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ARTICLE

Construction of Thiazines and Oxathianes via [3+3] Annulation of *N*-Tosylaziridinedicarboxylates and Oxiranes with 1,4-dithiane-2,5-diol: Application Towards the Synthesis of Bioactive Molecules

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Lewis acid catalyzed [3+3] annulation of *N*-tosylaziridinedicarboxylates and oxiranes with in situ generated mercaptoaldehyde for the synthesis of functionalized thiazine and oxathiane derivatives has been developed. Additionally, this method facilitate the derivatization of thiazine by detosylation and Krapcho monodecarboxylation.

Introduction,

There are numerous bioactive molecules whose skeleton include six membered ring containing two heteroatoms.[1] Out of these heteroatom containing six-membered rings, thiazines and oxathianes are of particular importance, as these scaffolds are core structural motifs of many natural products and bioactive heterocycles. 1,3-Thiazine derivatives possess various biological activities *viz.* cholecystokinin antagonist, antimycobacterial, antimalarial, antifungal and antithyroid activity.[2] On the other hand, oxathiane derivative constitutes the cyclic core structure of MIF (macrophage migration inhibitory factor) inhibitor.[3]

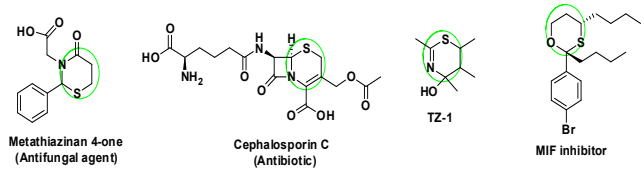
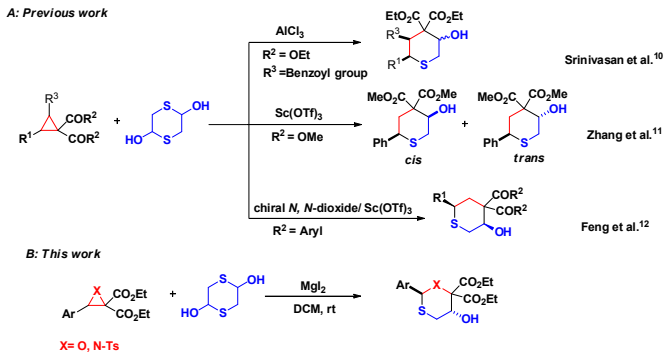


Fig. 1 Biologically active compounds containing thiazine, oxathiane and their derivative

In addition, 1,3-thiazines are being transformed into useful structures which are important constituents of biologically active compounds. These structure constitute the cyclic core structure of antibiotic cephalosporin C and TZ-1. TZ-1 exhibits antimycobacterial and antitubular activity.[4] Consequently, efficient construction of these scaffolds has received significant attention. In this context, we envisioned exploring the one step synthesis of thiazine and oxathiane from aziridine and oxiranes with 1,4-dithiane 2,5-diol.

Aziridines are multifaceted synthetic intermediate for the synthesis of nitrogen containing biologically active compounds. The chemistry of aziridine plays an important role due to its high reactivity of the C-N bond for nucleophilic opening of the heterocyclic ring.[5] The selective C-C heterolysis of aziridine has been less explored due to its relative high energy barrier.[6] In presence of Lewis acid, *N*-tosylarylaziridinyl dicarboxylate favor the C-C bond cleavage, which can undergo formal cycloaddition reactions with various dipolarophiles.[7] Similarly, the donor acceptor oxiranes (D-A Oxirane) has also emerged as versatile tool for the synthesis of numerous biologically active compounds for contemporary interest. The chemistry of oxiranes favors the C-O bond cleavage, but for the C-C bond cleavage harsh conditions are required. Herein, we report Lewis acid catalyzed chemoselective C-C bond cleavage of oxiranes, which are entrapped by dipolarophiles bearing C-X (X = O and C) multiple bonds.[8]

1,4-Dithiane 2,5-diol has been employed an efficient substrate for the synthesis of thiazine and oxathine via catalytic [3+3]



Scheme 1 Annulation of strained ring with 1,4-dithiane 2,5-diol

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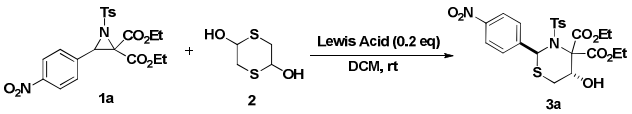
annulation. There are numerous reports in the literature for the synthesis of thiazines and oxathines, but synthesis employing [3+3] cycloaddition of heteroatom containing strained ring is not yet reported in literature.[9]

Srinivasan and coworkers reported one pot synthesis of tetrasubstitutedthiophene via [3+3] annulation of *trans*-2-aroyl-3-arylcyclopropane-1,1-dicarboxylates and mercaptoaldehyde in presence of catalytic amount of $AlCl_3$.[10] Zhang *et.al* in their seminal work, reported $Sc(OTf)_3$ catalyzed [3+3] annulation of cyclopropane 1,1-diester with mercatoaldehyde (Scheme 1B).[11] Feng *et.al* report a highly diastereo- and enatioselective [3+3] annulation of cyclopropyl ketone with mercaptoaldehyde catalyzed by a chiral *N,N'*-dioxide/scandium(III) complex.[12] Recently, our group explored the possibility of cycloaddition reaction of strained ring with other 2π component and another strained ring in presence of MgI_2.[13] Encouraged by these results, we became interested in assessing the reactivity of *N*-tosylaziridinedicarboxylate and oxirane with 1,4-dithiane 2,5-diol (Scheme 1)

Results and discussion,

We initiated the present investigation with donor-acceptor aziridines (D-A aziridines) **1a** (1 equiv.) and 1,4-dithiane 2,5-diol **2** to afford substituted thiazine. In order to optimize the reaction between **1a** and **2** to give **3a**, various Lewis acid were examined, MgI_2 was found to be most effective (Table 1). When 10 mol% MgI_2 was used the yield of the reaction was 70%. Gratifyingly, we got the desired product in 86% yield by increasing the MgI_2 loading up to 20 mol% (Table 1, entry 2).

Table 1 Optimization of reaction condition between 1a and 2a[a]

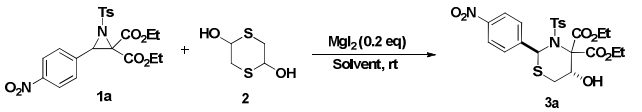


Entry	Lewis acid	LA [mol%]	*T*[°C]	Solvent	Isolated Yield[b] [%]
1	MgI_2	10	25	DCM	70
2	MgI_2	20	25	DCM	86
3	MgI_2	40	25	DCM	74
4	$MgBr_2$	20	80	DCE	80
5	$InCl_3$	20	25	DCM	60
6	$Sn(OTf)_2$	20	25	DCM	15
7	$Yb(OTf)_3$	20	25	DCM	18
8	$Zn(OTf)_2$	20	25	DCM	n.r.[c]
9	$FeCl_2$	20	25	DCM	n.r.[c]
10	AgOTf	20	25	DCM	12
11	$Mg(OTf)_2$	20	25	DCM	24
12	$MgCl_2$	20	25	DCM	14
13	$Cu(OTf)_2$	20	25	DCM	n.r.[c]
14	InI_3	20	25	DCM	76

[a]Reaction was carried out in inert atmosphere **1a** (0.21 mmol, 1 equiv), **2** (0.21 mmol, 1 equiv), Lewis Acid (0.04 mmol, 0.2 equiv) and DCM, [b]Isolated yield after flash column chromatography, [c]n.r = no reaction.

No further improvement in yield was achieved with higher increment of MgI_2 (40 mol%). The use of $MgBr_2$ gave excellent yield of **3a** at 80 °C. Indium containing Lewis Acid, $InCl_3$ and InI_3 gave desired product in moderate to excellent yield respectively (Table 1 entry 5 and 14). Other commercial available Lewis acids, such as $Zn(OTf)_2$, $FeCl_2$, $Cu(OTf)_2$ failed to catalyze the titled transformation (Table 1, entry 8-9 and 13). In case of $Sn(OTf)_2$,$Yb(OTf)_3$, AgOTf, $Mg(OTf)_2$ and $MgCl_2$, trace amount of **3a** was observed (Table 1, entry 6-7 and 10-12).

