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Facile and efficient synthesis of chiral sulfoxide esters: Versatile tool in asymmetric synthesis

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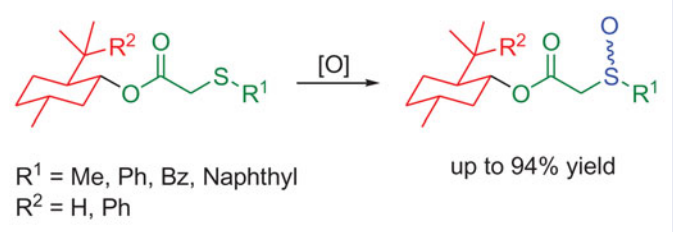
ABSTRACT

Facile and efficient synthesis of sulfoxide esters using menthols as chiral auxiliary is described. Phenylthio/benzylthio/naphthylthioacetic esters act as an efficient substrate for chiral sulfoxides via oxidation in one step. The structural and stereochemical aspects of target product were established on the basis of various spectroscopic studies, namely FT-IR, NMR (^{1}H NMR and ^{13}C NMR) and elemental analysis. This method is simple, fast, convenient and very efficient.

GRAPHICAL ABSTRACT



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β-Lactams; chiral sulfoxide ester; menthol; oxidation

Introduction

The asymmetric synthesis of novel substrates for the synthesis of chiral molecules constitutes an important field in synthetic organic chemistry. The use of chiral auxiliaries in asymmetric synthesis has gained much attention of the scientific community in the past few decades. With continuous efforts to explore the field of asymmetric synthesis has led to the discovery of numerous groups as effective and efficient chirality controller. The sulfinyl group is widely used as an important tool to bring about numerous asymmetric transformations due to its high optical stability and better accessibility of enantiomeric forms. Presently, the synthesis of chiral nonracemic sulfoxides with high enantiomeric purity has been a subject of constant interest.[1–5]

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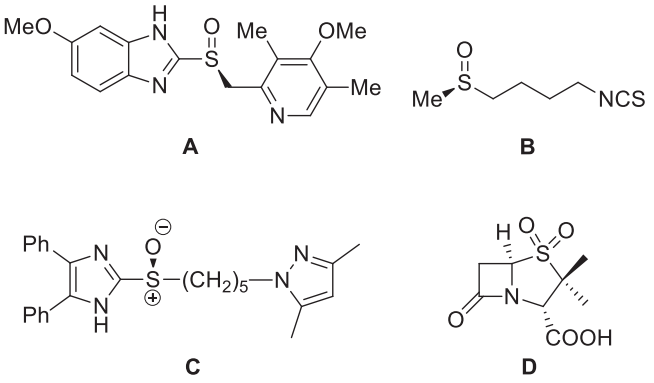


Figure 1. Biologically important sulfoxides.

The presence of stereogenic sulfinyl sulfur atom in many biologically active compounds has increased the importance of sulfinyl derivatives. Omeprazole and its optically pure (*S*)-form A are well known antiulcer agents.[6,7] In addition to this, sulforaphane B (anticancer drug), RP 73163 C (ACAT inhibitor) and many other sulfinyl containing drugs are presently available in the market (Fig. 1).[8,9] Further, the sulfoxide derivatives of *β*-lactams constitute a major class of mechanism-based *β*-lactamase inhibitors such as sulbactam D.[10]

Our research group has been continuously working to explore novel *β*-lactam precursors, various methodologies for the synthesis of monocyclic/spirocyclic/heteroaryl substituted *β*-lactams and their functionalization.[11,12] Recently, we have successfully utilized *β*-lactam sulfoxides/selenoxide for the synthesis of (*Z*)- and (*E*)-3-allylidene-*β*-lactams[13] and C-3 functionalized 3-sulfonyl-*β*-lactams.[14] Keeping in view of our interest in *β*-lactam sulfoxides and their transformation into novel heterocycles triggered us to carry out the synthesis of novel chiral sulfoxide esters which acts as versatile precursors for chiral *β*-lactams and other valuable heterocycles.

