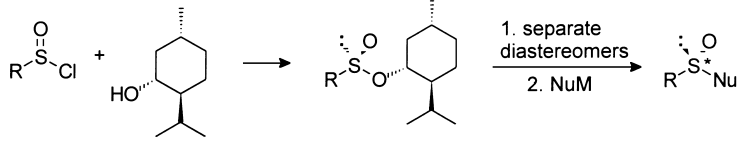
Abstract

(−)-Cholesteryl $(R)_S$-(*E*)-*t*-butylethenesulfinate **2** was prepared in enantiopure form through the reaction of (*E*)-*t*-butylethenesulfinyl chloride and (−)-cholesterol in the presence of quinine (ca. 36% yield). Diastereomerically enriched versions of (*S*)-**2** were prepared with d.e.s up to 75%. Grignard substitution reactions of **2** proceed with high stereospecificity to provide a new access to enantiomerically enriched (*E*)-2-*t*-butylethenylaralkyl sulfoxides in good yield and excellent e.e.

1. Introduction

The importance of enantiopure sulfoxides in synthetic chemistry is well-documented,[1] and versions of the Andersen strategy[2] remain the most popular approach for their preparation. The original Andersen protocol involves the reaction of menthol with a sulfinyl chloride. The resulting diastereomeric mixture of menthyl sulfinate esters must be separated prior to organometallic substitution directed toward enantiomerically pure sulfoxide formation (Scheme 1).



Scheme 1.

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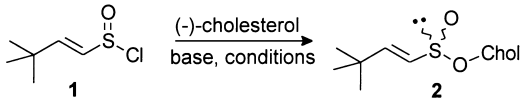
A number of useful adaptations of the Andersen approach have been developed. Some of the improvements include the use of other alcohols such as diacetone-D-glucose,[3] (1*R*,2*S*)-(−)-*trans*-2-phenylcyclohexanol[4] and cholesterol.[5] As part of that follow-up work, the kinetic selectivity of the alcoholysis of the sulfinyl chlorides has been exploited to provide d.e.s of sulfinate sometimes exceeding 97%.[3] More recently, it has been determined that chiral auxiliaries such as oxazolidinones[6] and Oppolzer's amide[7] serve as viable substitutes for optically active alcohols.

The approach has led to the preparation of several sulfoxides mostly with R groups of Me,[5] *p*-tolyl,[2,3] *t*Bu[3] and polysubstituted aryl,[8] driven by the need for such groups in subsequent sulfoxide chemistry and by the availability of the requisite sulfinyl chlorides. The first synthesis of 1-alkenesulfinyl chlorides was recently reported,[9] and it was viewed that application of the Andersen protocol to the 1-alkenesulfinyl chlorides may create a useful preparation of homochiral vinylic sulfoxides. α,β-Unsaturated sulfoxides possess considerable utility for the induction of carbon stereogenicity in organic synthesis.[10] Herein is our initial report of an ongoing study in this area; it describes our first success which originates from 3,3-dimethyl-2-butenesulfinyl chloride.[11]

2. Results and discussion

At the outset of the project we set broad goals, and consequently initial experiments covered a wide area in order to find the system that would prove most accommodating. In very small scale experiments, up to six 1-alkenesulfinyl chlorides were treated with various chiral alcohols including those established for the synthetic protocol: menthol, cholesterol, (1*R*,2*S*)-(−)-*trans*-2-phenylcyclohexanol and DAG. The three pieces of information that arose from these experiments were: (i) simple sulfinate formation following our established procedure[9] did not exhibit much kinetic selectivity; (ii) silica gel chromatography would not be an effective method of separation of the diastereomers; and (iii) whereas most of the alcohols led to oily reaction mixtures, cholesteryl esters were consistently solid mixtures of diastereomers, lending hope that crystallization would provide access to enantiopure 1-alkenesulfinate esters appropriate for conversion to sulfoxides.