Table 2 Effect of solvent[a]



Entry	MgI_2 [mol%]	Solvent	Time	Isolated Yield[c] [%]
1	20	DCM[b]	20 min.	86
2	20	DCE[b]	1h	82
3	20	$CHCl_3$	8h	76
4	20	THF[b]	1h	c.m.[d]
5	20	CH_3CN	1h 30 min	c.m.[d]
6	20	Toluene	12h	46

[a]Reaction was carried out in inert atmosphere **1a** (0.21 mmol, 1 equiv), **2** (0.21 mmol, 1 equiv), Lewis Acid (0.043 mmol, 0.2 equiv) and [b]DCM= Dichloromethane. DCE= dichloroethane. THF= tetrahydrofuran. [c]Isolated yield after flash column chromatography, [d]c.m. = complex mixture.

A brief screening of solvents revealed that chlorinated solvents like DCM, chloroform and DCE gave good to excellent yield of desired product **3a** (Table 2 entry 1,2 and 3). In case of CH_3CN and THF, the annulated product was not detected. (Table 2, entry 4 and 5). However, when toluene was chosen as reaction medium, moderate yield of the product was observed after 12h.

With the optimized reaction condition, the scope of the transformation assessed with various D-A Aziridines and 1,4-dithiane 2,5-diol. To our delight, D-A aziridines bearing electron withdrawing substituents gave excellent yield of the desired product in short time (Table 3, **3a**-**3d**). *p*-Bromophenyl substituted D-A aziridine shows higher yield of annulated product **3e** (78%) than *o*-bromophenyl substituted cycloadduct **3f** (74%). It may be due to the steric hindrance of *o*-bromo group. Less activated phenyl and napthyl substituted aziridines also produces substituted thiazine in good yield (Table 3 entry **3g** and **3h**). As expected, we obtained the desired products with *p*-methyl and *p*-isopropyl phenyl substituted D-A aziridines in good yield (Table 3 entry **3i** and **3j**). The aziridines substituted with strong electron-donating groups, such as methoxy, hydroxyl and dimethylamino leads to highly unstable substrates which could not be used for further the formation of cycloadduct. On the other hand, alkyl substituents, like cyclohexyl and isopropyl bearing aziridines gave complex mixture. Different ester group containing aziridines (**1k** and **1l**)

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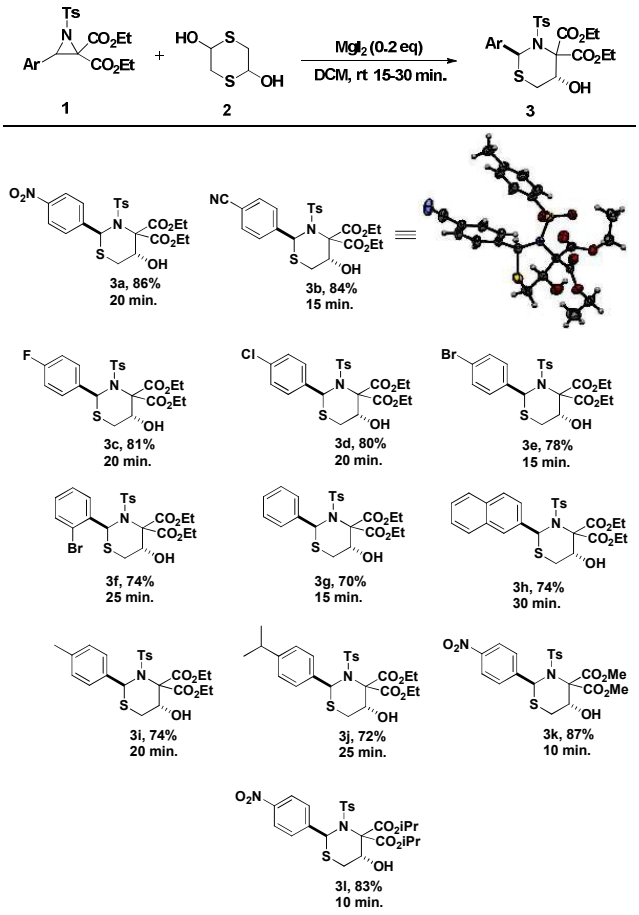
Table 3 Scope of the methodology[a]

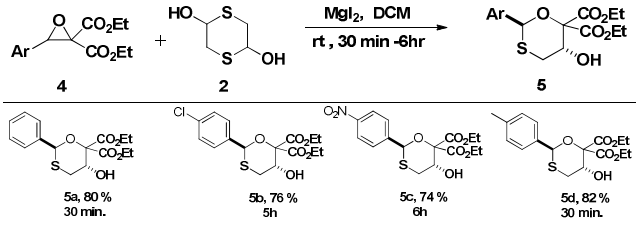


[a]Unless otherwise specified all reaction were carried out in DCM at rt with 1 equiv of **1** and 1 equiv of **2** in presence of Lewis acid (20 mol%).

Were used to check the effect of the size of the ester group in the transformation, annulated product was formed in excellent yield in all the cases (Table 3, entry **3k** and **3l**). Structure of **3b** was confirmed by single crystal X-ray analysis (see also the supporting information).[14]

To test the reactivity of different D-A oxiranes with 1,4-dithiane 2,5-diol, we carried out Lewis acid (MgI_2) catalyzed

Table 4 Scope of annulation reaction between 4 and 2[a]



[a]Unless otherwise specified all reaction were carried out in DCM at rt with 1 equiv of **4** and 1 equiv of **2** in presence of lewis acid (20 mol%).

reaction at room temperature using DCM as solvent (Table 4). Usually electron releasing D-A oxiranes performed better than electron withdrawing aryl substituted oxirane (Table 4, entry **5b**, **5c** and **5d**) which can be attributed to the destabilization of developed positive charge on adjacent C-atom of the dipole by electron deficient aryl moiety during the course of the reaction. In addition, phenyl substituted oxirane gave desired product in excellent yield of 80% (Table 4, entry **5a**). The geometry of **5a** was determined by using NOESY studies.

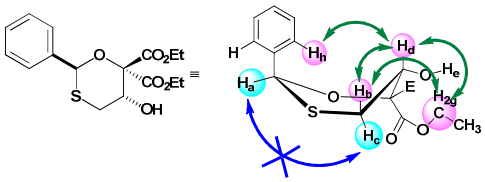
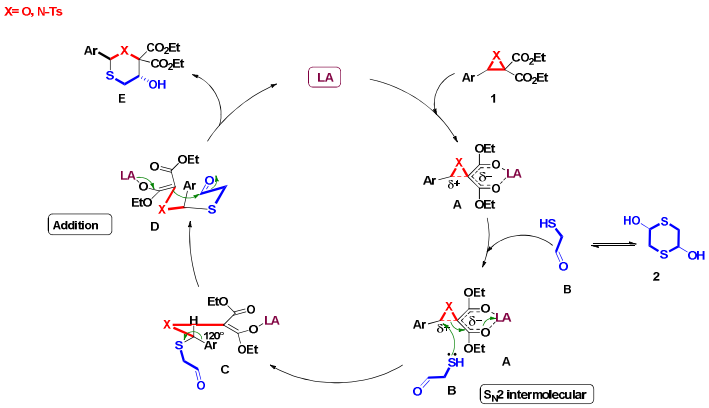


Fig. 2 NOESY correlation of compound **5a**

The plausible mechanism for both cycloaddition reactions is outlined in scheme 2. Initially Lewis acid coordinated with malonyl ester of strained ring **1**, which result in C-C bond cleavage to form complex **A**. The mercaptoaldehyde **B** which in



Scheme 2 Plausible mechanism

situ generated from **2** attack on aryl substituted C-atom of **A** in S_N2 fashion to give **C** which undergoes 120° rotation to bring the malonate anion closer to the aldehyde group to form intermediate **D**. The malonyl ester anion undergo nucleophilic addition on aldehyde group to give the cycloadduct **E**.

To check the potential of substituted thiazine **3a** for further synthetic application, we performed the detosylation reaction. In the presence of NaH at room temperature **3a** easily gave substituted imine **6** in excellent yield (80%). Moreover, the hydroxyl group of **3a** could be protected to give compound **7** in quantitative yield. Krapcho monodecarboxylation accompanied by elimination of the acetoxy group gave the monoester **8**. These structure is a scaffold of biologically active natural product and drug (Scheme 3).

