Synthesis of α-Aliphatic and β-Aromatic Substituted Taurines via Regioselective Ring Opening of Thiiranes with Ammonia

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Abstract: Thiiranes are important starting materials for the synthesis of substituted taurines. The regioselectivity of ring-opening reactions of thiiranes with ammonia in the presence of silver nitrate was investigated. The results of the ring-opening reaction and subsequent peroxy acid oxidation indicate that alkyl-substituted thiiranes give rise to 1-monoalkyl- and 1,1-dialkyltaurines, whereas aryl-substituted thiiranes produce 2-aryl-, 2-alkyl-2-aryl-, and 2,2-diaryltaurines. This shows that alkyl-substituted thiiranes were attacked on their less-substituted ring carbon atoms, while aryl-substituted thiiranes were attacked on their more substituted ring carbon atoms. The current method is an effective and atom-economic route for the synthesis of mono- and disubstituted α-alkyl- and β-aryl-substituted taurines.

Key words: amino acid, aminoalkanesulfonic acid, regioselectivity, ring-opening reaction, synthesis, thiirane, taurine

Taurine and substituted taurines have been found in many mammalian tissues[1] and in marine algae, fish, and shellfish.[2] They are involved in various physiological processes.[1,3] Taurine and its cyclic analogues show different effects on ATP-dependent calcium ion uptake and protein phosphorylation in rat retina.[4] Taurine and substituted taurines are not only a class of important, naturally occurring amino acids, but also very important sulfur analogues of naturally occurring aminocarboxylic acids. Additionally, they are building blocks for the synthesis of sulfonopeptides, which have been widely used as enzyme inhibitors and haptens in the development of catalytic antibodies during the last two decades because of their tetrahedral structural properties.[5–7]

Taurine and substituted taurines have been previously prepared from nitroalkenes by addition of sodium sulfite and subsequent reduction,[8] by the amino-sulfonation of olefins and hydrolysis,[9] by the peroxy acid oxidation of amino alcohol thioacetates,[10] or by sodium sulfite displacement of amino alcohol methanesulfonates[11] or sulfates.[12] Recently, we reported the preparation of substituted taurines via the thiolacetic acid ring-opening of aziridines and subsequent peroxy acid oxidation and hydrolysis under acidic conditions,[13] and via the sodium sulfite and bisulfite directed ring opening of aziridines.[14] We also found that aromatic geminally disubstituted aziridines show different regioselectivity in the sodium bisulfite ring-opening reaction.[14b,15] After successful application of aziridines in the synthesis of substituted taurines, we attempted to prepare substituted taurines from thiiranes, sulfur analogues of aziridines, via ring-opening reactions with nitrogen-containing nucleophiles and subsequent oxidation. Firstly, we realized the ring-opening reaction of 2-monosubstituted thiiranes with dibenzylamine.[16] The sterically hindered dibenzylamine can inhibit polymerization of the thiiranes in the ring-opening reactions; after peroxy acid oxidation and subsequent debenzylation under hydrogenlytic conditions, a series of 1-substituted taurines were synthesized. 2-Phenylthiirane, however, gave a mixture of 1-phenyl- and 2-phenyltaurines due to poor regioselectivity in the ring-opening reaction and 2,2-disubstituted thiiranes cannot undergo the ring-opening reaction with dibenzylamine possible due to steric hindrance.[17] Another disadvantage is that the synthetic method is not atom-economic because the amino group was introduced through the use of dibenzylamine. By using the Luhowy and Menechini method,[18] we achieved the direct ring-opening reaction of 2,2-dialkylthiiranes with ammonia in the presence of silver nitrate without polymerization of the thiiranes,[17] which occurred generally in the absence of silver cations. A series of 1,1-dialkyltaurines were synthesized from 2,2-dialkylthiiranes.[17] Compared to the ring-opening method with dibenzylamine,[16] the direct ring-opening method with ammonia is a more atom-economic route to 1,1-disubstituted taurines. Thus, we hope to extend this method to the synthesis of 1-substituted taurines from 2-substituted thiiranes and investigate the scope and limitation of the synthetic strategy. On the other hand, as ring-opening reactions of aromatic 2,2-disubstituted aziridines with sodium bisulfite show different regioselectivity,[14b] we also wish to investigate the regioselectivity of the ring-opening reaction of aliphatic and aromatic mono- and disubstituted thiiranes with ammonia. Herein, we present an atom-economic synthesis of α-alkyl- and β-aryl-substituted taurines via the regioselective ring opening of thiiranes with ammonia and subsequent peroxy acid oxidation.