Results and discussion

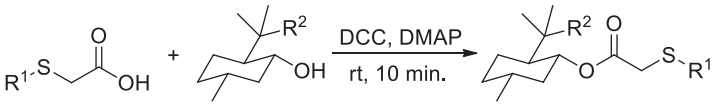
In continuation to above reports, it was envisaged to prepare esters **4** and **5** by the reaction of methylthio/phenylthio/benzylthio/naphthylthioacetic acid **1** with chiral auxiliaries such as (1*R*,2*S*,5*R*)-(−)-menthol/(1*R*,2*S*,5*R*)-(−)-8-phenylmenthol **2** in the presence of a condensing agent, DCC and catalytic amount of DMAP. These esters were further oxidized to give the corresponding pair of diastereomers **4–5**.

Starting substrates, i.e. methylthio/phenylthio/benzylthio/naphthylthioacetic acid **1a–d** were prepared from chloroacetic acid and appropriate thiols using reported methodology.[15] In order to prepare chiral esters **3a–g**, methylthio/phenylthio/benzylthio/naphthylthioacetic acid **1a–d** were treated with cyclohexyl-based chiral alcohols, namely (1*R*,2*S*,5*R*)-(−)-menthol **2a** and (1*R*,2*S*,5*R*)-(−)-8-phenylmenthol **2b** in the presence of a condensing agent, *N*,*N*-dicyclohexylcarbodiimide (DCC) and catalytic amount of 4-(dimethylamino)pyridine (DMAP) in dry dichloromethane under nitrogen atmosphere, at room temperature. The products **3a–g** were purified by silica gel column chromatography (ethyl acetate: hexane) and their structures were characterized on the basis of IR, ^{1}H NMR, ^{13}C NMR and elemental analysis. The results are summarized in Table 1 and Scheme 1.

Table 1. Chiral ester **3a–g**.

Entry	R^1	R^2	Chiral ester **3**	Yield[a] %
1	Me	H	**3a**	87
2	Ph	H	**3b**	59
3	Bz	H	**3c**	50
4	Naphthyl	H	**3d**	38
5	Me	Ph	**3e**	57
6	Ph	Ph	**3f**	51
7	Naphthyl	Ph	**3g**	59

[a]Isolated yields after chromatographic purification.



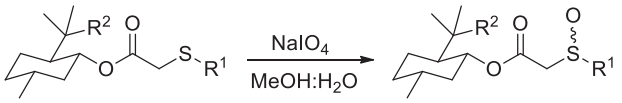
1a-d **2a-b** **3a-g**

Scheme 1. Synthesis of chiral esters **3a–g**.

Table 2. Chiral sulfoxide esters **4–5**.

Entry	Chiral ester **3**	Time (h)	Chiral sulfoxide esters **4–5**		Yielda %
1	**3a**	117	**4a**	**5a**	94
2	**3b**	23	**4b**	**5b**	85
3	**3c**	114	**4c**	**5c**	82
4	**3d**	15	**4d**	**5d**	85
5	**3e**	95	**4e**	**5e**	83
6	**3f**	17	**4f**	**5f**	66
7	**3g**	48	**4g**	**5g**	71

Reaction conditions: Chiral ester **3** (1 mmol), $NaIO_4$ (1.1 mmol), MeOH:H_2O (10:1), 0 °C to rt, stirring.
[a]Isolated yields after chromatographic purification.



3a-g **4-5a-g**

Scheme 2. Synthesis of chiral sulfoxide esters **4–5**.

After the successful introduction of chiral auxiliary, various chiral esters **3a–g** were oxidized by using different oxidizing agents to give a pair of diastereomers **4–5**. Initially, **3a** was oxidized with $NaIO_4$ using MeOH:H_2O as solvent system (H_2O is used to enhance the solubility of $NaIO_4$). The progress of the reaction was monitored by TLC. The TLC profile showed the appearance of a spot having R_f lower than the starting substrate. As soon as starting substrate completely disappeared, reaction was stopped and worked up. The crude product was purified by silica gel column chromatography eluting with 2% EtOAc/hexane. The product was identified as a mixture of two diastereomeric chiral sulfoxide esters **4a** and **5a** (Table 2, and Scheme 2 entry 1). In addition to this, no sulfone formation was observed in the reaction under controlled conditions.