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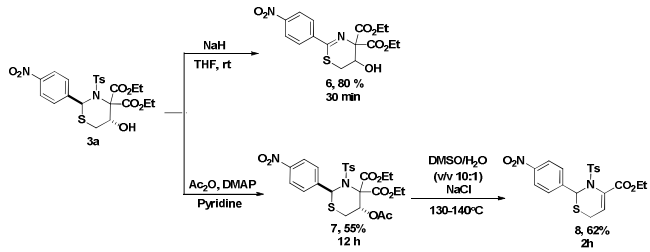

Scheme 3 Synthetic transformation of cycloadduct

Experimental

General information

All reactions were carried out under inert atmosphere using oven dried glassware. All solvents and reagents were obtained from commercial sources and were purified using standard procedure prior to use. The developed chromatogram was analyzed by UV lamp (254 nm), or *p*-anisaldehyde solution. Products were purified by flash chromatography on silica gel (mesh size 230-400). The ^{1}H and ^{13}C-NMR spectra were recorded in $CDCl_3$. Chemical shifts of ^{1}H and ^{13}C-NMR spectra are expressed in parts per million (ppm). All coupling constants are given in absolute values and are expressed in Hz. The description of the signals include: s = singlet, d = doublet, dd = doublet of doublet, t = triplet, dt = doublet of triplet, q = quartet, pent = pentet, br = broad and m = multiplet.

General procedure for synthesis of N-tosyl aziridine-2,2-dicarboxylate):

Aziridines were prepared according to the literature.[15]

Diethyl 3-(4-nitrophenyl)-1-tosylaziridine-2,2-dicarboxylate (1a):

4-methyl-*N*-(4-nitrobenzylidene)benzenesulfonamide (0.50 g, 1.64 mmol), 2-bromomalonate (0.43 g, 1.80 mmol), NaH (0.04 g, 1.80 mmol), dry CH_3CN (16 mL), Reaction time = 17 min., **1a** (0.63 g, Yield: 84%), Colorless oil. ^{1}H NMR (400 MHz): δ 8.14 (d, *J* = 7.6 Hz, 2H), 7.95 (d, *J* = 7.6 Hz, 2H), 7.45 (d, *J* = 7.6 Hz, 2H), 7.38 (d, *J* = 7.6 Hz, 2H), 4.92 (s, 1H), 4.35-4.47 (m, 2H), 3.90-4.04 (m, 2H), 2.47 (s, 3H), 1.38 (t, *J* = 6.6 Hz, 3H), 0.95 (t, *J* = 6.6 Hz, 3H).

Diethyl 3-(4-cyanophenyl)-1-tosylaziridine-2,2-dicarboxylate (1b):

N-(4-cyanobenzylidene)-4-methylbenzenesulfonamide (0.50 g, 1.75 mmol), 2-bromomalonate (0.57 g, 1.93 mmol), NaH (0.04 g, 1.93 mmol), dry CH_3CN (16 mL), Reaction time = 14 min., **1b** (0.70 g, Yield: 90%), Colorless oil. ^{1}H NMR (400 MHz): 7.94 (d, *J* = 8.0 Hz, 2 H), 7.58 (d, *J* = 8.0 Hz, 2 H), 7.31-7.41 (m, 4 H), 4.89 (s, 1 H), 4.34-4.45 (m, 2 H), 3.90-3.99 (m, 2H), 2.46 (s, 3 H), 1.37 (t, *J* = 7.0 Hz, 3 H), 0.92 (t, *J* = 7.0 Hz, 3 H).

Diethyl 3-(4-fluorophenyl)-1-tosylaziridine-2,2-dicarboxylate (1c):

N-(4-fluorobenzylidene)-4-methylbenzenesulfonamide (0.50 g, 1.83 mmol), 2-bromomalonate (0.59 g, 1.98 mmol), NaH (0.04 g, 1.98 mmol), dry CH_3CN (16 mL), Reaction time = 10 min., **1c** (0.67 g, Yield: 86%), Colorless oil. ^{1}H NMR (400 MHz): δ 7.95 (d, *J* = 8.4 Hz, 2 H), 7.36 (d, *J* = 8.4 Hz, 2 H), 7.21-7.28 (m, 2 H), 6.91-6.99 (m, 2 H), 4.85 (s, 1 H), 4.35-4.43 (m, 2H), 3.98 (q, *J* = 7.2 Hz, 2 H), 2.45 (s, 3 H), 1.37 (t, *J* = 7.2 Hz, 3 H), 0.93 (t, *J* = 7.20 Hz, 3H).

Diethyl 3-(4-chlorophenyl)-1-tosylaziridine-2,2-dicarboxylate (1d):

N-(4-chlorobenzylidene)-4-methylbenzenesulfonamide (0.50 g, 1.70 mmol), 2-bromomalonate (0.44 g, 1.87 mmol), NaH (0.04 g, 1.87 mmol), dry CH_3CN (17 mL), Reaction time = 15 min., **1d** (0.62 g, Yield: 80%), Colorless oil. ^{1}H NMR (400 MHz): δ 7.94 (d, *J* = 8.0 Hz, 2H), 7.36 (d, *J* = 8.0 Hz, 2H), 7.24 (d, *J* = 8.4 Hz, 2H), 7.19 (d, *J* = 8.4 Hz, 2H), 4.83 (s, 1H), 4.32-4.42 (m, 2H), 3.94-4.11 (m, 2H), 2.45 (s, 3H), 1.37 (t, *J* = 7.0 Hz, 3H), 0.95 (t, *J* = 7.2 Hz, 3H).

Diethyl 3-(4-bromophenyl)-1-tosylaziridine-2,2-dicarboxylate (1e):

N-(4-bromobenzylidene)-4-methylbenzenesulfonamide (0.50 g, 1.47 mmol), 2-bromomalonate (0.48 g, 1.62 mmol), NaH (0.03 g, 1.62 mmol), dry CH_3CN (16 mL), Reaction time = 12 min., **1e** (0.64 g, Yield: 88%), Colorless oil. ^{1}H NMR (400 MHz): δ 7.94 (d, *J* = 8.4 Hz, 2 H), 7.39 (d, *J* = 8.4 Hz, 2 H), 7.36 (d, *J* = 8.0 Hz, 2 H), 7.13 (d, *J* = 8.0 Hz, 2 H), 4.82 (s, 1 H), 4.30-4.50 (m, 2 H), 3.90-4.01 (m, 2 H), 2.45 (s, 3 H), 1.37 (t, *J* = 7.2 Hz, 3 H), 0.95 (t, *J* = 7.2 Hz, 3 H).

Diethyl 3-(2-bromophenyl)-1-tosylaziridine-2,2-dicarboxylate (1f):

N-(2-bromobenzylidene)-4-methylbenzenesulfonamide (0.50 g, 1.47 mmol), 2-bromomalonate (0.48 g, 1.62 mmol), NaH (0.03 g, 1.62 mmol), dry CH_3CN (16 mL), Reaction time = 17 min., **1f** (0.63 g, Yield: 87%), Colourless oil. ^{1}H NMR (400 MHz): δ 7.98 (d, *J* = 8.0 Hz, 2 H), 7.50-7.53 (m, 1 H), 7.38 (d, *J* = 8.0 Hz, 2 H), 7.13-7.19 (m, 2 H), 7.06-7.11 (m, 1 H), 5.01 (s, 1 H), 4.41 (q, *J* = 6.8 Hz, 2 H), 3.86-3.98 (m, 2 H), 2.46 (s, 3 H), 1.38 (t, *J* = 7.2 Hz, 3 H), 0.86 (t, *J* = 7.2 Hz, 3 H).

Diethyl 3-phenyl-1-tosylaziridine-2,2-dicarboxylate (1g):

N-benzylidene-4-methylbenzenesulfonamide (0.50 g, 1.92 mmol), 2-bromomalonate (0.50 g, 2.11 mmol), NaH (0.05 g, 2.11 mmol), dry CH_3CN (19 mL), Reaction time = 12 min., **1g** (0.67 g, Yield: 83%), Colorless oil. ^{1}H NMR (400 MHz): δ 7.96 (d, *J* = 7.6 Hz, 2H), 7.34 (d, *J* = 7.6 Hz, 2H), 7.20-7.27 (m, 5H), 4.89 (s, 1H), 4.36-4.42 (m, 2H), 3.86-4.00 (m, 2H), 2.43 (s, 3H), 1.36 (t, *J* = 7.0 Hz, 3H), 0.87 (t, *J* = 6.8 Hz, 3H).

Diethyl 3-(naphthalen-1-yl)-1-tosylaziridine-2,2-dicarboxylate (1h):

4-methyl-*N*-(naphthalen-1-ylmethylene)benzenesulfonamide (0.50 g, 1.61 mmol), 2-bromomalonate (0.43 g, 1.77 mmol), NaH (0.04 g, 1.77 mmol), dry CH_3CN (16 mL), Reaction time = 10 min., **1h** (0.61 g, Yield: 82%), Colorless oil. ^{1}H NMR (400 MHz): δ 8.24 (d, *J* = 8.0 Hz, 1H), 8.03 (d, *J* = 8.4 Hz, 2H), 7.83 (d, *J* = 8.0 Hz, 1H), 7.74-7.78 (m, 1H), 7.55-7.60 (m, 1H), 7.48-7.52 (m, 1 H), 7.39 (d, *J* = 8.0 Hz, 2H), 7.28-7.33 (m, 2H), 5.30 (s, 1H),

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4.48 (q, *J* = 7.2 Hz, 2H), 3.70 (q, *J* = 7.2 Hz, 2H), 2.47 (s, 3H), 1.42 (t, *J* = 7.2 Hz, 3H), 0.45 (t, *J* = 7.2 Hz, 3H).