Initially a series of 2-monoalkyl-substituted epoxides **1a**–**g** were purchased or prepared from 1-chloro-2,3-epoxy-

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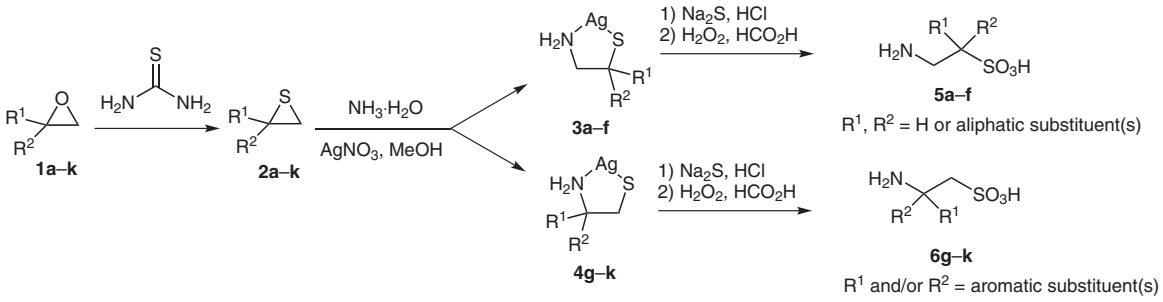
propane via the alkylation of benzylic alcohol, phenols, and dibenzylamine in aqueous sodium hydroxide solution. Epoxide **1h** and various geminally disubstituted epoxides **1i–k** were synthesized from the corresponding aldehydes and ketones via the Corey–Chaykovsky epoxidation.[19] The structurally diverse substituted epoxides **1a–k** were converted into the corresponding thiiranes **2a–k** by reaction with thiourea using a modified literature method.[20] It has been found that thiourea is a more efficient and convenient reagent than potassium isocyanate and silica gel absorbed potassium isocyanate in episulfidation. The synthesized thiiranes **2a–k** include 2-alkylthiiranes **2a–f**, 2-arylthiiranes **2g–h**, 2-alkyl-2-arylthiiranes **2i,j**, and a 2,2-diarylthiirane **2k**, but excluding 2,2-dialkylthiiranes because a series of 2,2-dialkylthiiranes have been previously investigated.[17]

Various 1- and 2-monosubstituted taurines and 1,1- and 2,2-disubstituted taurines have been prepared by our and other groups,[14,16,17] thus it is easier to identify the products of the regioselective ring-opening reactions of thiiranes with ammonia after subsequent oxidation to substituted taurines.

The ring-opening reaction of synthetic thiiranes with ammonia was conducted in the presence of silver nitrate, affording silver cation coordinated vicinal amino thiols **3a–f** or **4g–k**, respectively. Silver nitrate plays two crucial roles in the ring-opening reaction. Firstly it serves as a Lewis acid, coordinating with the sulfur atom of the thiirane, thus activating the thiirane ring. After the ring-opening reaction, it coordinates with the thus formed thiolate anions, hence avoiding further polymerization induced by attack of the strong nucleophilic thiolate anions on to the thiirane. The silver vicinal amino thiolate complexes **3a–f** or **4g–k** were dissolved in dichloromethane and decomposed after treatment with hydrogen sulfide, generated in situ from sodium sulfide and concentrated hydrochloric acid in a balloon-capped and sealed reaction system, avoiding escape of the uncomfortable odor of hydrogen sulfide from the reaction system. After neutralization with sodium hydroxide and filtration of silver sulfide precipitates, the obtained crude free amino thiols were dissolved in formic acid and oxidized directly with performic acid to afford substituted taurines **5a–f** or **6g–k**, respectively, in satisfactory overall yields (from thiiranes **2**) (Table 1). 2,2-Diphenylthiirane (**2k**) gave rise to 2,2-diphenyltaurine (**6k**) in relatively low yield compared with other substituted thiiranes because it is unstable under the reaction conditions; it could undergo desulfurization to form sulfur and 1,1-diphenylethene. The desulfurization could be accelerated by silver nitrate because the coordination between silver and the sulfur atom in 2,2-diphenylthiirane (**2k**) weakened the C–S bonds in the thiirane.

