Synthesis of Homotaurine and 1-Substituted Homotaurines from α,β-Unsaturated Nitriles

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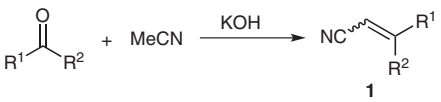
Abstract: Homotaurine and a series of 1-substituted homotaurines were readily synthesized in satisfactory to good yields via the Michael addition of thioacetic acid to aliphatic and aromatic α,β-unsaturated nitriles followed by lithium aluminum hydride mediated reduction and performic acid oxidation. The synthesis of 1,1-disubstituted homotaurines was attempted with β,β-disubstituted acrylonitriles as starting materials but failed due to steric hindrance. The current process is an efficient method for the synthesis of 1-substituted homotaurines.

Key words: acrylonitrile, amino thiols, Michael addition, nucleophile, reduction, oxidation, thioacetic acid

Homotaurine (3-aminopropanesulfonic acid) and taurine (2-aminoethanesulfonic acid) are two powerful inhibitory amino acids with anticonvulsant properties against various experimental models of focal epilepsy.[1] Homotaurine, as a sulfur-containing amino acid, has attracted much attention in recent years as a drug candidate for the treatment of Alzheimer's disease and haemorrhagic stroke.[2] Recent studies indicate that it binds to soluble amyloid β-peptide (Aβ) and decreases Aβ42-induced cell death in neuronal cell culture.[3] It is believed that the reduction or inhibition of amyloid deposition in the brain and cerebral vasculature is responsible for the beneficial effects observed in vivo studies.[2] Moreover, calcium 3-acetylaminopropanesulfonate (acamprosate) is one of the few medications currently approved for the prevention of alcohol relapse in detoxified alcohol dependent patients both in Europe and USA.[4] Both homotaurine and substituted homotaurine derivatives are considered as bioisosteres of γ-aminobutyric acid (GABA).[5]

Homotaurine was synthesized from 3-aminopropanol via bromination with hydrogen bromide and subsequent displacement with sodium bisulfite or sulfite,[6,7] and via addition of acrylonitrile with sodium bisulfite and subsequent reduction.[8] 2-Substituted homotaurines were prepared as competitive antagonists of the GABA receptor through addition of isobutenal with sodium bisulfite and subsequent reductive amination,[9] via addition of 1-arylacrylonitriles with sodium bisulfate and subsequent reduction,[10] via the oxygen-catalyzed radical addition of bisulfite to 2-arylallylamines or their *N*-phthalyl derivatives,[11] and via ring-opening reactions of 2-alkylpropane-1,3-sultones with ammonia or with sodium azide followed by reduction.[12] 3-Substituted homotaurines were synthesized through oxidation of homocysteine,[13] via reduction of amino esters to amino aldehydes, which underwent the Horner–Wadsworth–Emmons reaction with ethyl (diethoxyphosphoryl)methanesulfonate in the presence of butyllithium and subsequent hydrogenation and deprotection.[14] 3-Nitroalkanesulfonic acids are precursors of 1,3-disubstituted homotaurines and were obtained through addition of arylmethanesulfonates to nitroolefins in the presence of *n*-butyllithium.[15] Recently, *cis*- and *trans*-2-aminomethylcyclopropane-1-sulfonic acids were synthesized as conformationally restricted GABA analogues as pharmacological tools to study GABA receptor subtypes.[16] However, there is no general reported method for the synthesis of 1-substituted homotaurines. Recently, we prepared substituted taurines through Michael addition of thioacetic acid and sodium *O*-ethyl xanthate to nitroolefins and subsequent oxidation and reduction.[17] As a part of our continuing interest in the synthesis and biological applications of aminoalkanesulfonic acids, we became interested in the preparation of 1-substituted homotaurines, especially salt-free preparations. Herein, we present the synthesis of 1-substituted homotaurines from α,β-unsaturated nitriles.

