Available online at **www.joac.info**

ISSN: 2278-1862

Journal of Applicable Chemistry

2019, 8 (3): 1223-1230

(International Peer Reviewed Journal)

A Rapid and Efficient Protocol for Chiral Sulfoxide Amides: Versatile Asymmetric Synthon

Reshma[1], Jitender Bhalla[2]*, Aman Bhalla[3], Shamsher S. Bari[3] and Renu Thapar[4]

1. Department of Chemistry, DAV College, Chandigarh-160 011, **INDIA**
2. Department of Chemistry, Dev Samaj College for Women, Chandigarh-160 047, **INDIA**
3. Department of Chemistry and Centre of Advanced Studies in Chemistry, Panjab University, Chandigarh-160 014, **INDIA**
4. University Institute of Engineering and Technology, Panjab University, Chandigarh-160 014, **INDIA**

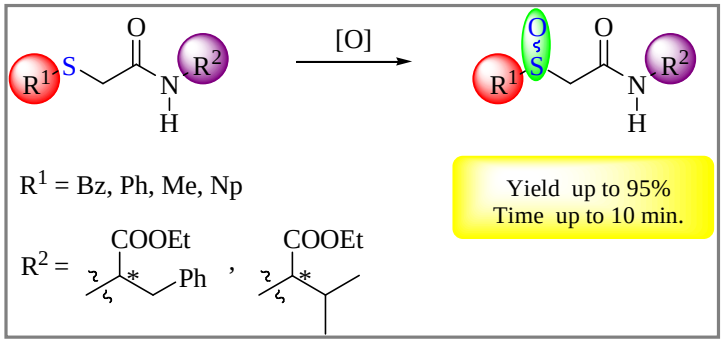
Email: jitenderbhalladscw@gmail.com, amanbhalla@pu.ac.in

Accepted on 11th April, 2019

ABSTRACT

A novel strategy for synthesis of chiral sulfoxide amides using aliphatic amino esters as chiral auxiliary is described. The condensation of benzyl/phenyl/methyl/naphthylthioethanoic acids with chiral amino esters followed by oxidation resulted in formation of chiral sulfoxide amides. All the new products were characterized on the basis of various spectroscopic techniques such as FT-IR, ^{1}H NMR, ^{13}C NMR and CHN elemental analysis. The methodology provides simple, fast and convenient access towards synthetically useful chiral sulfoxide amides.

Graphical Abstract



Keywords: Chiral sulfoxide amides, Amino esters, Substituted ethanoic acids, Oxidation, β-Lactams.

INTRODUCTION

One of the most important and widely explored areas of organic chemistry is asymmetric synthesis. The discovery of non-racemic compounds having unique and interesting properties has significantly enhanced the importance of this field. A number of approaches/strategies have been developed and

utilized for preparation of chiral frameworks using chiral substrates/reagents/auxiliaries/catalysts [**1, 2**]. Further, use of chiral auxiliaries has wide range of scope as well as applications in asymmetric synthesis.

A large number of chiral auxiliaries have been reported in literature among which chiral sulfoxides has shown promising applications in asymmetric synthesis. The synthesis of chiral non-racemic sulfoxides with high enantiomeric purity has drawn considerable attention of synthetic organic chemists over the years due to wide range of synthetic utility [**3-5**]. The important feature of sulfinyl functional group includes activation of adjacent carbon-hydrogen bonds toward base followed by alkylation [**6, 7**] or acylation [**7, 8**] of the anions with high diastereoselectivity. Moreover, diastereoselectivity can also be incorporated at positions far from chiral sulfur centre [**9**].

In addition to this, chiral sulfoxides has also exhibited a number of pharmacological applications such as (*S*)-oxisurane **A** (immunosuppressor) [**10**], Esomeprazole (*S*)-form **B** (proton pump inhibitor) [**11**] and sparsomycin **C** (anticancer drug) [**12**] (Figure 1). Further, amino acid sulfoxides of type **D** show a wide range of biological activities including cholesterol catabolism regulation, antibiotic activities and precursors of flavors and aroma (Figure 1) [**13**].Moreover, sulphonamides (analogues of sulfoxides) represent another important class of biologically active compounds [**14-19**].

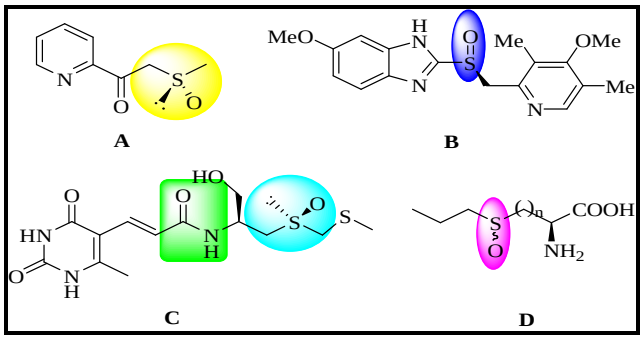


Figure 1. Biologically important chiral sulfoxides.