Table 1 Synthesis of α-Alkyl- and β-Aryl-Substituted Taurines via Regioselective Ring Opening of Various Thiiranes with Ammonia



Entry	R^1	R^2	Product	Yield (%)	Product	Yield[a] (%)
1	H	Bu	**2a**	90	**5a**	50
2	H	$(CH_2)_5Me$	**2b**	92	**5b**	43
3	H	CH_2OBn	**2c**	92	**5c**	49
4	H	CH_2OPh	**2d**	80	**5d**	63
5	H	4-$MeC_6H_4OCH_2$	**2e**	98	**5e**	47
6	H	CH_2NBn_2	**2f**	87	**5f**	59
7	H	Ph	**2g**	58	**6g**	47
8	H	4-MeC_6H_4	**2h**	59	**6h**	44
9	Me	Ph	**2i**	60	**6i**	68
10	Et	Ph	**2j**	54	**6j**	44
11	Ph	Ph	**2k**	30	**6k**	11

[a] From thiirane **2**.

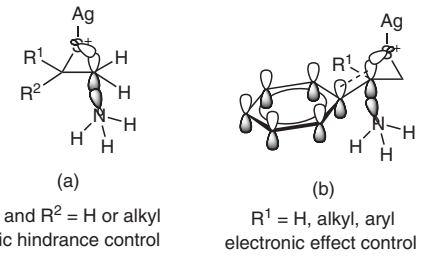


Figure 1 Different transition states in the ring-opening reaction of alkyl- and aryl-substituted thiiranes with ammonia in the presence of silver nitrate: (a) Attack on the less substituted carbon atom in alkyl-substituted thiiranes (steric effect control). (b) Attack on the more substituted carbon atom in aryl-substituted thiiranes (electronic effect control).

Several 1-alkyltaurines,[10d] 1- and 2-phenyltaurines,[10d,14] 1,1- and 2,2-diphenyltaurines,[14b] 1-methyl-1-phenyl- and 2-methyl-2-phenyltaurines,[10f,14b] and 2-ethyl-2-phenyltaurine[10f] have been prepared previously by us, all structures of key substituted taurines, including **5b–d**, **6g**, and **6i–k**, were identified conveniently through comparison of their ^{1}H and ^{13}C NMR spectral data with reported data. These provided the regioselectivity for various substituted thiiranes in the ring-opening reaction with ammonia. The results indicated that all alkyl-substituted thiiranes (including 2-alkyl- and 2,2-dialkylthiiranes[17]) give rise to α-alkyl-substituted taurines, whereas all aryl-substituted thiiranes (including 2-aryl-, 2-alkyl-2-aryl-, and 2,2-diarylthiiranes) produce aromatic β-substituted or β,β-disubstituted taurines, thus showing that all alkyl-substituted thiiranes were attacked on their less substituted ring carbon atom, but all aryl-substituted thiiranes (including monoaryl- and diarylthiiranes) were attacked on their more substituted ring carbon atom. Aryl-substituted thiiranes show different regioselectivity from alkyl-substituted thiiranes in their ring-opening reaction with ammonia. The results could be rationalized that silver-coordinated alkylthiiranes are attacked on their less substituted ring carbon atom due to lower steric hindrance; the regioselectivity is controlled by the steric hindrance [Figure 1 (a)]. Whereas silver-coordinated arylthiiranes are attacked on their more substituted ring carbon atom because their phenyl group could stabilized the benzylic carbocation formed in the transition state of the ring-opening reaction through the p–π conjugative effect [Figure 1 (b)]; the regioselectivity is controlled by the electronic effect. Compared with the direct dibenzylamine ring opening of 2-arylthiiranes, the regioselectivity in the silver-catalyzed ring-opening reaction with ammonia was obviously improved. The steric hindrance of the nucleophiles (ammonia vs dibenzylamine) may also contribute to the improved regioselectivity.