α,β-Unsaturated nitriles **1c–j** were prepared conveniently in satisfactory to good yields through condensation of aldehydes or ketones and acetonitrile, respectively, in the presence of potassium hydroxide by referring to the reported method (Scheme 1);[18] acrylonitrile (**1a**) and crotonitrile (**1b**) are commercially available. In most cases, (*E*)-α,β-unsaturated nitriles were obtained. However, a mixture of *Z*- and *E*-isomers was obtained for α,β-unsaturated nitriles cinamonitrile (**1c**) and (3-chlorophenyl)acrylonitrile (**1e**) in *Z*/*E* ratios of 1:3 and 1:6, respectively.



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Scheme 1 Preparation of α,β-unsaturated nitriles **1**

The Michael addition of acrylonitrile and 1-arylacrylonitriles with sodium bisulfite has been applied in the synthesis of homotaurine and 2-arylhomotaurines.[8,10] However, separation and purification of intermediate 2-cyanoal-

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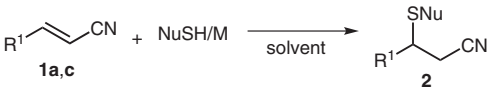
kanesulfonic acids from the inorganic salts during the workup is difficult and tedious due to their large polarity and good solubility in water, especially for low molecular weight derivatives. To simplify the purification procedure, we hoped to develop a salt-free route to the synthesis of 1-substituted homotaurines from α,β-unsaturated nitriles. Thus, Michael additions of α,β-unsaturated nitriles **1** with different sulfur nucleophiles, such as potassium isothiocyanate, potassium thioacetate, thioacetic acid, and xanthate derivatives, were investigated with acrylonitrile (**1a**) and cinamonitrile (**1c**) as representatives; the results are summarized in Table 1. When simple sulfur-containing salts potassium isothiocyanate and potassium thioacetate were used as nucleophiles in the reactions with acrylonitrile (**1a**), no desired product was observed (Table 1, entries 1 and 2). Thioacetic acid reacted with acrylonitrile (**1a**) to afford the adduct *S*-2-cyanoethyl thioacetate (**2a**) in good yield (72%) in the presence of triethylamine (Table 1, entry 3). Xanthate derivatives sodium *O*-ethyl xanthate and piperidine-1-xanthate, generated in situ from piperidine and carbon disulfide, reacted with acrylonitrile (**1a**) to produce the corresponding products in 52% yield in acetic acid and in 62% yield in water, respectively (Table 1, entries 4 and 5). The reaction of piperidine-1-xanthate and acrylonitrile (**1a**) realized 91% yield under solvent-free conditions (Table 1, entry 6). However, sodium *O*-ethyl xanthate reacted with cinamonitrile (**1c**) to give the corresponding product in less than 10% yield. For piperidine-1-xanthate and cinamonitrile (**1c**), no reaction occurred. Thus, we focused on the reaction with thioacetic acid as the sulfur nucleophile. To monitor the reaction progress conveniently with TLC and to explore the influence of substituents on the yield, the reaction of thioacetic acid and cinamonitrile (**1c**) was selected as a model reaction to optimize reaction conditions. The reaction produced the desired product *S*-2-cyano-1-phenylethyl thioacetate (**2c**) in 33% yield in refluxing toluene, an aprotic solvent, under the catalysis of triethylamine. However, it gave rise to only trace amounts of the product in refluxing methanol, a protic solvent. Considering that the Michael addition is a reversible reaction and that the reaction is generally favorable to the adduct at lower temperatures. To reduce the refluxing temperature and to screen different solvents, the reaction was conducted in refluxing tetrahydrofuran (bp 66 °C) and carbon tetrachloride (bp 77 °C), respectively, affording the adduct in 36 and 40% yields. To evaluate the efficiency of different catalysts, the reaction was also performed in refluxing carbon tetrachloride under the catalysis of tributylamine, giving rise to the adduct in 40% yield. Carbon tetrachloride is not an environment-friendly solvent, therefore, the reaction was finally carried out in toluene at 80 °C under the catalysis of tributylamine. Under these optimal reaction conditions, the desired adduct was obtained in 42% yield.