Till now, we have been engaged in synthesis of novel β-lactam precursors, 3-oxo/thio/seleno/ chloro substituted monocyclic β-lactams and their transformation to bicyclic, spirocyclic and heterocyclic substituted derivatives [**20-23**]. In addition to this, we have recently reported β-lactam sulfoxides/selenoxides mediated synthesis of 3-allylidene-β-lactams [**24**] and preparation of functionalized 3-phenylsulfonyl/sulfinyl-β-lactams [**25**]. In view of our interest towards synthesis of novel β-lactam sulfoxides and their transformation into useful products, we envisaged to synthesize novel chiral sulfoxide amides using a simple, fast and efficient approach.

MATERIALS AND METHODS

FT-IR spectra were recorded on a Thermo scientific Nicolet iS50 (FT-IR) spectrophotometer (υ_{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 (δ = 0 ppm) for ^1H NMR, $CDCl_3$ (δ = 77.0 ppm) for ^{13}C NMR. The elemental analysis (C, H, N) were recorded on Flash 2000 Organic elemental analyzer. Analytical thin-layer chromatography (TLC) was performed on precoated silica gel F254 aluminium plates and visualized under UV light.

General procedure for the synthesis of chiral sulfoxide amides (4-5, a-h): To a stirred solution of amide **3** (0.107 mmol)in 5 mL dry methylene chloride was added *m*-CPBA (0.107 mmol) at 0 ^oC. The progress of the reaction was monitored by TLC. After completion, reaction mixture was poured into aqueous 10% sodium sulfite(5 mL) and stirred. The aqueous mixture was extracted with methylene chloride (3 x 10 mL) and the combined organic layer was washed with 5% $NaHCO_3$ (10 mL)

followed by brine (10 mL) and dried over anhydrous Na_2SO_4. The residue after solvent evaporation *in vacuo*, was purified by silica gel column chromatography using 10% ethyl acetate: hexanes as the eluant to furnish a mixture of **4** and **5**.

3-Phenyl-2-(2-phenylmethanesulfinylacetylamino)-propionic acid ethyl ester (4a and 5a): Viscous oil; Yield 80%; FT-IR ($CHCl_3$) ν: 1028, 1072 (S=O), 1672 (C=O), 1737 (C=O) cm^{-1}; ^1H NMR spectrum (300 MHz, $CDCl_3$), δ, ppm (*J*, Hz): 1.14-1.20 (m, 6H, CH_2CH_3, both isomers), 2.93-3.20 (m, 6H, CH_2, both isomers), 3.45 (d, *J* = 14.4 Hz, 2H, CH_2, one isomer), 3.75 (d, *J* = 12.9 Hz, 1H, CH_2, other isomer), 3.83 (d, *J* = 12.9 Hz, 1H, CH_2, other isomer), 4.06-4.16 (m, 4H, CH_2CH_3, both isomers), 4.17 (d, *J* = 6.6 Hz, 1H, CH_2, one isomer), 4.25 (d, *J* = 12.6 Hz, 1H, CH_2, one isomer), 4.70-4.77 (m, 1H, CH, one isomer), 4.81-4.88 (m, 1H, CH, other isomer), 7.10-7.31 (m, 20H, ArH, both isomers), 7.36 (d, *J* = 7.8 Hz, 1H, NH, one isomer), 7.64 (d, *J* = 7.2 Hz, 1H, NH, other isomer);^{13}C NMR spectrum (75 MHz, $CDCl_3$), δ, ppm (for both isomers): 14.0, 37.5, 37.8, 50.4, 51.1, 53.7, 53.9, 56.4, 56.7, 61.5, 127.1, 128.5, 128.9, 129.0, 129.1, 129.2, 130.2, 130.3, 135.8, 136.0, 163.8, 164.4, 170.9, 171.2; Elemental analysis: found (%): C, 64.04; H, 6.11; N, 3.69. $C_{20}H_{23}NO_4S$ calculated (%): C, 64.32; H, 6.21; N, 3.75.

2-(2-Benzenesulfinyl-acetylamio)-3-phenyl-propionic acid ethyl ester (4b and 5b): Viscous oil; Yield 76%; FT-IR ($CHCl_3$) ν: 1032, 1065 (S=O), 1675 (C=O), 1737 (C=O) cm^{-1}; ^1H NMR spectrum (300 MHz, $CDCl_3$), δ, ppm (*J*, Hz): 1.10-1.16 (m, 6H, CH_2CH_3, both isomers), 2.87-3.12 (m, 4H, CH_2, both isomers), 3.400 (d, *J* = 14.4 Hz, 1H, CH_2, one isomer), 3.402 (d, *J* = 14.1 Hz, 1H, CH_2, other isomer), 3.54 (d, *J* = 14.1 Hz, 1H, CH_2, other isomer), 3.64 (d, *J* = 14.4 Hz, 1H, CH_2, one isomer), 4.07 (q, *J* = 6.9 Hz, 4H, CH_2CH_3, both isomers), 4.58 (q, *J* = 6.9 Hz, 1H, CH, one isomer), 4.71 (q, *J* = 6.6 Hz, 1H, CH, other isomer), 7.06-7.56 (m, 22H, NH and ArH, both isomers);^{13}C NMR spectrum (75 MHz, $CDCl_3$), δ, ppm (for both isomers): 14.0, 37.8, 38.1, 53.7, 54.2, 58.8, 59.5, 61.4, 61.4, 124.0, 127.1, 128.5, 128.6, 129.2, 129.3, 131.4, 131.5, 135.7, 135.8, 141.6, 141.9, 163.3, 163.4, 170.7, 170.9; Elemental analysis: found (%): C, 63.09; H, 5.81; N, 3.85. $C_{19}H_{21}NO_4S$ calculated (%): C, 63.49; H, 5.89; N, 3.90.