Diethyl 3-(*p*-tolyl)-1-tosylaziridine-2,2-dicarboxylate (1i):

4-methyl-*N*-(4-methylbenzylidene)benzenesulfonamide (0.50 g, 1.82 mmol), 2-bromomalonate (0.47 g, 2.0 mmol), NaH (0.05 mg, 2.0 mmol), dry CH_3CN (18 mL), Reaction time = 10 min., **1i** (0.6 g, Yield: 77%), Colorless oil. ^{1}H NMR (400 MHz): δ 7.95 (d, *J* = 8.0 Hz, 2H), 7.34 (d, *J* = 8.0 Hz, 2H), 7.12 (d, *J* = 8.0 Hz, 2H), 7.05 (d, *J* = 8.0 Hz, 2H), 4.85 (s, 1 H), 4.32-4.44 (m, 2H), 3.97 (q, *J* = 7.0 Hz, 2H), 2.45 (s, 3H), 2.28 (s, 3H), 1.37 (t, *J* = 7.0 Hz, 3H), 0.93 (t, *J* = 7.0 Hz, 3H).

Diethyl 3-(4-isopropylphenyl)-1-tosylaziridine-2,2-dicarboxylate (1j):

N-(4-isopropylbenzylidene)-4-methylbenzenesulfonamide (0.50 g, 1.65 mmol), 2-bromomalonate (0.43 g, 1.81 mmol), NaH (0.04 g, 1.81 mmol), dry CH_3CN (16 mL), Reaction time = 10 min., **1j** (0.6 g, Yield: 79%),Colorless oil, ^{1}H NMR (400 MHz): δ 7.96 (d, *J* = 7.6 Hz, 2H), 7.34 (d, *J* = 7.6 Hz, 2H), 7.15 (d, *J* = 7.6 Hz, 2H), 7.10 (d, *J* = 7.6 Hz, 2H), 4.87 (s, 1H), 4.36-4.43 (m, 2H), 4.07-4.17 (m, 1H), 3.89-4.01 (m, 2H), 2.44 (s, 3H), 1.36 (t, *J* = 6.8 Hz, 3H), 1.17 (d, *J* = 6.4 Hz, 6H), 0.84 (t, *J* = 6.8 Hz, 3H).

Dimethyl 3-(4-nitrophenyl)-1-tosylaziridine-2,2-dicarboxylate (1k):

4-methyl-*N*-(4-nitrobenzylidene)benzenesulfonamide (0.50 g, 1.64 mmol), 2-bromomalonate (0.37 g, 1.80 mmol), NaH (0.04 g, 1.80 mmol), dry CH_3CN (12 mL), Reaction time = 12 min., **1k** (0.63 g, Yield: 84%), yellow solid, ^{1}H NMR (400 MHz): δ 8.14 (d, *J* = 8.73 Hz, 2H), 7.94 (d, *J* = 8.47 Hz, 2H) 7.44 (d, *J* = 8.73 Hz, 2H), 7.38 (d, *J* = 8.28 Hz, 2H), 4.91 (s, 1H), 3.95 (s, 3H), 3.51 (s, 3H), 2.47 (s, 3H).

diisopropyl 3-(4-nitrophenyl)-1-tosylaziridine-2,2-dicarboxylate (1l):

4-methyl-*N*-(4-nitrobenzylidene)benzenesulfonamide (0.50 g, 1.64 mmol), 2-bromomalonate (0.48 g, 1.80 mmol), NaH (0.04 g, 1.80 mmol), dry CH_3CN (12 mL), Reaction time = 16 min., **1l** (0.69 g, Yield: 86%), white solid, ^{1}H NMR (400 MHz): δ 8.13 (d, *J* = 8.83 Hz, 2H), 7.96 (d, *J* = 8.36 Hz, 2H), 7.42 (d, *J* = 8.91 Hz, 2H), 7.37 (d, *J* = 8.51 Hz, 2H0, 5.27- 5.23 (m, *J* = 6.46, 6.38 Hz, 1H), 4.90 (s, 1H), 4.82-4.77 (m, *J* = 5.95, 6.48 Hz, 1H), 2.46 (s, 1H), 1.36 (q, *J* = 6.31, 7.38 Hz, 6H), 1.07 (d, *J* = 6.26 Hz, 3H), 0.76 (d, *J* = 6.42 Hz, 3H).

2.2 General procedure for synthesis of Oxirane:[16]

A solution of the alkene (5 mmol) in CH_3CN (3 mL) is added to neutral alumina (4.5 g). Then 2N aqueous NaOCl solution (commercial beach 5 mL) is added slowly at room temperature under stirring. When the reaction is complete, the epoxide is extracted with CH_2Cl_2 (2 x 25 mL), the solvent removed and the product is purified by silica gel chromatography to afford oxiranes (yield 48-96 %).

Diethyl 3-phenyloxirane-2,2-dicarboxylate (4a):

^{1}H NMR (400 MHz): δ 7.32 (s, 5H), 4.57 (s, 1H), 4.32 (q, *J* = 7.0 Hz, 2H), 4.02 (q, *J* = 7.0 Hz, 2H), 1.33 (t, *J* = 7.0 Hz, 3H), 0.97 (t, *J* = 7.0 Hz, 3H).

Diethyl 3-(4-chlorophenyl)oxirane-2,2-dicarboxylate (4b):

^{1}H NMR (400 MHz): δ 7.32 (d, *J* = 8.5 Hz, 2H), 7.29 (d, *J* = 8.5 Hz, 2H), 4.53 (s, 1H), 4.32 (q, *J* = 7.0 Hz, 2H), 4.06 (q, *J* = 7.0 Hz, 2H), 1.32 (t, *J* = 7.0 Hz, 3H), 1.03 (t, *J* = 7.0 Hz, 3H).

Diethyl 3-(4-nitrophenyl)oxirane-2,2-dicarboxylate (4c):

^{1}H NMR (400 MHz);δ 8.20 (d, *J* = 8.8 Hz, 2H), 7.52 (d, *J* = 8.8 Hz, 2H), 4.65 (s, 1H), 4.32 (q, *J* = 7.32 Hz, 2H), 4.04 (q, *J* = 7.2 Hz, 2H), 1.33 (t, *J* = 7.2 Hz, 3H), 1.02 (t, *J* = 7.2 Hz, 3H).

Diethyl 3-(*p*-tolyl)oxirane-2,2-dicarboxylate (4d):

^{1}H NMR (400 MHz): δ 7.22 (d, *J* = 7.6 Hz, 2 H), 7.14 (d, *J* = 7.6 Hz, 2 H), 4.53 (s, 1 H), 4.32 (q, *J* = 7.2 Hz, 2 H), 4.06 (q, *J* = 7.2 Hz, 2 H), 2.33 (s, 3 H), 1.34 (t, *J* = 7.2 Hz, 3 H), 1.02 (t, *J* = 7.2 Hz, 3 H).

Representative procedure for Cycloaddition reaction of N-tosyl aziridine-2,2-dicarboxylate and 2,5-dihydroxy-1,4-dithiane.

To a round bottom flask equipped with a magnetic stir bar was added with *N*-tosylaziridine-2,2-dicarboxylate (1 equiv.) and 2,5-dihydroxy-1,4-dithiane and MgI_2 (0.2 equiv.) under nitrogen atmosphere. DCM was added as a solvent to the reaction mixture and stirred at room temperature until completion of the reaction (as monitored by TLC). Reaction mixture was passed through small pad of celite and solvent was evaporated in rotary evaporator. Crude mixture was further purified by flash column chromatography on silica gel with EtOAc/Hexane as eluent.

Scope of N-tosyl aziridine-2,2-dicarboxylate and 2,5-dihydroxy-1,4-dithiane

(2S,5S)-diethyl 5-hydroxy-2-(4-nitrophenyl)-3-tosyl-1,3-thiazinane-4,4-dicarboxylate (3a)

Reaction Time: 20 min., **1a** (0.10 g, 0.21 mmol), **2** (0.03 g, 0.21 mmol), yellow viscous liquid, 0.10 g, Yield: 86%, R_f-value: 0.42 (EtOAc/Hexane) 4:10 (v/v).