α,β-Unsaturated nitriles **1a**–**g** underwent the Michael addition with thioacetic acid to produced 1-substituted 2-cyanoethyl thioacetates **2a**–**g** in satisfactory to good yields under the optimized reaction conditions (Table 2, entries 1–7). However, for α,β-unsaturated nitriles **1h**–**j**, which are β,β-disubstituted acrylonitriles, no reaction occurred under the same reaction conditions (Table 2, entries 8–10), revealing that the Michael addition is very sensitive towards steric hindrance. This is consistent with the observation that the sterically hindered nucleophile piperidine-1-xanthate cannot undergo the Michael addition with bulky cinamonitrile (**1c**) due to steric hindrance. The obtained *S*-1-substituted 2-cyanoethyl thioacetates **2a**–**g** were reduced with lithium aluminum hydride to give rise to the corresponding 1-aminoalkane-3-thiols **3a**–**g**, which were directly oxidized with peroxyformic acid without purification. The residues were recrystallized from a mixture of ethanol and diethyl ether to afford 1-substituted homotaurines **4b**–**g** as colorless crystals in acceptable to good yields (Table 2, entries 2–7). However, homotaurine (**4a**) was not obtained following the same procedure.

Table 1 Michael Addition of α,β-Unsaturated Nitriles **1a** and **1c** with Sulfur Nucleophiles

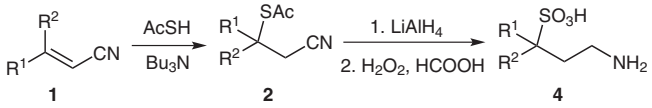


Entry	1	NuSH/M	Base	Solvent	Time (h)	Temp (°C)	Yield (%)
1	**1a**	KSCN	–	MeOH	6	reflux	0
2	**1a**	KSAc	–	MeOH	6	reflux	0
3	**1a**	AcSH	Et_3N	toluene	6	reflux	72
4	**1a**	$EtOCS_2Na$	–	AcOH	6	0	52
5	**1a**	piperidine + CS_2		H_2O	6	r.t.	62
6	**1a**	piperidine + CS_2		–	6	r.t.	91
7	**1c**	$EtOCS_2Na$	–	AcOH	6	0	<10
8	**1c**	piperidine + CS_2		–	72	r.t.	0
9	**1c**	AcSH	Et_3N	toluene	12	reflux	33
10	**1c**	AcSH	Et_3N	MeOH	12	reflux	trace
11	**1c**	AcSH	Et_3N	toluene	12	r.t.	0
12	**1c**	AcSH	Et_3N	THF	12	reflux	33
13	**1c**	AcSH	Et_3N	CCl_4	5	reflux	36
14	**1c**	AcSH	Bu_3N	CCl_4	5	reflux	40
15	**1c**	AcSH	Bu_3N	toluene	5	reflux	42

It can be seen from Table 2 that 1-arylhomotaurines **4c**–**g** were obtained in higher yields than 1-methylhomotaurine (**4b**). Homotaurine (**4a**) was not obtained by following the same procedure. We assumed that 3-aminopropane-1-thiol (**3a**) and 1-aminobutane-3-thiol (**3b**) may be more hydrophilic than 3-amino-1-arylpropane-1-thiols **3c**–**g**. Because of their high water-solubility it was only possible to extract **3b** in a lower yield, and **3a** could not be extracted at all. However, when 1-substituted taurines were syn-