2-(2-methanesulfinyl-acetylamino)-3-phenyl-propionic acid ethyl ester(4c and 5c): Viscous oil; Yield 91%; FT-IR ($CHCl_3$) ν: 1033, 1670 (S=O), 1736 (C=O) cm^{-1}; ^1H NMR spectrum (300 MHz, $CDCl_3$), δ, ppm (*J*, Hz):1.14-1.20 (6H, m, CH_2CH_3, both isomers), 2.34 (3H, s, CH_3S, one isomer),2.66 (3H, s, CH_3S, other isomer), 2.90-2.98 (2H, m, CH_2, both isomers), 3.06-3.22 (4H, m, CH_2, both isomers), 3.51-3.57 (2H, m, CH_2, both isomers), 4.05-4.13 (4H, m, CH_2H_3, both isomers), 4.63-4.70 (1H, m, CH, one isomer), 4.72-4.79 (1H, m, CH, other isomer), 7.08-7.23 (10H, m, ArH, both isomers),7.46 (1H, d, *J* = 7.8 Hz, NH, one isomer),7.64 (1H, d, *J* = 7.5 Hz, NH, other isomer);^{13}C NMR spectrum (75 MHz, $CDCl_3$), δ, ppm (for both isomers):14.0, 36.9, 37.0, 37.6, 37.8, 53.7, 53.8, 54.5, 55.3, 61.5, 61.6, 127.1, 128.6, 129.1, 129.3, 135.8, 135.9, 163.6, 164.1, 171.0, 171.2; Elemental analysis: found (%): C, 56.31; H, 6.35; N, 4.66. $C_{14}H_{19}NO_4S$ calculated (%): C, 56.55; H, 6.44; N, 4.71.

2-[2-(Naphthalene-2-sulfinyl)acetylamino]-3-phenyl-propionic acid ethyl ester (4d and 5d): Viscous oil; Yield 93%; FT-IR ($CHCl_3$) ν: 1030, 1069 (S=O), 1676 (C=O), 1737 (C=O) cm^{-1}; ^1H NMR spectrum (300 MHz, $CDCl_3$), δ, ppm (*J*, Hz): 1.05-1.18 (m, 6H, CH_2CH_3, both isomers), 2.87-3.14 (m, 4H, CH_2, both isomers), 3.47 (d, *J* = 14.4 Hz, 1H, CH_2, one isomer), 3.52 (d, *J* = 14.7 Hz, 1H, CH_2, other isomer), 3.63 (d, *J* = 14.4 Hz, CH_2, one isomer), 3.69 (d, *J* = 14.1 Hz, 1H, CH_2, other isomer), 3.94-4.08 (m, 4H, CH_2CH_3, both isomers), 4.59 (q, *J* = 6.6 Hz, 1H, CH, one isomer), 4.69 (q, *J* = 6.0 Hz, 1H, CH, other isomer), 6.98-8.15 (m, 26H, NH and ArH, both isomers);^{13}C NMR spectrum (75 MHz, $CDCl_3$), δ, ppm (for both isomers): 13.9, 37.8, 38.1, 53.6, 54.1, 59.2, 61.4, 119.5, 124.8, 125.1, 127.1, 127.3, 127.4, 128.0, 128.5, 129.1, 129.2, 129.3, 129.6, 132.7, 132.8, 134.6, 135.7, 138.8, 163.3, 170.7, 170.8; Elemental analysis: found (%): C, 67.01; H, 5.56; N, 3.37. $C_{23}H_{23}NO_4S$ calculated (%): C, 67.46; H, 5.66; N, 3.42.