All aryl-substituted thiiranes show different regioselectivity from alkyl-substituted thiiranes in the ring-opening reaction with ammonia in the presence of silver nitrate. However, for aziridines, only aromatic geminally disubstituted aziridines show different regioselectivity from other aziridines. The difference may be caused by the different bond energies of C–N and C–S in these two different three-membered heterocycles.

Comparison of the current method with the previous dibenzylamine ring-opening method[16] shows that it has higher overall yields and a shorter synthetic route. Thus, the current procedure is an atom-economic and efficient method for the synthesis of substituted taurines, such as 1-alkyltaurines and 1,1-dialkyltaurines,[17] 2-aryltaurines, 2-alkyl-2-aryltaurines, and 2,2-diaryltaurines. However, for 2,2-diaryltaurines, the yield may be unsatisfactory due to the desulfurization of 2,2-diarylthiiranes.

In summary, the regioselectivity of unsymmetrical thiiranes in the ring-opening reaction with ammonia in the presence of silver nitrate and their application in the synthesis of substituted taurines were investigated. The results indicate that alkyl-substituted thiiranes give rise to 1-monoalkyl- and 1,1-dialkyltaurines, whereas aryl-substituted thiiranes produce 2-monoaryl- and 2,2-diaryltaurines, after the ring-opening reaction and subsequent oxidation, because aliphatic thiiranes were attacked on their less substituted ring carbon atoms (steric effect control) while aromatic thiiranes were attacked on their more substituted ring carbon atoms (electronic effect control) in the ring-opening reaction. The current route is an effective and atom-economic method for synthesis of mono- and disubstituted α-alkyl- and β-aryl-substituted taurines.

Melting points were measured on a Yanaco MP-500 melting point apparatus and are uncorrected. ^{1}H and ^{13}C NMR spectra were recorded on Varian Mercury Plus 300 (300 MHz) spectrometer in $CDCl_3$ (internal standard, TMS), in D_2O [internal standards, HDO $\delta(^1H) = 4.67$; HCO_2H $\delta(^{13}C) = 166.3$ or DMSO], DMSO-d_6, or 88% HCO_2H [internal standard, HCO_2H $\delta(^{13}C) = 166.3$]. Mass spectra were obtained on a Brucker ESQUIRE–LCTM ESI ion trap mass spectrometer. HRMS data was carried out on an Agilent LC/MSD TOF mass spectrometer. IR spectra were determined on a Nicolet AVATAR 330 FT-IR spectrophotometer. PE refers to petroleum ether (bp 30–60 °C). Epoxides **1a**, **1b**, and **1g** are commercially available (Alfa Chemical Co.). Epoxides **1c–f** were prepared in good yields via the alkylation of benzylic alcohol, phenol, 4-methylphenol, and dibenzylamine, respectively, with 1-chloro-2,3-epoxypropane in aq NaOH soln. Epoxides **1h–k** were prepared in satisfactory to good yields from 4-methylbenzaldehyde and the corresponding ketones via the Corey–Chaykovsky epoxidation according to the literature method.[19] The analytical data of all known compounds are identical to those previously reported in the literature.

Thiiranes 2; General Procedure

Thiiranes were prepared using a modified literature procedure.[20] To a stirring soln of epoxide **1** (10 mmol) in MeOH (30 mL) was added thiourea (1.52 g, 20 mmol); when it was completely dissolved, the resulting soln was refluxed for 1.5 h. After removal of solvent, H_2O (20 mL) was added. The soln was extracted with CH_2Cl_2 (3 × 15 mL) and the combined organic extracts were dried ($MgSO_4$). The solvent was removed under reduced pressure and the residue was purified by flash chromatography (Et_3N-neutralized silica gel, PE–EtOAc, 20:1) to afford thiirane **2** in moderate to good yields (30–98%, Table 1).