thesized from thiiranes via the silver nitrate-catalyzed nucleophilic ring opening with ammonia, 1-aminoalkane-2-thiols could be extracted from aqueous solution without any problem to afford 1-substituted taurines in satisfactory to good yields.[19] To verify the assumption, after the reduction of 2-cyanoethyl thioacetate (**2a**) with lithium aluminum hydride and usual workup, the generated 3-aminopropane-1-thiol (**3a**) in the resulting aqueous solution was directly reacted with benzyl chloroformate in the presence of triethylamine to increase the hydrophobicity and aid in the extraction (Scheme 2). After usual workup, benzyl *N*-(3-mercaptopropyl)carbamate (**5**) was obtained in 25% yield, illustrating that the efficiency of the extraction was clearly improved. Compound **5** was further oxidized with performic acid to afford homotaurine (**4a**) in an excellent yield (97%; overall yield 24% from thioacetate **2a**). The results indicate lower molecular weight 1-aminoalkane-3-thiols are indeed hydrophilic and more difficult to extract from the aqueous solution than the corresponding 1-aminoalkane-2-thiols.

Table 2 Synthesis of Homotaurine (**4a**) and 1-Substituted Homotaurines **4b–g**



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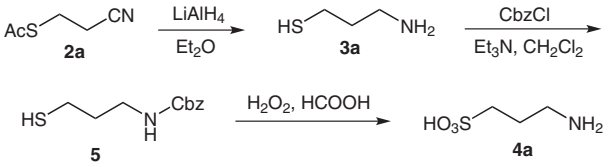
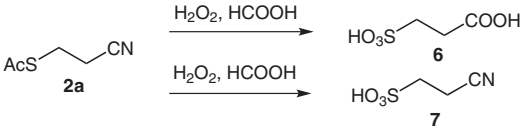
Entry	Nitrile **1**	R^1	R^2	Yield (%)	
				2	**4**
1	**1a**	H	H	72.6	24.3[a]
2	**1b**	Me	H	45.5	54.0
3	**1c**	Ph	H	41.5	62.5
4	**1d**	2-ClC_6H_4	H	68.3	85.6
5	**1e**	3-ClC_6H_4	H	67.5	75.2
6	**1f**	4-ClC_6H_4	H	66.0	74.8
7	**1g**	4-MeC_6H_4	H	31.2	82.3
8	**1h**	Et	Et	0	–
9	**1i**	Ph	Me	0	–
10	**1j**	Ph	Ph	0	–

[a] Overall yield from **2a** and after N-protection of 3-aminopropanethiol (**3a**) with benzyl chloroformate and subsequent oxidation with performic acid.



Scheme 2 Preparation of homotaurine (**4a**) from 2-cyanoethyl thioacetate (**2a**)

Alternatively, we also attempted to oxidize 2-cyanoethyl thioacetates **2** and then reduce the corresponding cyanoethanesulfonic acid. However, *S*-2-cyanoethyl thioacetate (**2a**) generated 3-sulfonopropanoic acid (**6**) in an excellent yield (98%) rather than cyanoethanesulfonic acid (**7**; Scheme 3).



Scheme 3 Oxidation of *S*-2-cyanoethyl thioacetate (**2a**) with performic acid

In summary, homotaurine and a series of 1-substituted homotaurines were conveniently synthesized through the Michael addition of thioacetic acid to α,β-unsaturated nitriles and subsequent reduction with lithium aluminum hydride and oxidation with peroxyformic acid. The current method is a general and convenient synthetic route to 1-substituted homotaurines. Compared with the previously reported methods, the current method is a general and convenient approach to the synthesis of 1-substituted homotaurines.

Melting points were measured with a Yanaco MP-500 melting point apparatus and are uncorrected. ^1H and ^{13}C NMR spectra were recorded with a Varian 300 plus (300 MHz) or a Bruker AV 400 (400 MHz) spectrometer either in $CDCl_3$ with TMS as an internal standard or in D_2O (with HCO_2H as an internal standard for ^{13}C NMR spectra). HRMS were carried out with an Agilent LC/MSD TOF mass spectrometer. IR spectra were determined with a Nicolet AVATAR 330 FT-IR spectrometer.