3-Methyl-2-(2-phenylmethanesulfinyl-acetylamino)-butyric acid ethyl ester (4e and 5e): Viscous oil; Yield 92%; FT-IR ($CHCl_3$) ν: 1026 (S=O), 1672 (C=O), 1736 (C=O) cm^{-1}; ^1H NMR spectrum (300 MHz, $CDCl_3$), δ, ppm (*J*, Hz): 0.85-0.98 (m, 12H, CH_3, both isomers), 1.19-1.25 (m, 6H, CH_2CH_3, both isomers), 2.14-2.23 (m, 2H, $CH(CH_3)_2$, both isomers), 3.09 (d, *J* = 14.7 Hz, 1H, $PhCH_2$, one isomer), 3.21 (d, *J* = 14.1 Hz, 1H, $PhCH_2$, other isomer), 3.55 (d, *J* = 14.1 Hz, 1H, CH_2, other isomer), 3.58 (d, *J* = 14.1 Hz, 1H, CH_2, one isomer), 4.04-4.22 (m, 6H, CH_2CH_3, CH_2, both isomer), 4.26 (d, *J* = 12.9 Hz, 1H, CH_2, one isomer), 4.34 (d, *J* = 12.9 Hz, 1H, CH_2, other isomer), 4.41 (dd, *J* = 4.8, 8.4 Hz, 1H, CH, one isomer), 4.49 (dd, *J* = 4.8, 8.4 Hz, 1H, CH, other isomer), 7.19 (d, *J* = 7.8 Hz, 1H, NH, other isomer), 7.28-7.33 (m, 10H, ArH, both isomers), 7.74 (d, *J* = 7.8 Hz, 1H, NH, one isomer);^{13}C NMR spectrum (75 MHz, $CDCl_3$), δ, ppm (for both isomers): 14.1, 14.2, 17.6, 17.8, 19.2, 30.2, 30.8, 50.2, 51.7, 56.5, 57.2, 57.9, 61.3, 128.6, 128.9, 129.1, 130.3, 163.8, 165.0, 171.1, 171.5; Elemental analysis: found (%): C, 58.77; H, 6.99; N, 4.26. $C_{16}H_{23}NO_4S$ calculated (%): C, 59.05; H, 7.12; N, 4.30.

2-(2-Benzenesulfinyl-acetylamino)-3-methyl-butyric acid ethyl ester (4f and 5f): Viscous oil; Yield 95%; FT-IR ($CHCl_3$) ν: 1031 (S=O), 1673 (C=O), 1733 (C=O) cm^{-1}; ^1H NMR spectrum (300 MHz, $CDCl_3$), δ, ppm (*J*, Hz): 0.76 (d, *J* = 6.9 Hz, 3H, CH_3, one isomer), 0.81 (d, *J* = 7.2 Hz, 3H, CH_3, other isomer), 0.900 (t, *J* = 6.9 Hz, 3H, CH_2CH_3, one isomer), 0.903 (t, *J* = 7.8 Hz, 3H, CH_2CH_3, other isomer), 1.19 (d, *J* = 7.2 Hz, 3H, CH_3, one isomer), 1.21 (d, *J* = 6.9 Hz, 3H, CH_3, other isomer), 1.96-2.090 (m, 1H, $CH(CH_3)_2$, one isomer), 2.095-2.15 (m, 1H, $CH(CH_3)_2$, other isomer), 3.49 (d, *J* = 13.8 Hz, 1H, CH_2, other isomer), 3.56 (d, *J* = 14.1 Hz, 1H, CH_2, one isomer), 3.63 (d, *J* = 14.1 Hz, 1H, CH_2, other isomer), 3.73 (d, *J* = 14.4 Hz, 1H, CH_2, one isomer), 4.07-4.17 (m, 4H, CH_2CH_3, both isomers), 4.31 (dd, *J* = 4.8, 8.1 Hz, 1H, CH, one isomer), 4.41 (dd, *J* = 5.1, 8.7 Hz, 1H, CH, other isomer), 7.23 (d, *J* = 7.5 Hz, 1H, NH, one isomer), 7.29 (d, *J* = 9.0 Hz, 1H, NH, other isomer), 7.44-7.62 (m, 16H, ArH, both isomer);^{13}C NMR spectrum (75 MHz, $CDCl_3$), δ, ppm (for both isomers): 14.1, 17.6, 17.8, 18.7, 18.9, 30.8, 31.2, 57.5, 57.7, 58.6, 59.7, 61.1, 61.2, 124.0, 124.1, 129.3, 131.4, 131.5, 141.7, 141.9, 163.6, 163.7, 171.1; Elemental analysis: found (%): C, 57.38; H, 6.68; N, 4.44. $C_{15}H_{21}NO_4S$ calculated (%): C, 57.86; H, 6.80; N, 4.50.