It was apparent from these experiments that one of the more obliging pair of reactants would be *t*-butylethenesulfinyl chloride **1**[9,12] and (−)-cholesterol (Scheme 2). On this basis, experiments were undertaken to optimize the product of their condensation, cholesteryl (*E*)-*t*-butylethenesulfinate **2**. The reactants were brought together under a variety of conditions with parameters such as identity and configuration of base, reaction temperature and sequence of addition of reactants. Formation of the sulfinate in high chemical yield and high d.e. was viewed as the ideal outcome.



1 **2**

Scheme 2.

Table 1 indicates some moderate d.e.s that could be obtained upon formation and isolation of sulfinate **2**, but more importantly, after a maximum of two recrystallizations, enantiopure sulfinates were isolated.[13] D.e.s of **2** could readily be measured through ^{1}H NMR in C_6D_6 while the use of (*R*)-(−)-2,2,2-trifluoro-1-(9-anthryl)ethanol allowed configurational assignment of the diastereomers.[14] Samples of **2** enriched in the *S*-isomer were obtained from the mother liquor once substantial amounts of the *R*-isomer crystallized. Alternatively, the use of quinidine promotes preferential formation of (*S*)-**2**, and the d.e. of these samples can be increased slightly through recrystallization from acetone (Table 1, entry 7).

Table 1
Preparative approaches to cholesteryl (R)$_S$-(E)-t-butylethenesulfinate (**2**, Scheme 2)

	Conditions[a]			Yield / de[b]	Recrystallizations[c]	
	Base	Temp. (°C)	Add'n[d]		de	yield
1	K_2CO_3	-78 to -20	A	42% / 0%	76%[R] (100%[R])	20% (8%)
2	K_2CO_3	-78 to rt	B	53% / 4%[R]	92%[R]	20%
3	pyridine	-78 to -20	B	89% / 8%[S][e]	90%[R]	18%
4	quinine	-78 to rt	B	83% / 39%[R]	95%[R] (100%[R])	42% (36%)
5	quinine[f]	-78 to -20	B	89% / 27%[R]	89%[R]	40%
6	quinidine	-78	B	94% / 65%[S]	68%[S]	46%[g]
7	quinidine	-78 to -20	B	82% / 63%[S]	70%[S] (75%[S])	31%[g] (12%)[g]

a Solvent was CH_2Cl_2 unless otherwise noted.

b Sulfinate **2** was obtained as a mixture of diastereomers; de refers to initial de after chromatography.

c No parentheses: 1st recrystallization; parentheses: 2nd recrystallization. Recrystallization solvent was hexanes unless otherwise noted.

d Addition mode A: alcohol and base added to sulfinyl chloride sol'n; addition mode B: sulfinyl chloride added to alcohol and base sol'n.

e When run in THF these conditions afforded **2** in 98% chemical yield; de = 1%[S].

f Solvent was 50:50 toluene: CH_2Cl_2 mixture.

g Recrystallized from acetone.

Optically active forms of **2** were subjected to a number of sulfinate substitution reactions with *n*BuMgCl to find the preferred conditions for efficient sulfoxide formation (Table 2, Scheme 3). Reactions in benzene[15] with that Grignard reagent afforded sulfoxide in high yield while maintaining the stereochemical integrity of the sulfinyl group (entries 5 and 6), and hence these conditions were adopted for reactions with other Grignard reagents. Reactions of enantiopure (*R*)-**2** with commercial Grignard reagents were efficient and stereoselective affording a series of *t*-butylethenyl sulfoxides **3**.[16]

The sulfoxides **3** were readily separated from the cholesterol by flash chromatography and their configurations and enantiomeric excesses were established using (*R*)-(−)-2,2,2-trifluoro-1-(9-anthryl)ethanol. Good yields were found in all cases and e.e.s >90% were obtained for all Grignard reagents employed except for MeMgBr. Experiments with that Grignard reagent were repeated several times and the e.e.s obtained were consistently near 85%. The use of (*S*)-**2** with 71% d.e. demonstrates the high stereospecificity of the displacement reactions and provides a route to vinylic sulfoxides enriched in the other enantiomer.