3a: ^{1}H NMR (400 MHz): δ 7.86 (d, *J* = 8.90 Hz, 2H), 7.61 (d, *J* = 8.57 Hz, 2H), 7.44 (d, *J* = 8.57 Hz, 2H), 7.07 (d, *J* = 8.36 Hz, 2H), 6.12 (s, 1H), 4.51-4.43 (m, 4H), 4.32 (m, 2H), 2.90 (m, 1H), 2.57 (m, 1H), 2.29 (s, 3H), 1.47 (t, *J* = 7.38 Hz, 3H), 1.42 (t, *J* = 7.27 Hz, 3H). ^{13}C NMR (100 MHz): δ 170.8, 168.1, 147.1, 146.7, 144.6, 136.3, 129.3, 128.4, 127.6, 122.9, 73.8, 71.8, 63.3, 58.2, 28.0, 21.5, 13.8. IR (neat)ν_{max} 3739, 3676, 3617, 3414, 2924, 2855, 2312, 1740, 1705, 1604, 1523, 1457, 1343, 1263, 1159, 1100, 1028, 896, 858, 811, 703, 663 cm^{-1}. HRMS (ESI) Calcd for $C_{23}H_{26}N_2O_9S_2Na$ [M+Na] 561.0977 found 561.0967.

(2S,5S)-diethyl 2-(4-cyanophenyl)-5-hydroxy-3-tosyl-1,3-thiazinane-4,4-dicarboxylate (3b)

Reaction Time: 15 min., **1b** (0.10 g, 0.22 mmol), **2** (0.03 g, 0.22 mmol), white solid m.p. 136°C, 0.09 g, Yield: 84%, R_f-value: 0.64 (EtOAc/Hexane) 4:10 (v/v).

3b: ^{1}H NMR (400 MHz): δ 7.59 (d, *J* = 8.41 Hz, 2H), 7.39 (d, *J* = 8.47 Hz, 2H), 7.29 (d, *J* = 8.63 Hz, 2H), 7.07 (d, *J* = 8.31 Hz, 2H), 6.08 (s, 1H), 4.51-4.41 (m, 4H), 4.31 (m, *J* = 9.66, 2.44 Hz, 2H), 2.89 (m, 1H), 2.55 (m, 1H), 2.32 (s, 3H), 1.46 (t, *J* = 7.44 Hz, 3H), 1.41 (t, *J* = 7.11 Hz, 3H). ^{13}C NMR (100 MHz): δ 170.8, 168.1, 145.2, 144.5, 136.4, 131.5, 129.2, 128.4, 127.4, 118.4, 110.0, 73.8, 63.3, 58.4, 28.0, 21.5, 13.8. IR (neat)ν_{max} 3740, 3679, 3618, 3533, 2976, 2926, 2380, 2313, 2218, 1733, 1602, 1506, 1457, 1403, 1351, 1302, 1248, 1194, 1157, 1085, 1033, 971, 896, 843, 822, 757, 707, 660 cm^{-1}. HRMS (ESI) Calcd for $C_{24}H_{26}N_2O_7S_2Na$ [M+Na] 541.1079 found 541.1066.

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(2S,5S)-diethyl 2-(4-fluorophenyl)-5-hydroxy-3-tosyl-1,3-thiazinane-4,4-dicarboxylate (3c)

Reaction Time: 20 min., **1c** (0.10 g, 0.22 mmol), **2** (0.03 g, 0.22 mmol), white viscous liquid, 0.08 g, Yield: 76%, R_f-value: 0.45 (EtOAc/Hexane) 4:10 (v/v)

3c: ^{1}H NMR (400 MHz): δ 7.62 (d, *J* =8.12 Hz, 2H), 7.24 (m, 2H), 7.08 (d, *J* = 8.37 Hz, 2H), 6.68 (t, *J* = 8.61 Hz, 2H), 6.06 (s, 1H), 4.50-4.40 (m, 4H), 4.38-4.28 (m, 2H), 2.92 (dd, *J* = 7.46, 4.96 Hz, 1H), 2.56 (dd, *J* = 7.91, 4.93 Hz, 2H), 2.32 (s, 3H), 1.46 (t, *J* =7.01 Hz, 3H), 1.41 (t, *J* = 7.43 Hz, 3H). ^{13}C NMR (100 MHz): δ 176.0, 171.0, 160.5, 144.1, 136.7, 135.0, 129.2, 128.6, 128.4, 114.6, 73.8, 63.2, 58.6, 28.1, 21.5, 13.9. IR (neat)ν_{max} 3475, 2923, 2856, 1744, 1711, 1600, 1504, 1455, 1344, 1257, 1227, 1156, 1095, 1032, 883, 844, 761, 709, 660 cm^{-1}. HRMS (ESI) Calcd for $C_{23}H_{26}FNO_7S_2Na$ [M+Na] 534.1032 found 534.1022.

(2S,5S)-diethyl 2-(4-chlorophenyl)-5-hydroxy-3-tosyl-1,3-thiazinane-4,4-dicarboxylate (3d)

Reaction Time: 20 min., **1d** (0.10 g, 0.22 mmol), **2** (0.03 g, 0.22 mmol), white viscous liquid, 0.09 g, Yield: 80%, R_f-value: 0.48 (EtOAc/Hexane) 4:10 (v/v).

3d: ^{1}H NMR (400 MHz): δ 7.61 (d, *J* = 8.34 Hz, 2H), 7.19 (d, *J* = 8.60 Hz, 2H), 7.08 (d, *J* = 8.34 Hz, 2H), 6.97 (d, *J* = 8.75 Hz, 2H), 6.04 (s, 1H), 4.49-4.41 (m, 4H), 4.37-4.28 (m, 2H), 2.92 (q, *J* = 7.66, 5.08 Hz, 1H), 2.55 (q, *J* = 7.55, 4.82 Hz, 1H), 2.32 (s, 3H), 1.45 (t, *J* = 7.10 Hz, 3H), 1.41 (t, *J* = 7.10 Hz, 3H). ^{13}C NMR (100 MHz): δ 170.9, 168.2, 144.2, 137.9, 136.5, 133.0, 129.2, 128.4, 128.1, 127.8, 73.8, 63.2, 58.5, 28.0, 21.5, 13.8. IR (neat)ν_{max} 3740, 3476, 2925, 1743, 1595, 1484, 1452, 1346, 1257, 1158, 1093, 1031, 895, 813, 719, 659 cm^{-1}. HRMS (ESI) Calcd for $C_{23}H_{26}ClNO_7S_2Na$ [M+Na] 550.0737 found 550.0725.

(2S,5S)-diethyl 2-(4-bromophenyl)-5-hydroxy-3-tosyl-1,3-thiazinane-4,4-dicarboxylate (3e)

Reaction Time: 15 min., **1e** (0.10 g, 0.20 mmol), **2** (0.03 g, 0.20 mmol), white solid m.p. 71℃, 0.09 g, Yield: 82%, R_f-value: 0.74 (EtOAc/Hexane) 2:10 (v/v).

3e: ^{1}H NMR (400 MHz): δ 7.60 (d, *J* = 8.70 Hz, 2H), 7.12 (s, 4H), 7.08 (d, *J* = 7.67 Hz, 2H), 6.01 (s, 1H), 4.50-4.40 (m, 4H), 4.38-4.28 (m, 2H), 2.92 (dd, *J* = 7.59, 5.37 Hz, 1H), 2.55 (dd, *J* = 7.59, 5.06 Hz, 1H), 2.33 (s, 3H), 1.46 (t, *J* =7.19 Hz, 3H), 1.41 (t, *J* = 7.11 Hz, 3H). ^{13}C NMR (100 MHz): δ 170.9, 168.2, 144.2, 138.5, 136.5, 130.8, 129.2, 128.4, 121.2, 73.8, 71.9, 63.2, 58.6, 28.0, 21.5, 13.8. IR (neat)ν_{max} 3740, 3677, 3617, 2975, 2926, 2380, 2312, 1742, 1481, 1348, 1258, 1159, 1096, 1035, 893, 816, 703, 660 cm^{-1}. HRMS (ESI) Calcd for $C_{23}H_{26}BrNO_7S_2Na$ [M+Na] 596.0388 found 596.0196.

(2S,5S)-diethyl 2-(2-bromophenyl)-5-hydroxy-3-tosyl-1,3-thiazinane-4,4-dicarboxylate (3f)

Reaction Time: 25 min., **1j** (0.10 g, 0.20 mmol), **2** (0.03 g, 0.20 mmol), white solid m.p. 145℃, 0.08 g, Yield: 78%, R_f-value: 0.74 (EtOAc/Hexane) 2:10 (v/v).