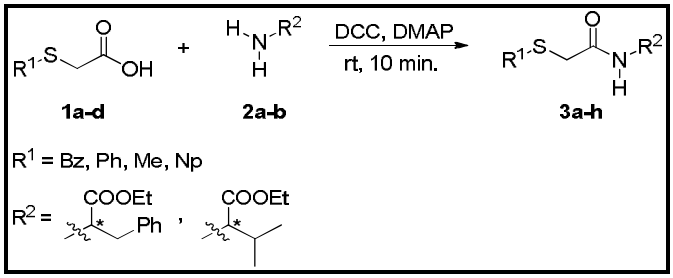
2-(2-Methanesulfinyl-acetylamino)-3-methyl-butyric acid ethyl ester (4g and 5g): Viscous oil; Yield 68%; FT-IR ($CHCl_3$) ν: 1025 (S=O), 1656 (C=O), 1737 (C=O) cm^{-1}; ^1H NMR spectrum (300 MHz, $CDCl_3$), δ, ppm (*J*, Hz): 0.87-0.95 (m, 12H, CH_3, both isomers), 1.21 (t, *J* = 6.9 Hz, 3H, CH_2CH_3, one isomer), 1.22 (t, *J* = 7.2 Hz, 3H, CH_2CH_3, other isomer), 2.11-2.24 (m, 2H, $CH(CH_3)_2$, both isomers) 2.65 (s, 3H, CH_3S, one isomer), 2.76 (s, 3H, CH_3S, other isomer), 3.21 (d, *J* = 14.7 Hz, 1H, CH_2, other isomer), 3.32 (d, *J* = 13.8 Hz, 1H, CH_2, one isomer), 3.70 (d, *J* = 14.1 Hz, 1H, CH_2, one isomer), 3.72 (d, *J* = 14.4 Hz, 1H, CH_2, other isomer), 4.09-4.20 (m, 4H, CH_2CH_3, both isomers), 4.38 (dd, *J* = 4.5, 8.4 Hz, 1H, CH, other isomer), 4.47 (dd, *J* = 5.1, 8.4 Hz, 1H, CH, one isomer), 7.23 (d, *J* = 7.5 Hz, 1H, NH, one isomer), 7.63 (d, *J* = 7.2 Hz, 1H, NH, other isomer);^{13}C NMR spectrum (75 MHz, $CDCl_3$), δ, ppm (for both isomers): 14.1, 17.6, 17.7, 19.1, 24.8, 25.5, 30.2, 30.8, 33.8, 36.8, 37.6, 49.1, 54.0, 55.5, 57.8, 57.8, 61.2, 61.3, 163.6, 164.7, 171.2, 171.4; Elemental analysis: found (%): C, 47.72; H, 7.56; N, 5.56. $C_{10}H_{19}NO_4S$ calculated (%): C, 48.17; H, 7.68; N, 5.62.

3-Methyl-2-[2-(naphthalene-2-sulfinyl)-acetylamino]butyric acid ethyl ester (4h and 5h): Viscous oil; Yield 76%; FT-IR ($CHCl_3$) ν: 1048, 1069 (S=O), 1668 (C=O), 1735 (C=O) cm^{-1}; ^1H NMR spectrum (300 MHz, $CDCl_3$), δ, ppm (*J*, Hz): 0.69 (d, *J* = 6.6 Hz, 3H, CH_3, one isomer), 0.78 (d, *J* = 6.9 Hz, 3H, CH_3, other isomer), 0.910 (t, *J* = 6.9 Hz, 3H, CH_2CH_3, one isomer), 0.913 (t, *J* = 7.2 Hz, 3H, CH_2CH_3, other isomer), 1.12-1.23 (m, 6H, CH_3, both isomers), 1.91-2.02 (m, 1H, $CH(CH_3)_2$, one isomer), 2.06-2.14 (m, 1H, $CH(CH_3)_2$, other isomer), 3.51 (d, *J* = 14.1 Hz, 1H, CH_2, other isomer), 3.60 (d, *J* = 14.1 Hz, 1H, CH_2, one isomer), 3.70 (d, *J* = 14.1 Hz, 1H, CH_2, other isomer), 3.79 (d, *J* = 14.1 Hz, 1H, CH_2, one isomer), 3.97-4.16 (m, 4H, CH_2CH_3, both isomers), 4.26 (dd, *J* = 4.5, 8.5 Hz, 1H, CH, one isomer), 4.37 (dd, *J* = 5.1, 8.7 Hz, 1H, CH, other isomer), 7.27 (d, *J* = 8.1 Hz, 1H, NH, one isomer), 7.39 (d, *J* = 8.7 Hz, 1H, NH, other isomer), 7.47-8.21 (m, 14H, ArH, both isomers);^{13}C NMR spectrum (75 MHz, $CDCl_3$), δ, ppm (for both isomers): 14.2, 14.3, 17.8, 17.9,

18.8, 19.1, 30.9, 31.3, 57.4, 57.7, 58.3, 59.1, 61.0, 61.1, 119.7, 125.2, 125.3, 127.3, 127.4, 128.0, 128.1, 128.5, 128.7, 129.6, 132.9, 134.6, 134.7, 139.0, 163.4, 163.6, 170.9; Elemental analysis: found (%): C, 62.74; H, 6.29; N, 3.81. $C_{19}H_{23}NO_4S$ calculated (%): C, 63.13; H, 6.41; N, 3.88.

RESULTS AND DISCUSSION

Starting substrates i.e. differently substituted ethanoic acids **1a-d** were synthesized using reported methodology [26]. Initially, diversely substituted chiral amides **3a-h** were prepared by condensation reaction between benzyl/phenyl/methyl/naphthylthioethanoic acids **1a-d** and chiral amino esters **2a-b** (L-phenylalanine ethyl ester, L-valine ethyl ester) in the presence of *N*,*N*-dicyclohexylcarbodiimide (DCC) as condensing agent and 4-(dimethylamino)pyridine (DMAP) as catalyst in dry methylene chloride at room temperature, under nitrogen atmosphere (Scheme 1) [27].



Scheme 1. Synthesis of chiral amides 3a-h.