As well as offering the initial results for a new procedure for enantiomerically enriched vinylic sulfoxides, our experiments also suggest that Grignard substitution reactions with α,β-unsaturated sulfinates proceed with inversion of configuration, a result in keeping with previous observations with

Table 2
Sulfoxides from Grignard substitutions of **2** (Scheme 3)

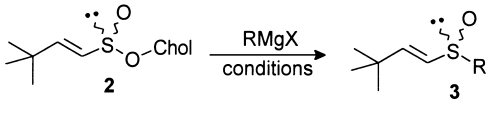
	Grignard[a] Reagent	Initial De of **2**	Temp. (°C)/ solvent	sulfoxide **3** structure	%yield	%ee (conf)	Chol.[b]
1	*n*BuMgCl	100%[R]	-78 to rt/Et_2O	**3a**, R = *n*Bu	61	83[S]	89
2		100%[R]	-78/Et_2O		68	66[S]	82
3		89%[R]	-78 to -40/Et_2O		84	88[S]	73
4		88%[R]	-6/Et_2O:C_6H_{12}		72	83[S]	86
5		88%[R]	+6/C_6H_6		78	88[S]	75
6		100%[R]	+6/C_6H_6		86	>97[S]	79
7	MeMgBr	100%[R]	+6/C_6H_6	**3b**, R = Me	56-67	85-86[S]	83-92
8	*i*PrMgCl	100%[R]	+6/C_6H_6	**3c**, R = *i*Pr	85	98[S]	92
9	*c*C_6H_{11}MgCl	100%[R]	+6/C_6H_6	**3d**, R = *c*C_6H_{11}	86	>97[S]	72
10	$PhCH_2MgCl$[c]	100%[R]	+6/C_6H_6	**3e**, R = $PhCH_2$	78	91[S]	94
11	*p*TolMgBr	100%[R]	+6/C_6H_6	**3f**, R= *p*Tol	86	94[R][d]	96
12	*i*PrMgCl	71%[S]	+6/C_6H_6	**3c**, R = *i*Pr	76	71[R]	82
13	*c*C_6H_{11}MgCl	71%[S]	+6/C_6H_6	**3d**, R = *c*C_6H_{11}	79	71[R]	89

a Organolithium reagents proved ineffective. Two equiv. of the organometal were employed unless otherwise noted.

b Yield of recovered cholesterol.

c Experiment was done with one equiv. of $PhCH_2MgBr$.

d The obtention of the *R*-isomer is consistent with an inversion mechanism. The apparent configurational change from earlier entries in the Table is a consequence of differences in atomic priorities of the groups surrounding the sulfur.



Scheme 3.

other sulfinates.[10a,17] We are currently pursuing additional homochiral α,β-unsaturated sulfinates in order to generalize the utility of this chemistry.

Acknowledgements

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11. We prefer to use the trivial terminology of *t*-butylethenesulfinyl chloride or *t*-butylethenesulfinate, depending on the species.
12. Sulfinate (*R*)-**2** readily demonstrated an ability to selectively crystallize from hexanes. Other cholesteryl sulfinates such as cyclohexenyl or those bearing H, $PhCH_2CH_2$ and Ph groups in place of *t*-Bu were not so obliging. The sulfinate with CO_2Me in place of *t*-Bu crystallized well but its reactions with Grignard agents were not satisfactory.
13. General preparation of **2** (method B): *t*-Butylethenesulfinyl chloride, generated as usual (Ref. 9), was transferred to a solution of cholesterol (0.85 equiv.) and organic base (1.2 equiv.) in CH_2Cl_2 stirring at −78°C. The mixture was warmed to −20°C and stirred at that temperature overnight. Concentration and flash chromatography (3–5% EtOAc/hexanes) followed by one or two crystallizations (hexanes) afforded optically pure (*R*)-**2**; mp 153–154°C; $[\alpha]_D^{25}$=−23.2 (*c* 1.30, $CHCl_3$).
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