3f: ^{1}H NMR (400 MHz): δ 7.48 (d, *J* = 8.21 Hz, 1H), 7.40 (d, *J* = 7.92 Hz, 1H), 7.07 (d, *J* = 7.99 Hz, 1H), 6.88 (m, 3H), 6.73 (t, *J* = 7.77 Hz, 1H), 6.30 (s, 1H), 4.68 (m, 1H), 4.61 (d, *J* = 1.84 Hz, 1H), 4.54-4.43 (m, 4H), 2.98 (dd, *J* = 7.85, 5.06 Hz, 1H), 2.52 (dd, *J* = 6.89, 6.38 Hz, 1H), 2.20 (s, 3H), 1.50 (t, *J* = 7.11 Hz, 3H), 1.42 (t, *J* = 7.11 Hz, 3H) ^{13}C NMR (100 MHz): δ 171.5, 168.3, 143.8, 137.0, 136.6, 133.4, 128.9, 128.1, 126.6, 122.3, 75.1, 71.8, 63.3, 59.0, 28.2, 21.4, 13.8. IR (neat)ν_{max} 3739, 3673, 3613, 2973, 2925, 2377, 2311, 1734, 1651, 1518, 1462, 1379, 1262, 1158, 1093, 1033, 954, 811 cm^{-1}. HRMS (ESI) Calcd for $C_{23}H_{26}BrNO_7S_2Na$ [M+Na] 596.0388 found 596.0196.

(2S,5S)-diethyl 5-hydroxy-2-phenyl-3-tosyl-1,3-thiazinane-4,4-dicarboxylate (3g)

Reaction Time: 15 min., **1g** (0.10 g, 0.23 mmol), **2** (0.03 g, 0.23 mmol), white viscous liquid, 0.08 g, Yield: 70%, R_f-value: 0.56 (EtOAc/Hexane) 2:10 (v/v).

3g: ^{1}H NMR (400 MHz): δ 7.61 (d, *J* = 8.48 Hz, 2H), 7.24 (d, *J* = 6.70 Hz, 2H), 7.02 (m, 5H), 6.10 (s, 1H), 4.50-4.44 (m, 4H), 4.43-4.41 (m, 1H), 4.29 (d, *J* = 11.90 Hz, 1H), 2.92 (dd, *J* = 8.20, 5.47 Hz, 1H), 2.53 (dd, *J* = 8.34, 5.19 Hz, 1H), 2.29 (s, 3H), 1.46 (t, *J* = 7.11 Hz, 3H), 1.41 (t, *J* = 7.11 Hz, 3H). ^{13}C NMR (100 MHz): δ 171.1, 168.3, 143.9, 139.2, 136.8, 129.1, 128.5, 127.7, 127.2, 126.7, 73.9, 72.0, 63.1, 59.2, 28.1, 21.5, 13.9. IR (neat)ν_{max} 3740, 3478, 2980, 2929, 1745, 1710, 1597, 1445, 1345, 1255, 1157, 1095, 1032, 896, 813, 774, 728, 660 cm^{-1}. HRMS (ESI) Calcd for $C_{23}H_{27}NO_7S_2Na$ [M+Na] 516.1127 found 516.1117.

(2S,5S)-diethyl 5-hydroxy-2-(naphthalen-2-yl)-3-tosyl-1,3-thiazinane-4,4-dicarboxylate (3h)

Reaction Time: 30 min., **1h** (0.10 g, 0.21 mmol), **2** (0.03 g, 0.21 mmol), white viscous liquid, 0.08 g, Yield: 74%, R_f-value: 0.46 (EtOAc/Hexane) 2:10 (v/v).

3h: ^{1}H NMR (400 MHz): δ 8.04, (d, *J* = 8.59 Hz, 1H), 7.78 (d, *J* = 8.01 Hz, 1H), 7.51 (m, *J* = 7.10. 10.03, 8.99 Hz, 3H), 7.37 (d, *J* = 8.27 Hz, 1H), 6.83 (t, *J* = 8.20 Hz, 1H), 6.76 (d, *J* = 7.88 Hz, 1H), 4.83 (m, *J* = 7.68, 4.49, 3.51 Hz, 1H), 4.60 (s, 1H), 4.57-4.47 (m, 4H), 2.93 (dd, *J* = 8.59, 4.82 Hz, 1H), 2.49 (dd, *J* = 6.97, 6.12 Hz, 1H), 2.16 (s, 3H), 1.54 (t, *J* = 7.36 Hz, 3H), 1.44 (t, *J* = 7.16 Hz, 3H). ^{13}C NMR (100 MHz): δ 171.9, 168.5, 143.6, 136.8, 133.9, 132.7, 129.3, 129.1, 128.7, 128.1, 126.1, 125.6, 125.0, 124.2, 123.4, 74.6, 63.3, 56.8, 28.8, 21.4, 13.9. IR (neat)ν_{max} 3741, 3677, 3618, 3417, 2974, 2925, 2856, 2380, 2312, 1834, 1742, 1705, 1651, 1525, 1461, 1345, 1262, 1159, 1101, 1035, 896, 860, 808, 718, 662 cm^{-1}. HRMS (ESI) Calcd for $C_{27}H_{29}NO_7S_2Na$ [M+Na] 566.1283 found 566.1272.

(2S,5S)-diethyl 5-hydroxy-2-(p-tolyl)-3-tosyl-1,3-thiazinane-4,4-dicarboxylate (3i)

Reaction Time: 20 min., **1i** (0.10 g, 0.23 mmol), **2** (0.03 g, 0.23 mmol), white viscous liquid, 0.08 g, Yield: 74%, R_f-value: 0.48 (EtOAc/Hexane) 2:10 (v/v).

3i: ^{1}H NMR(400 MHz): δ 7.62 (d, *J* = 8.39 Hz, 2H), 7.13 (d, *J* = 7.70 Hz, 2H), 7.06 (d, *J* = 8.21 Hz, 2H), 6.80 (d, *J* = 8.14 Hz, 2H), 6.05 (s, 1H), 4.48-4.40 (m, 5H), 4.27 (d, *J* = 11.79 Hz, 1H), 2.92 (dd, *J* = 7.92, 4.84 Hz, 1H), 2.54 (dd, *J* = 8.10, 4.55 Hz, 1H), 2.30 (s, 3H), 2.20 (s, 3H), 1.45 (t, *J* = 7.34 Hz, 3H), 1.41 (t, *J* = 5.28 Hz, 3H). ^{13}C NMR (100 MHz): δ 171.1, 168.4, 143.8, 136.9, 136.8, 136.1, 129.1, 128.5, 128.4, 126.3, 73.8, 63.1, 59.2, 28.1, 21.5, 21.0, 13.9. IR (neat)ν_{max} 3740, 3478, 2978, 2928, 1746, 1711, 1600, 1450, 1346, 1258, 1159, 1097, 1034, 896, 854, 814, 775, 702, 662 cm^{-1}. HRMS (ESI) Calcd for $C_{24}H_{29}NO_7S_2Na$ [M+Na] 530.1218 found 530.1274.

(2S,5S)-diethyl 5-hydroxy-2-(4-isopropylphenyl)-3-tosyl-1,3-thiazinane-4,4-dicarboxylate (3j)

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Reaction Time: 25 min., **1j** (0.10 g, 0.21 mmol), **2** (0.03 g, 0.21 mmol), white viscous liquid, 0.08 g, Yield: 72%, R_f-value: 0.48 (EtOAc/Hexane) 2:10 (v/v).

3j: ^{1}H NMR (400 MHz): δ 7.58 (d, *J* = 8.58 Hz, 2H), 7.11 (d, *J* = 7.12 Hz, 2H), 7.01 (d, *J* = 7.95 Hz, 2H), 6.82 (d, *J* = 8.58 Hz, 2H), 6.06 (s, 1H), 4.53-4.41 (m, 5H), 4.30 (d, *J* = 11.72 Hz, 1H), 2.97 (dd, *J* = 7.74, 4.82 Hz, 1H), 2.75 (m, 1H), 2.53 (dd, *J* = 7.58, 4.82 Hz, 1H), 2.27 (s, 3H), 1.46 (t, *J* = 7.11 Hz, 3H), 1.41 (t, *J* = 7.26 Hz, 3H), 1.13 (d, *J* = 6.90 Hz, 6H). ^{13}C NMR (100 MHz): δ 168.3, 147.9, 143.6, 136.9, 136.3, 129.0, 128.4, 126.7, 125.7, 74.0, 63.1, 59.1, 33.6, 28.2, 24.1, 23.9, 21.5, 13.9. IR (neat)ν_{max} 3369, 3018, 2923, 2852, 1793, 1605, 1526, 1384, 1262, 1217, 1157, 1123, 1093, 1029, 857, 771, 668, 579 cm^{-1}. HRMS (ESI) Calcd for $C_{26}H_{33}NO_7S_2Na$ [M+Na] 558.1596 found 558.1581.