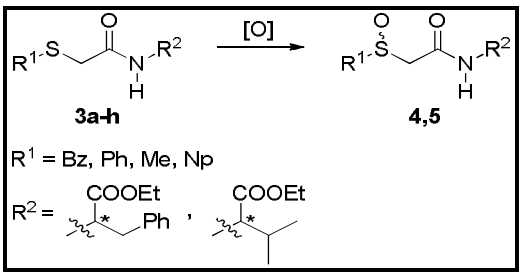
The crude amides **3a-h** were purified using silica gel column chromatography followed by structural elucidation on the basis of various spectroscopic studies such as FT-IR, NMR (^{1}H, ^{13}C) and CHN elemental analysis. The results are summarized in table 1.

Table 1. Chiral amides 3a-h

Entry	Chiral amine	R^1	Chiral amide 3	Yield[a] %
1	L-Phenylalanine ethyl ester	Bz	**3a**	57
2	L-Phenylalanine ethyl ester	Ph	**3b**	69
3	L-Phenylalanine ethyl ester	Me	**3c**	65
4	L-Phenylalanine ethyl ester	Naphthyl	**3d**	71
5	L-Valine ethyl ester	Bz	**3e**	55
6	L-Valine ethyl ester	Ph	**3f**	59
7	L-Valine ethyl ester	Me	**3g**	61
8	L-Valine ethyl ester	Naphthyl	**3h**	56

[a] Isolated yields after chromatographic purification.

In the next step, chiral amides **3a-h** was transformed into diversely substituted chiral sulfoxide amides **4-5a-h**. For this purpose, chiral amide **3a** was initially oxidized with 30% hydrogen peroxide (H_2O_2) using CH_3COOH as solvent medium (Scheme 2). After completion, crude product was purified by silica gel column chromatography using 10% EtOAc/hexane as eluant. The product was



Scheme 2. Synthesis of chiral sulfoxide amides 4-5.

obtained as non-separable diastereomeric mixture and identified as chiral sulfoxide amides **4a** and **5a** on the basis of FT-IR, ^{1}H NMR, ^{13}C NMR and CHN elemental analysis (Table 2, entry 1).

Table 2. Oxidation of chiral amides

Entry	Chiral amide 3	Reagent Time (4+5, Yield[a])			
		30% H_2O_2 in CH_3COOH	30% H_2O_2/ ClCOOEt in CH_2Cl_2	$NaIO_4$ in CH_3OH:H_2O	*m*-CPBA in CH_2Cl_2
1	**3a**	8 h (85%)	45 h (52%)	48 h (94%)	10 min. (80%)
2	**3b**	3 h (80%)	0.5 h (67%)	23 h (75%)	20 min. (76%)
3	**3c**	1 h 20 min (68%)	4 h (78%)	45 h (90%)	10 min. (91%)
4	**3d**	–	–	–	10 min. (93%)
5	**3e**	–	–	–	90 min. (92%)
6	**3f**	–	–	–	90 min. (95%)
7	**3g**	–	–	–	10 min. (68%)
8	**3h**	–	–	–	10 min. (76%)

[b] Isolated yields of chiral sulfoxide amides after chromatographic purification.

The diastereomeric ratio (*dr*) of chiral sulfoxide amides **4a** and **5a** was found to be 1:1 as evident from C*H* signal of both the isomer in ^{1}H NMR. In order to improve reaction yields, time and diastereoselectivity, chiral amides **3a-c** were also oxidized with other reagents such as H_2O_2/ClCOOEt in CH_2Cl_2, H_2O_2 in C_5H_5N, $NaIO_4$ in MeOH:H_2O, *m*-CPBA in CH_2Cl_2 (Table 2, entries 1-3). It was found in the results that excellent yields were obtained when oxidation was carried out with either $NaIO_4$ (up to 94%) or *m*-CPBA (up to 95%). Further, in case of *m*-CPBA, the reaction time was significantly reduced (up to 10 min.). However, no significant improvement in diastereoselectivity was observed. The reaction was found to be general in all these cases. Finally, chiral amides **3d-h** were oxidized with *m*-CPBA and results are summarized in table 2 (entries 4-8). The mechanism of sulfide oxidation is well established and fast oxidation in case of *m*-CPBA might be attributed to the involvement of highly polar transition state [**28, 29**].

APPLICATION

The chiral sulfoxide amides **4-5** can be transformed into wide range of synthetically important chiral molecules such as esters, cyclic amides and fused heterocycles (Figure 2). In this regard, considerable efforts are being pursued in our laboratory.