Substituted Taurines 5 and 6; General Procedure

To a stirred soln of NH_3 (11.2 mmol) in MeOH (11.2 mL) was added $AgNO_3$ (0.21 g, 1.23 mmol). After completely dissolved, a soln of thiirane **2** (1.12 mmol) in MeOH (1 mL) was added dropwise at r.t. over a period of 0.5 h. After stirring for a further 3 h, the solvent was removed to afford yellow solid **3** or **4**, which was suspended in CH_2Cl_2 (20 mL). After addition of $Na_2S{\cdot}9\ H_2O$ (1.75 g, 7.29 mmol), to the suspended soln was added dropwise concd HCl (3.74 mL, 44.8 mmol) through a pressure-equilibrium addition funnel capped with a balloon to keep that the mixture was stirred under the atmosphere of H_2S for 6 h. The soln was adjusted to basic with 2 M NaOH, the mixture was filtered, and the AgS precipitates were washed with CH_2Cl_2. The washings and filtrate were combined and separated. The aqueous phase was extracted with CH_2Cl_2 (3×5 mL). The combined organic phases were washed with H_2O (10 mL) and brine (10 mL) and dried ($MgSO_4$). After removal of the solvent under reduced pressure, the residue was diluted with HCO_2H (2 mL) and used directly in the next step without purification.

To a performic acid soln, prepared by mixing and stirring 30% H_2O_2 (0.76 mL, 6.72 mmol) and 88% HCO_2H (6.72 mL) at r.t. for 1 h, cooled in an ice bath, was added dropwise the above prepared soln at 0 °C over a period of 10 min. The resulting mixture was stirred and allowed to warm to r.t. for 1.5 d. After removal of solvent, the residue was crystallized (MeOH) to give colorless crystals of substituted taurines.

1-Aminohexane-2-sulfonic Acid (5a)

Colorless crystals; overall yield: 50% (from thiirane **2a**); mp 339–340 °C (dec.).

IR: 3420 (br, OH, NH), 1221 (SO_2), 1150 cm^{-1} (SO_2).

^1H NMR (300 MHz, D_2O, HDO): δ = 3.25 (dd, *J* = 3.0, 13.8 Hz, 1 H, C*H*HN), 3.15 (dd, *J* = 9.0, 13.8 Hz, 1 H, CH*H*N), 2.95 (m, 1 H, CHS), 1.79 (m, 1 H, C*H*H), 1.48–1.18 (m, 5 H, CH_2CH_2; 1 H, CH*H*), 0.78 (t, *J* = 7.2 Hz, 3 H, CH_3).

^{13}C NMR (75.5 MHz, D_2O, HCO_2H): δ = 57.5, 39.8, 28.6, 27.8, 22.4, 13.7.

MS (ESI): *m*/*z* = 182 $[M + H]^+$.

HRMS: *m*/*z* [M + H] calcd for $C_6H_{16}NO_3S$: 182.0851; found: 182.0847.

1-Aminooctane-2-sulfonic Acid (5b)

Colorless crystals; overall yield: 43% (from thiirane **2b**); mp 345–346 °C (Lit.[16] >360 °C).

^{13}C NMR (75.5 MHz, DMSO-d_6): δ = 55.6, 39.5, 31.1, 28.6, 27.9, 26.2, 22.1, 14.0.

1-Amino-3-(benzyloxy)propane-2-sulfonic Acid (5c)

Colorless crystals; overall yield: 49% (from thiirane **2c**); mp 269–270 °C (Lit.[16] 227–229 °C).

^{13}C NMR (75.5 MHz, D_2O, HCO_2H): δ = 130.6, 130.28, 130.27, 129.8, 59.7, 57.8, 51.8.

1-Amino-3-phenoxypropane-2-sulfonic Acid (5d)

Colorless crystals; overall yield: 63% (from thiirane **2d**); mp 329–331 °C (Lit.[16] 307–309 °C).

^{13}C NMR (75.5 MHz, D_2O, HCO_2H): δ = 157.7, 129.9, 122.0, 114.8, 65.1, 56.4, 39.2.

1-Amino-3-(4-methylphenoxy)propane-2-sulfonic Acid (5e)

Colorless crystals; overall yield: 47% (from thiirane **2e**); mp 323–325 °C.

IR: 3375 (br, NH, OH), 1247 (SO_2), 1198 cm^{-1} (SO_2).

^1H NMR (300 MHz, D_2O, HDO): δ = 2.07 (s, 3 H, CH_3), 3.35–3.46 (m, 3 H, CH, CH_2), 4.08 (dd, *J* = 7.2, 10.5 Hz, 1 H, C*H*H), 4.31 (dd, *J* = 3.6, 10.5 Hz, 1 H, CH*H*), 6.76 (d, *J* = 8.7 Hz, 2 H, ArH), 7.01 (d, *J* = 8.7 Hz, 2 H, ArH).