(2S,5S)-dimethyl 5-hydroxy-2-(4-nitrophenyl)-3-tosyl-1,3-thiazinane-4,4-dicarboxylate (3k)

Reaction Time: 15 min., **1k** (0.10 g, 0.23 mmol), **2** (0.03 g, 0.23 mmol), white solid m.p. 152°C, 0.10 g, Yield: 87%, R_f -value: 0.20 (EtOAc/Hexane) 4:10 (v/v).

3j: ^{1}H NMR (400 MHz): δ 7.85 (d, *J* = 8.65 Hz, 2H), 7.58 (d, *J* = 8.54 Hz, 2H), 7.41 (d, *J* = 8.43 Hz, 2H), 7.06 (d, *J* = 8.32 Hz, 2H), 6.09 (s, 1H), 4.33-4.24 (m, 2H), 3.97 (d, *J* = 3.28 Hz, 6H), 2.88-2.86 (q, *J* = 7.12 , 5.58 Hz, 1H), 2.55-2.51 (q, *J* = 7.34, 5.36 Hz, 1H), 2.28 (s, 3H). ^{13}C NMR (100 MHz): δ 171.6, 168.5, 146.9, 144.8, 136.1, 129.4, 128.4, 127.6, 123.0, 74.6, 71.7, 58.3, 54.0, 28.0, 21.5. IR (neat)ν_{max} 3483, 2958, 2933, 2852, 1745, 1712, 1521, 1342, 1309, 1278, 1263, 1228, 1188, 1163, 1116, 1091, 1047, 1031, 958, 891, 860, 808, 773, 671, 655, 570, 559, 543, 478, 459cm^{-1}.HRMS (ESI) Calcd for $C_{21}H_{22}N_2O_9S_2Na$ [M+Na] 533.0664 found 533.0670.

(2S,5S)-diisopropyl 5-hydroxy-2-(4-nitrophenyl)-3-tosyl-1,3-thiazinane-4,4-dicarboxylate (3l)

Reaction Time: 20 min., **1l** (0.10 g, 0.20 mmol), **2** (0.03 g, 0.20 mmol), white solid m.p. 149°C, 0.94 g, Yield: 83%, R_f-value: 0.76 (EtOAc/Hexane) 2:10 (v/v).

3l: ^{1}H NMR (400 MHz): δ 7.84 (d, *J* = 8.75 Hz, 2H), 7.62 (d, *J* = 8.41 Hz, 2H), 7.43 (d, *J* = 8.86 Hz, 2H), 7.05 (d, *J* = 8.19 Hz, 2H), 6.11 (s, 1H), 5.33-5.26 (m, 2H), 4.36-4.28 (m, 2H), 2.91-2.88 (q, *J* = 8.08, 5.27 Hz, 1H), 2.59-2.56 (q, *J* = 7.52, 5.27 Hz, 1H), 2.27 (S, 3H), 1.47-1.37 (m, 12H). ^{13}C NMR (100 MHz): δ 170.1, 167.7, 147.3, 146.7, 144.5, 136.5, 129.3, 128.4, 127.6, 122.9, m73.7, 71.9, 71.6, 71.2, 58.1, 28.0, 21.5. IR (neat) ν_{max} 3452, 2980, 2914, 1743, 1712, 1597, 1517, 1429, 1348, 1278, 1259, 1165, 1101, 1089, 1031, 893, 862, 813, 754, 574, 542 cm^{-1}. HRMS (ESI) Calcd for $C_{25}H_{30}N_2O_9S_2Na$ [M+Na] 589.1290 found 589.1293.

Scope of Oxirane 2,2-dicarboxylate and 2,5-dihydroxy-1,4-dithiane.

(2S,5S)-diethyl 5-hydroxy-2-phenyl-1,3-oxathiane-6,6-dicarboxylate (5a)

Reaction Time: 30 min., **4a** (0.10 g, 0.37 mmol), **2** (0.05 g, 0.21 mmol), white viscous liquid, 0.10 g, Yield: 78%, R_f-value: 0.70 (EtOAc/Hexane) 2:10 (v/v).

5a: ^{1}H NMR (400 MHz): δ 7.46 (dd, *J* = 1.72, 6.66 Hz, 2H), 7.24-7.19 (m, 2H), 5.32 (s, 1H), 5.04 (dd, *J* = 4.93, 6.13 Hz, 1H), 4.35-4.21 (m, 2H), 3.81-3.76 (m, 2H), 3.48 (m, 1H), 2.97 (dd, *J* = 5.00, 6.06 Hz, 1H), 2.92 (d, *J* = 7.40 Hz, 1H), 1.27 (t, *J* = 7.05 Hz, 3H), 0.78 (t, *J* = 7.23 Hz, 3H). ^{13}C NMR (100 MHz): δ 168.4, 168.0, 138.9, 129.4, 128.1, 127.9, 79.4, 62.2, 61.5, 51.9, 37.8, 14.1, 13.9. IR (neat)ν_{max} 3493, 2979, 1720, 1452, 1376, 1257, 1193, 1084, 1023, 860, 810, 742, 696 cm^{-1}. HRMS (ESI) Calcd for $C_{16}H_{20}O_6SNa$ [M+Na] 363.0878 found 363.0768.

(2S,5S)-diethyl 2-(4-chlorophenyl)-5-hydroxy-1,3-oxathiane-6,6-dicarboxylate (5b)

Reaction Time: 6h, **4b** (0.10 g, 0.33 mmol), **2** (0.05 g, 0.33 mmol), yellow viscous liquid, 0.10 g, Yield: 82%, R_f-value: 0.61 (EtOAc/Hexane) 2:10 (v/v).

5b: ^{1}H NMR (400 MHz): δ 7.47 (d, *J* = 8.61 Hz, 2H), 7.24 (d, *J* = 8.61 Hz, 2H), 5.32 (s, 1H), 5.00 (m, 1H), 4.33-4.22 (m, 2H), 3.87 (m, 2H), 3.54 (dd, *J* = 7.35, 8.78 Hz, 1H), 2.98 (dd, *J* = 4.43, 6.93 Hz, 1H), 2.77 (d, *J* = 7.88 Hz, 1H), 1.27 (t, *J* = 7.46 Hz, 3H), 0.851 (t, *J* = 7.06 Hz, 3H). ^{13}C NMR (100 MHz): δ 168.1, 167.6, 137.2, 133.7, 131.9, 130.8, 128.1, 127.9, 79.5, 62.3, 61.6, 51.2, 38.1, 14.1, 13.4. IR(neat)ν_{max} 3435, 2923, 2852, 1728, 1617, 1525, 1490, 1456, 1386, 1260, 1197, 1158, 1092, 858, 827, 773, 691, 575 cm^{-1}. HRMS (ESI) Calcd for$C_{16}H_{19}ClO_6SNa$ [M+Na] 397.0489 found 397.0489 Molecular formula.

(2S,5S)-diethyl 5-hydroxy-2-(4-nitrophenyl)-1,3-oxathiane-6,6-dicarboxylate (5c)

Reaction Time: 5h, **4c** (0.10 g, 0.32 mmol), **2** (0.04 g, 0.32 mmol), yellow viscous liquid, 0.09 g, Yield: 74%, R_f-value: 0.56 (EtOAc/Hexane) 2:10 (v/v).

5c: ^{1}H NMR (400 MHz):δ 8.13 (d, *J* = 8.79 Hz, 2H), 7.71 (d, *J* = 8.77 Hz, 2H), 5.45 (s, 1H), 5.03 (q, *J* = 3.94, 3.61 Hz 1H), 4.33-4.24 (m, *J* = 3.88, 3.56, 3.56, 7.18, 9.27 Hz, 2H), 3.93-3.86 (m, 2H), 3.51 (dd, *J* = 7.08, 3.87 Hz, 1H), 3.03 (dd, *J* = 3.62, 7.58 Hz, 1H), 2.72 (d, *J* = 7.25 Hz, 1H), 1.27 (t, *J* = 7.08 Hz, 3H), 0.826 (t, *J* = 7.25 Hz, 3H). ^{13}C NMR (100 MHz): δ 167.8, 167.2, 146.2, 130.6, 123.1, 79.8, 62.5, 61.7, 51.4, 38.7, 14.1, 13.5. IR (neat)ν_{max} 3391, 3018, 2924, 2399, 1605, 1525, 1384, 1263, 1216, 1026, 928, 770, 669 cm^{-1}. HRMS (ESI) Calcd for $C_{16}H_{20}NO_8SNa$ [M+Na] 386.091 found 386.0864.