The identification of the characteristic peaks in NMR spectra of **4f** and **5f** confirmed the formation of products, namely in the ^1H and ^{13}C NMR spectrum, the most desheilded aliphatic peak corresponds to methine proton directly attached to O of ester

Table 3. Utility of other oxidizing agents.

Entry	Chiral ester **3**	Reagent Time (**4** + **5**, Yield[a])			
		30% H_2O_2 in CH_3COOH	30% H_2O_2/ClCOOEt in CH_2Cl_2	*m*-CPBA in CH_2Cl_2	30% H_2O_2/C_5H_5N in CH_2Cl_2
1	**3a**	22 h (84%)	46 h (79%)	1.5 h (96%)	–
2	**3b**	51 h (76%)	10 h (75%)	40 min (58%)	–
3	**3c**	30 min (93%)[b]	1.5 h (76%)	4 h (80%)	–
4	**3d**	17 h (36%)	4 h (53%)	15 min (82%)	45 h (36%)
5	**3e**	1.5 h (52%)	2.5 h (70%)	–	–
6	**3f**	1 h (75%)[b]	45 min (86%)	–	–
7	**3g**	–	–	10 min (76%)	–

[a]Isolated yields of chiral sulfoxide esters (**4** + **5**) after chromatographic purification.
[b]Temperature 60 °C.

group (i.e. 4.82, 75.6 in **4f** and 4.80, 75.9 in **5f**). Further, two sets of doublets having same coupling constant (*J*) values (2.73, 3.15 in **4f** and 2.95, 3.06 in **5f**) in ^{1}H NMR and desheilded peak (61.2 in **4f** and 60.8 in **5f**) due to the presence of C = O group in the neighborhood corresponds to CH_2CO group.

The diastereomeric ratio (*dr*) of chiral sulfoxide esters **4a** and **5a** was calculated from ^{1}H NMR. Since the signal for methine proton of the chiral auxiliary did not give much information about the ratio of the two isomers due to its complex nature, therefore the signal for the methyl (C5′–Me) of both the isomers were analyzed for *dr* calculations. The *dr* of **4a** and **5a** was found to be 1:1 as evident from ^{1}H NMR analysis.

Further, the scope of the reaction was analyzed by treating various chiral esters **3b–d** [R^2 = H; (1*R*,2*S*,5*R*)-(–)-menthol as chiral auxiliary] with varying R^1 groups under similar reaction conditions which resulted in the formation of products in excellent yields (Table 2, entries 2–4). However, products were obtained as non-separable mixture. Therefore, in order to increase the utility of sulfoxide esters, oxidation of chiral esters **3e–g** having bulky aryl group (R^2 = Ph) was carried out and separable mixture of chiral sulfoxide esters was obtained in case of chiral esters **3f–g** (Table 2, entries 6–7). In case of chiral ester **3f–g**, the chiral sulfoxide esters **4f, 4g** and **5f, 5g** were easily separated by column chromatography and assigned (*S*)- and (*R*)- configuration, respectively.[16] The reaction was found to be general in all the cases and results are summarized in Table 2. The structure of chiral sulfoxide esters **4–5**(**b–g**) was confirmed on the basis of FT-IR, ^{1}H NMR, ^{13}C NMR and elemental analysis.