^{13}C NMR (75.5 MHz, HCO_2H): δ = 155.9, 132.0, 130.7, 115.2, 66.0, 56.6, 38.9, 20.1.

MS (ESI): *m*/*z* = 246 $[M + H]^+$.

HRMS: *m*/*z* [M + H] calcd for $C_{10}H_{16}NO_4S$: 246.0800; found: 246.0798.

1-Amino-3-(dibenzylamino)propane-2-sulfonic Acid (5f)

Colorless crystals; overall yield: 59% (from thiirane **2f**); mp 190–192 °C.

IR: 3431 (br, NH, OH), 2438 ($Bn_2NH^+CH_2$), 1243 (SO_2), 1214 cm^{-1} (SO_2).

^1H NMR (300 MHz, D_2O, HDO): δ = 2.99 (m, 2 H, CH_2), 3.36 (m, 2 H, CH_2), 3.42 (m, 1 H, CH), 4.14 (m, 2 H, 2 C*H*H), 4.46 (m, 2 H, 2 CH*H*), 7.20–7.20 (m, 10 H, ArH).

^{13}C NMR (75.5 MHz, HCO_2H): δ = 131.3, 131.1, 130.2, 129.1, 59.1, 51.8, 51.6, 38.3.

MS (ESI): *m*/*z* = 335 $[M + H]^+$.

HRMS: *m*/*z* [M + H] calcd for $C_{17}H_{23}N_2O_3S$: 335.1423; found: 335.1418.

2-Amino-2-phenylethanesulfonic Acid (6g)

Colorless crystals; overall yield: 47% (from thiirane **2g**); mp 314–315 °C (Lit.[9] 314–315 °C).

^{13}C NMR (75.5 MHz, D_2O, HCO_2H): δ = 134.6, 130.3, 129.7, 127.3, 53.2, 52.9.

2-Amino-2-(4-methylphenyl)ethanesulfonic Acid (6h)

Colorless crystals; overall yield: 44% (from thiirane **2h**); mp 290–291 °C (dec.) (Lit.[21] 347 °C).

^1H NMR (300 MHz, D_2O, HDO): δ = 2.14 (s, 3 H, CH_3), 3.25 (dd, *J* = 4.8, 14.4 Hz, 1 H, NCH_2), 3.40 (dd, *J* = 9.0, 14.4 Hz, 1 H, NCH_2), 4.57 (dd, *J* = 4.8, 9.0 Hz, 1 H, CH), 7.12 (d, *J* = 8.6 Hz, 2 H, ArH), 7.15 (d, *J* = 8.6 Hz, 2 H, ArH).

^{13}C NMR (75.5 MHz, HCO_2H): δ = 140.9, 132.1, 130.6, 127.6, 53.6, 52.7, 20.8.

MS (ESI): *m*/*z* = 216 $[M + H]^+$.

HRMS: *m*/*z* [M + H] calcd for $C_9H_{14}NO_3S$: 216.0674; found: 216.0662.

2-Amino-2-phenylpropanesulfonic Acid (6i)

Colorless crystals; overall yield: 68% (from thiirane **2i**); mp 236–238 °C (Lit.[10f] 236–238 °C).

^{13}C NMR (75.5 MHz, D_2O, DMSO): δ = 147.4, 130.4, 128.9, 127.1, 64.4, 55.7, 31.1.

2-Amino-2-phenylbutanesulfonic Acid (6j)

Colorless crystals; overall yield: 44% (from thiirane **2j**); mp 253–255 °C (Lit.[10f] 253–255 °C).

^{13}C NMR (75.5 MHz, D_2O, DMSO): δ = 139.0, 131.5, 131.0, 127.5, 63.3, 59.3, 34.3, 9.1.

2-Amino-2,2-diphenylethanesulfonic Acid (6k)

Colorless crystals; overall yield: 11% (from thiirane **2j**); mp 239–242 °C (dec.) [Lit.[10f] 239–242.5 °C (dec.)].

^{13}C NMR (75.5 MHz, D_2O, DMSO): δ = 147.1, 130.4, 129.3, 128.4, 62.2, 61.8.

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