(2S,5S)-diethyl 5-hydroxy-2-(p-tolyl)-1,3-oxathiane-6,6-dicarboxylate (5d)

Reaction Time: 30 min., **4d** (0.10 g, 0.35 mmol), **2** (0.05 g, 0.21 mmol), white viscous liquid, 0.09 g, Yield: 76%, R_f-value: 0.54 (EtOAc/Hexane) 2:10 (v/v).

5d: ^{1}H NMR (400 MHz): δ 7.31 (d, *J* = 8.29 Hz, 2H), 7.04 (d, *J* = 8.04 Hz, 2H), 5.25 (s, 1H), 5.01 (m, 1H), 4.33-4.19 (m, 2H), 3.83-3.69 (m, 2H), 3.50 (m, 1H), 2.93 (dd, *J* = 5.29, 5.53 Hz, 1H), 2.88 (d, *J* = 7.58 Hz, 1H), 2.27 (s, 3H), 1.25 (t, *J* = 7.44 Hz, 3H), 0.79 (t, *J* = 7.08 Hz, 3H). ^{13}C NMR (100 MHz): δ 168.4, 168.0, 137.6, 135.8, 130.3, 129.2, 128.7, 128.5, 79.1, 62.2, 61.5, 51.6, 37.4, 29.7, 21.1, 14.1, 13.3. IR (neat)ν_{max} 3682, 3434, 3019, 2926, 2854, 2400, 2371, 2341, 1723, 1606, 1522, 1385, 1262, 1215, 1123, 1156, 1094, 928, 850,768, 669, 626 cm^{-1}. HRMS (ESI) Calcd for $C_{17}H_{22}O_6SNa$ [M+Na] 377.1035 found 377.1029.

Diethyl 5-hydroxy-2-(4-nitrophenyl)-5,6-dihydro-4H-1,3-thiazine-4,4-dicarboxylate (6)

Under argon atmosphere NaH (0.01 g, 0.47 mmol) filled in single necked round bottom flask then add THF (4 mL). The solution of **3a** (0.18 g, 0.31 mmol) in THF (4 mL) was added dropwise to the stirred solution at 0 °C then the reaction was allow to stir at room temperature for 30 min. After completion

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of the reaction (monitored by TLC), the reaction was quenched with cold water. The organic solution was extracted with diethyl ether (3 times) and dried with anhydrous Na_2SO_4. The solution was concentrated in under reduced pressure. The crude mixture was further purified by silica gel column chromatography.

Reaction Time: 30 min., yellow viscous liquid, 0.05 g, Yield: 80%, R_f-value: 0.51 (EtOAc/Hexane) 2:10 (v/v).

^{1}H NMR (400 MHz): δ 8.22 (d, *J* = 8.78 Hz, 2H), 8.02 (d, *J* = 8.96 Hz, 2H), 4.63 (m, 1H), 4.39-4.27 (m, 2H), 3.69 (d, *J* = 5.07 Hz, 1H), 3.32 (dd, *J* = 3.35, 9.23 Hz, 1H), 3.27 (dd, *J* = 6.34, 7.06 Hz, 1H), 1.33 (t, *J* = 7.15 Hz, 3H), 1.29 (t, *J* = 5.16 Hz, 3H). ^{13}C NMR (100 MHz): δ 169.1, 167.7, 161.3, 149.5, 143.6, 128.1, 123.7, 63.0, 61.5, 29.2, 14.1. IR (neat)ν_{max} 3682, 3370, 3020, 2400, 2341, 1727, 1600, 1525, 1385, 1215, 1156, 1124, 1030, 929, 850, 757, 669, 627 cm^{-1}. HRMS (ESI) Calcd for $C_{16}H_{18}N_2O_7SNa$ [M+Na] 405.0732 found 405.0723.

(2S,5S)-diethyl 5-acetoxy-2-(4-nitrophenyl)-3-tosyl-1,3-thiazinane-4,4-dicarboxylate (7)

Under an argon atmosphere, **3a**, (0.10 g, 0.18 mmol), pyridine (0.02 g, 0.27 mmol), and DMAP (2 mg) were added to CH_2Cl_2 (7 mL) at 0 °C. Then a solution of Ac_2O (0.03 ml, 0.03 mmol) in CH_2Cl_2 (1.0 mL) was added with vigorous stirring. The reaction mixture was gradually warmed to room temperature, and stirred for 12 h. Then the reaction was quenched with saturated aqueous $NaHCO_3$ (2 mL), and the mixture was extracted with ethyl acetate (3 X 20 mL). The organic layer was dried with Na_2SO_4, and concentrated in *vacuo*. The residue was purified by silica gel column chromatography to give **7**. Yellow viscous liquid, 0.05 g, Yield: 55%, R_f-value: 0.48 (EtOAc/Hexane) 2:10 (v/v).

^{1}H NMR (400 MHz): δ 7.92 (m, 2H), 7.68 (d, *J* = 8.35 Hz, 2H), 7.61 (d, *J* = 8.35 Hz, 2H), 7.11 (d, *J* = 8.06, 2H), 6.14 (s, 1H), 5.62 (q, *J* = 7.34, 8.20 Hz, 1H), 4.44-4.38 (m, 2H), 4.32-4.24 (m, 2H), 3.00-2.89 (m, 2H), 2.33 (s, 3H), 2.04 (s, 3H), 1.39 (t, *J* = 7.19 Hz, 3H), 1.36 (t, *J* = 4.03 Hz, 3H). ^{13}C NMR (100 MHz): δ 169.0, 167.5, 166.6, 147.1, 145.9, 144.6, 136.7, 129.3, 128.6, 128.3, 123.0, 71.7, 63.1, 59.0, 21.5, 20.7, 13.9. IR (neat)ν_{max} 2985, 2929, 2337, 1757, 1737, 1597, 1514, 1469, 1438, 1344, 1278, 1261, 1238, 1219, 1190, 1165, 1111, 1080, 1039, 1012, 941, 902, 846, 813, 775, 756, 734, 675, 655, 596, 574, 542, 464 cm^{-1}. HRMS (ESI) Calcd for $C_{25}H_{28}N_2O_{10}S_2Na$ [M+Na] 603.1083 found 603.1075.

(S)-Ethyl 2-(4-nitrophenyl)-3-tosyl-3,6-dihydro-2H-1,3-thiazine-4-carboxylate (8)

Compound **7** (0.08 g, 0.14 mmol) and NaCl (0.008 g, 0.14 mmol) were added to a mixture of DMSO and H_2O (v/v 10:1), and the solution was stirred at 130-140 °C for 2h. Then EtOAc (20 mL) was added, and the mixture was washed with H_2O. The organic layer was dried with Na_2SO_4, and concentrated in *vacuo*. The residue was purified by silica gel column chromatography to give **8**. Yellow viscous liquid, 0.03 g, Yield: 62%, R_f-value: 0.62 (Acetone/Hexane) 2:10 (v/v).

^{1}H NMR (400 MHz): δ 8.16 (d, *J* = 8.99 Hz, 2H), 7.89 (d, *J* = 9.20 Hz, 2H), 7.80 (d, *J* = 8.46 Hz, 2H), 7.34 (d, *J* = 8.05 Hz, 2H), 6.30 (dd, *J* =3.02,1.81 Hz, 1H), 6.09 (s, 1H), 4.45-4.30 (m, 2H), 3.01-2.88 (m, *J* = 5.10, 4.96, 6.64 Hz, 2H), 2.49 (s, 3H), 1.42 (t, *J* = 6.98 Hz, 3H). ^{13}C NMR (100 MHz): δ 165.1, 147.7, 145.1, 144.4, 133.9, 131.1, 129.9, 128.7, 128.3, 123.8, 123.6, 62.2, 59.0, 21.8, 14.8. IR (neat)ν_{max} 2981, 2929, 2854, 1735, 1678, 1595, 1521, 1479, 1367, 1346, 1276, 1217, 1188, 1165, 1109, 1089, 1037, 1012, 983, 937, 900, 862, 848, 813, 734, 717, 673, 578, 543 cm^{-1}. HRMS (ESI) Calcd for $C_2H_{20}N_2O_6S_2Na$ [M+Na] 471.0660 found 471.0654.

Conclusions

In conclusion, we have developed an efficient protocol for the synthesis of two heteroatom containing substituted 1,3–thiazine and 1,3–oxathiane through [3+3] cycloaddition of *N*-tosylaziridinedicarboxylate and oxirane with 1,4-dithiane 2,5-diol. Additionally, we also demonstrated the chemical conversion of substituted 1,3-thiazine in to various structure which have immense biological application like cephalosporin and TZ-1.

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