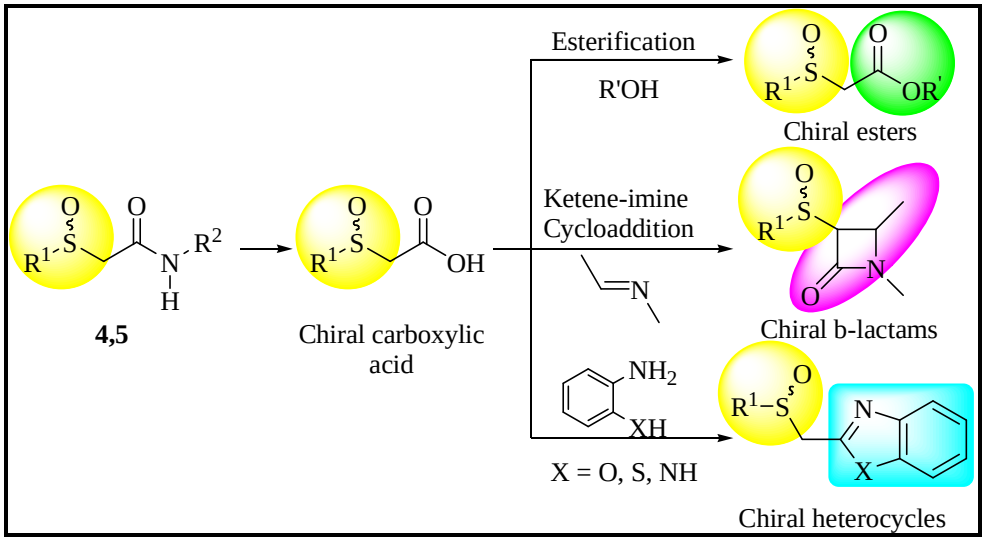


Figure 2. Synthetic utility of chiral sulfoxide amides.

CONCLUSION

In conclusion, a simple, fast and efficient strategy has been successfully developed for the synthesis of novel chiral sulfoxide amides using amino ester based chiral auxiliaries. Moreover, attempts are being pursued towards improving diastereoselectivity and separation of isomers. In addition to this, a detailed report elaborating synthetic utility of these synthons and their biological screening will be published in near future.

ACKNOWLEDGEMENTS

Reshma acknowledges the financial support from Council of Scientific and Industrial Research, (CSIR), New Delhi. AB gratefully acknowledges the financial support for this work from Department of Science and Technology (DST), New Delhi, Government of India. Project No. SR/FT/CS-037/2010 dated 28-10-2010. JB acknowledge the financial support from University Grants Commission (UGC) vide sanction No. F.17-7(J)/2004 (SA-I) dated 03-10-2011.

REFERENCES

[1] A. Moyano, R. Rios, Asymmetric Organocatalytic Cyclization and Cycloaddition Reactions, *Chem. Rev*., **2011**,111, 4703-4832.
[2] K. C. Nicolaou, C. R. H. Hale, C.Nilewski, H. A.Ioannidou, Constructing Molecular Complexity and Diversity: Total Synthesis of Natural Products of Biological and Medicinal Importance, *Chem. Soc. Rev*., **2012**, 41, 5185–5238.
[3] G. Solladié, In *Comprehensive Organic Synthesis*; B. M. Trost, I. Fleming, Eds.; Pergamon: Oxford, **1991**; Vol. 6, pp 148.
[4] N. Khiar, I. Fernández, A. Alcudia, F. Alcudia, In *Advances in Sulfur Chemistry 2;*C. M. Rayner, Ed.; JAI Press Inc.; Stamford, CT, **2000**; Chapter 3, pp 57.
[5] B. M. Trost, M. Rao, Development of Chiral Sulfoxide Ligands for Asymmetric Catalysis, *Angew. Chem. Int. Ed*., **2015**, 54, 5026–5043.
[6] P. Bravo, G. Resnati, F.Viani, Synthesis of Optically Pure α-Methylene-γ-lactones from (+)-R-(4-Methylphenyl)-alkylsulphoxides, *Tetrahedron Lett*., **1985**, 26, 2913–2916.
[7] G. Solladié, Asymmetric Synthesis Using Nucleophilic Reagents Containing a Chiral Sulfoxide Group, *Synthesis*, **1981**, 185–196.
[8] G. Solladié, R. Zimmerman, R. Bartsch, H. M.Walborsky, Chiral Sulfoxides in Asymmetric Synthesis: A New Chiral Synthesis of Optically Active 4-Substituted Cyclohexylideneacetic Acid Esters, *Synthesis*, **1985**, 662–665.
[9] F. M. Hauser, S. R. Ellenberger, J. C. Clardy, L. S. Bass, Sulfoxide-mediated Intramolecular Hydroxylation of a Remote Olefin in an Acyclic System, *J. Am. Chem. Soc*., **1984**, 106, 2458–2459.
[10] N. Farrell, D. M. Kiley, W. Schmidt, M. P. Hacker, Chemical Properties and Antitumor Activity of Complexes of Platinum Containing Substituted Sulfoxides [PtCl(R'R"SO)(diamine)]NO_3. Chirality and Leaving-group Ability of Sulfoxide Affecting Biological Activity, *Inorg. Chem.*, **1990**, 29, 397-403.
[11] S. Thitiphuree, N. Talley, Esomeprazole, A New Proton Pump Inhibitor: Pharmacological Characteristics and Clinical Efficacy, *Int. J. Clin. Pract*., **2000**, 54, 537–541.
[12] M. P. Ortega, M. D. C. Garcia, M. A. Gijon, M. F. D. Casa-Juana, J. G.Priego, M. S. Crespo, C.Sunkel, 1,4-Dihydropyridines, A New Class of Platelet-Activating Factor Receptor Antagonists: In vitro Pharmacologic Studies, *J. Pharmacol. Exp. Ther*., **1990**, 255, 28–33.
[13] R. Kubec, M.Svobodova, J.Velisek, Distribution of *S*-Alk(en)ylcysteine Sulfoxides in Some *Allium* Species. Identification of a New Flavor Precursor: *S*-Ethylcysteine Sulfoxide (Ethiin), *J. Agric. Food. Chem.*, **2000**, 48, 428–433.