The chiral esters **3a–g** were successfully oxidized using $NaIO_4$ in MeOH:H_2O solvent system and the products were obtained excellent yields. However, the time required for the completion of reaction was very high. Therefore, the oxidation of chiral esters **3a–g** was tried with different oxidizing agents and reaction conditions were optimized. For this purpose, chiral esters **3a-g** were oxidized using different oxidizing systems, namely 30% H_2O_2 in CH_3COOH, 30% H_2O_2/ClCOOEt in CH_2Cl_2 and *m*-CPBA in CH_2Cl_2 and the results are summarized in Table 3. The oxidation of chiral esters **3a–g** with various oxidizing agents afforded the products in very good to excellent yields as shown in Table 3. Furthermore, *m*-CPBA in CH_2Cl_2 was found to be the best system for oxidation of chiral esters **3a–g** as time required for the completion of reaction was greatly reduced in addition to excellent yields.

This is further supported by the kinetic study reported in the literature that oxidation of sulfides using peracetic acids occurred very fast.[17] In general, both $NaIO_4$ and *m*-

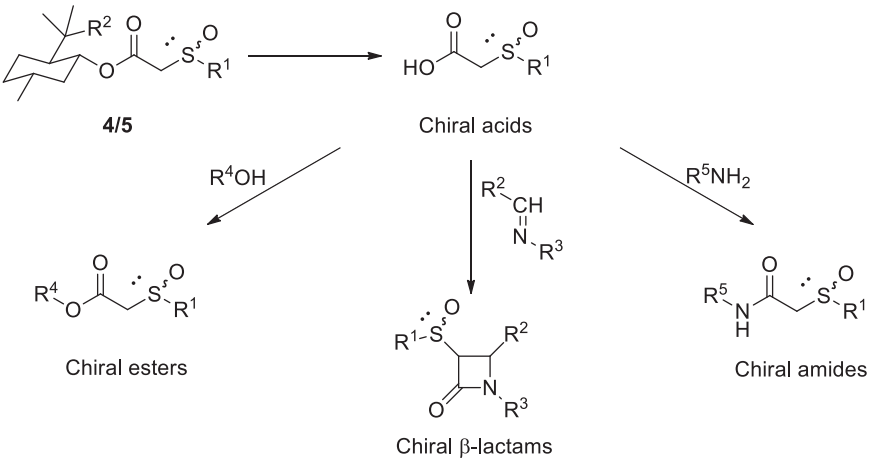


Figure 2. Synthetic applications of chiral sulfoxide esters.

CPBA are very good reagents for oxidation of sulfides.[18] The actual mechanisms are unknown, but more polar transition state formed during electrophilic transfer of oxygen to sulfur using *m*-CPBA might be the primary cause of fast oxidation. Further, lack of diastereoselectivity might be attributed to the presence of chiral auxiliary at the opposite side of sulfoxide group and diastereoselectivity can be improved by increasing the proximity of chiral auxiliary to the sulfide group.

Further, transformation of chiral sulfoxide esters **4–5** into various synthetically useful molecules, namely chiral acids, esters, amides and β-lactams is currently being pursued in our laboratory (Fig. 2).

Conclusion

To summarize, novel chiral sulfoxide esters were prepared using a simple, efficient and fast methodology using cyclohexyl based chiral auxiliaries. Further, improving diastereoselectivity and transformation of these chiral synthons into corresponding chiral β-lactams/other valuable heterocycles has been pursued in our laboratory. Further, a detailed report elaborating synthesis and biological evaluation of chiral β-lactams will be published in near future.

Experimental

Melting points were determined in an open capillary on melting point apparatus (Perfit GSI-MP-3) and are uncorrected. Fourier transform infrared spectra were recorded on a Thermo Scientific Nicolet iS50 (FT-IR) spectrophotometer (ν_{max} in cm^{-1}). ^1H (300 MHz) and ^{13}C (75 MHz) NMR spectra were recorded on JEOL AL 300 (300 MHz) spectrometer. Chemical shifts are given in ppm relative to Me_4Si as an internal standard ($\delta = 0$ ppm) for ^1H NMR, $CDCl_3$ ($\delta = 77.0$ ppm) for ^{13}C NMR. The elemental analysis (C, H) were recorded on Flash 2000 Organic elemental analyzer. Column chromatography was performed using Merck Silica Gel (60–120 mesh) using EtOAc:hexane

(10:90) as an eluant system. Analytical thin-layer chromatography (TLC) was performed on precoated silica gel F254 aluminum plates with visualization under UV light.