[14] G. Khan, S. Sreenivasa, G. Shivaraja, V. Chandramohan, Synthesis, Biological Evaluation and Docking Studies of Sulfonyl Piperazine Derivatives: Part-A, *J. Applicable Chem.*, **2019**, 8, 586–597.
[15] S. Kumar A, J. Kudwa, Synthesis, Characterization and Antimicrobial Activity Studies of Bis-SulfonamideDerivatives, *J. Applicable Chem.*, **2018**, 7, 1575-1581.
[16] A. Faraz, S. C. Ameta, Y. H. Talia, Synthesis and Antimicrobial Evaluation of Some Novel Sulfonamide Derivatives Containing Oxazole Moiety, *J. Applicable Chem.*, **2018**, 7, 1275-1284.
[17] C. S. Ananda Kumar, B. Veeresh, K. C. Ramesha, C. S. Ashok Raj, K. M. Mahadevaiah, S. B. Benaka Prasad, S. Naveen, M. Madaiah, K. S. Rangappa, Antidiabetic Studies of 1-Benzhydryl-piperazine Sulfonamide and Carboxamide Derivatives, *J. Applicable Chem.*, **2017**, 6, 232–240.
[18] S. Sreenivasa, G. Shivaraja, V. Chandramohan, S. N. Shwetha, Aliyaarif, K. S. Guruprasad, Synthesis, Characterization, Antibacterial and Docking Studies of SulfonamideDerivatives, *J. Applicable Chem.*, **2016**, 5, 1089-1096.
[19] M. R. Nadigar, S. Sreenivasa, K. E. Manojkumar, T. M. C. Rao, Synthesis and In-vitro Antibacterial Activity of Some Novel Sulfonamide Derivatives bearing 1,4-Disubstituted-1,2,4-oxadiazole Moiety, *J. Applicable Chem.*, **2013**, 2, 722–729.
[20] A. Bhalla, S. S. Bari, J. Bhalla, Synthesis of Novel Pyrazolylmethylene-Pyrimidine Heterocycles: Potential Synthons for Hybrid B-Lactams, *Can. Chem. Trans.*, **2015**, 3, 72–84 and references cited therein.
[21] J. Bhalla, S. S. Bari, A. Bhalla, Facile Synthesis of Novel Benzothiazolylpyrazolyl anchored 3-Thio/seleno/chloro-β-lactams: Synthetic Intermediates for Novel 3-Sulfenyl/sulfonyl, C-3 Functionalized Monocyclic and Spirocyclic β-Lactams, *Synth. Commun.*, **2018**, 48, 2675–2682.
[22] A. Bhalla, S. S. Bari, J. Bhalla, S. Khullar, S. Mandal, Facile Synthesis of Novel Halogenated 4-Pyrazolylspirocyclic-β-lactams: Versatile Heterocyclic Synthons, *Tetrahedron Lett.*, **2016**, 57, 2822–2828 and references cited therein.
[23] S. S. Bari, A. Bhalla, Reshma,G. Hundal, Facile Synthesis of Novel Bicyclic β-Lactams: Analogues of C-fused Penicillin Type Ring Systems, *Tetrahedron Lett.*, **2013**, 54, 483–486.
[24] A. Bhalla, S. S. Bari, J. Bhalla, K. Sharma, D. Narula, One Pot, Simple, and Efficient Synthesis of (*E*)- and (*Z*)-3-Allylidene-β-lactams from 3-Allyl-3-phenylseleno-β-lactams: Analogues of β-Lactamase Inhibitors, *Tetrahedron Lett.*, **2016**, 57, 4763–4766.
[25] A. Kumari, S. S. Bari, G. Modi, S. Berry, S. Khullar, S. Mandal, A. Bhalla, Comprehensive Study Towards the Desulfonylation/desulfinylation of *cis*-3-Functionalized 3-Phenylsulfonyl/ sulfinyl-β-lactams to Access Novel *cis*-3-Monosubstituted-β-lactams, *Tetrahedron*, **2018**, 74, 4400-4408.
[26] W. J. Kenney, J. A. Walsh, Davenport, D. A. An Acid-catalyzed Cleavage of Sulfoxides, *J. Am. Chem. Soc.*, **1961**, 83, 4019-4022.
[27] J. C. Sheehan, G. P. Hess, A New Method of Forming Peptide Bonds, *J. Am. Chem. Soc.*, **1955**, 77, 1067-1068.
[28] C. G. Overberger, R. W. Cummins, Mechanism of the Oxidation of *p,p*'-DichlorobenzylSulfide by Peroxybenzoic and *para* substituted Peroxybenzoic acids, *J. Am. Chem. Soc.*,**1953**, 75, 4250-4254.
[29] M. Madesclaire, Synthesis of Sulfoxides by Oxidation of Thioethers, *Tetrahedron*, **1986**, 42, 5459–5495.