General procedure for the synthesis of chiral sulfoxide esters (4–5, a–g)

To a stirred solution of ester **3f** (0.078 mmol) in 5 mL methanol, sodium metaperiodate (0.079 mmol) dissolved in minimum amount of water at 0 °C was added. The progress of the reaction was monitored by TLC. After the completion of reaction, the solvent was evaporated under reduced pressure and product was extracted with methylene chloride (3 × 10 mL) and the contents were washed with water (2 × 10 mL). The combined organic extracts were dried over anhydrous Na_2SO_4 and filtered. The residue after solvent evaporation in vacuum, was purified by silica gel column chromatography using 10% EtOAc/hexane as eluent to furnish chiral sulfoxide esters **4** and **5**. Their structures were confirmed on the basis of following spectral data.

Benzenesulfinyl-acetic acid 5′-methyl-2′-(1″-methyl-1″-phenyl-ethyl)-cyclohexyl ester (**4f**) Pale white solid; Yield 37%; mp 123–124 °C; FT-IR ($CHCl_3$) ν: 1045 (S = O), 1721 (C = O) cm^{-1}; ^1H NMR spectrum (300 MHz, $CDCl_3$), δ, ppm (J, Hz): 0.82–2.17 (17H, m), 2.73 (1H, d, J = 13.7 Hz, CH_2), 3.15 (1H, d, J = 13.7 Hz, CH_2), 4.82 (1H, dt, J = 4.5, 10.8 Hz, CH), 7.11–7.58 (10H, m, ArH); ^{13}C NMR spectrum (75 MHz, $CDCl_3$), δ, ppm: 21.7 (CH_3), 22.2 (CH_3), 26.1 (CH_2), 30.1 (CH_3), 31.3 (CH), 34.4 (CH_2), 39.4 (CMe_2Ph), 41.3 (CH_2), 50.0 (CH), 61.2 (CH_2CO), 75.6 (CH–O), 124.4 (Ar-C), 125.1 (Ar-C), 125.5 (Ar-C), 128.1 (Ar-C), 129.3 (Ar-C), 131.6 (Ar-C), 143.4 (Ar-C), 152.0 (Ar-C), 164.0 (C=O); Elemental analysis: found (%): C, 72.23; H, 7.51. $C_{24}H_{30}O_3S$ calculated (%): C, 72.32; H, 7.59.

Benzenesulfinyl-acetic acid 5′-methyl-2′-(1″-methyl-1″-phenyl-ethyl)-cyclohexyl ester (**5f**)

Crystalline solid; Yield 29%; mp 110–111 °C; FT-IR ($CHCl_3$) ν: 1041 (S = O), 1721 (C = O) cm^{-1}; ^1H NMR spectrum (300 MHz, $CDCl_3$), δ, ppm (J, Hz): 0.82–2.02 (17H, m), 2.95 (1H, d, J = 14.2 Hz, CH_2), 3.06 (1H, d, J = 14.1 Hz, CH_2), 4.80 (1H, dt, J = 4.5, 10.8 Hz, CH), 7.20–7.61 (10H, m, ArH); ^{13}C NMR spectrum (75 MHz, $CDCl_3$), δ, ppm: 21.8 (CH_3), 22.8 (CH_3), 26.2 (CH_2), 29.7 (CH_3), 31.3 (CH), 34.4 (CH_2), 39.4 (CMe_2Ph), 41.5 (CH_2), 50.0 (CH), 60.8 (CH_2CO), 75.9 (CH-O), 124.5 (Ar-C), 125.1 (Ar-C), 125.4 (Ar-C), 128.0 (Ar-C), 129.2 (Ar-C), 131.6 (Ar-C), 143.2 (Ar-C), 151.8 (Ar-C), 164.2 (C=O); Elemental analysis: found (%): C, 72.11; H, 7.06. $C_{24}H_{30}O_3S$ calculated (%): C, 72.32; H, 7.59.

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