Thioacetic acid, acrylonitrile, and crotonitrile were purchased commercially. Et_2O was heated at reflux with sodium and diphenyl ketone until the color of system was blue, and freshly distilled prior to use. TLC analysis was performed on glass pre-coated silica gel YT257–85 (10–40 μm) plates; spots were visualized with UV light or iodine. Column chromatography was performed on silica gel zcx II (200–300 mesh). Petroleum ether (PE), where used, had a boiling range 60–90 °C.

Synthesis of α,β-Unsaturated Nitriles 1c–j from Aldehydes and Ketones; General Procedure

A 100-mL, three-necked, round-bottomed flask, equipped with a pressure equalizing addition funnel, reflux condenser, N_2 purge, and magnetic stirring bar, was charged with KOH (2.8 g, 50 mmol) and anhydrous MeCN (40 mL). The mixture was heated to reflux and a solution of an aldehyde or ketone (50 mmol) in MeCN (20 mL) was added in a stream. After the addition was complete, stirring was continued for the specified time (20 s–24 h; reaction monitored by TLC analysis) and then the hot solution was poured onto cracked ice. The mixture was extracted with CH_2Cl_2 (3 × 75 mL), dried over anhydrous Na_2SO_4, and evaporated under reduced pressure (during evaporation, the bath temperature was maintained at ca 30 °C in order to minimize decomposition). The crude product thus obtained was purified by flash column chromatography on silica gel (PE–EtOAc, 10:1) to afford the corresponding α,β-unsaturated nitrile. The analytical data of **1c–j** are identical to those reported in literature.[18,20]

Synthesis of *S*-2-Cyanoethyl Thioacetates 2 from α,β-Unsaturated Nitriles 1 and Thioacetic Acid; General Procedure

A 50 mL, three-necked, round-bottomed flask, equipped with a pressure equalizing addition funnel, reflux condenser, N_2 purge, and magnetic stirring bar, was charged with α,β-unsaturated nitrile **1** (5 mmol) and Bu_3N (3 drops) in anhydrous toluene (20 mL). The mixture was heated to 75–85 °C, and AcSH (0.5 mL, 0.46 g, 6 mmol) was slowly added dropwise. After the addition, the resulting solution was stirred for 5 h and then the mixture was evaporated in vacuo to remove the excess AcSH and solvent. The residue was purified by flash column chromatography on silica gel (PE–EtOAc, 8:1), affording *S*-2-cyanoethyl thioacetate [R_f = 0.50–0.65 (PE–EtOAc, 8:1)].

***S*-2-Cyanoethyl Thioacetate (2a)[21]**

Yield: 468 mg (72.6%); yellowish liquid; R_f = 0.65 (PE–EtOAc, 8:1).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.37 (s, 3 H, CH_3CO), 2.66 (t, *J* = 6.9 Hz, 2 H, CH_2), 3.10 (t, *J* = 6.9 Hz, 2 H, CH_2).

***S*-2-Cyanopropan-2-yl Thioacetate (2b)[22]**

Yield: 326 mg (45.5%); brown oil; R_f = 0.62 (PE–EtOAc, 8:1).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.42 (d, *J* = 7.2 Hz, 3 H, CH_3CO), 2.31 (s, 3 H, CH_3CO), 2.67 (dd, *J* = 6.4, 17.0 Hz, 1 H, CH_2CN), 2.73 (dd, *J* = 5.2, 17.0 Hz, 1 H, CH_2CN), 3.74 (ddq, *J* = 5.2, 6.4, 7.2 Hz, 1 H, CHS).

***S*-2-Cyano-1-phenylethyl Thioacetate (2c)[22]**

Yield: 426 mg (41.5%); yellow needle crystals; mp 76–77 °C; R_f = 0.59 (PE–EtOAc, 8:1).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.38 (s, 3 H, CH_3CO), 3.02 (d, *J* = 8 Hz, 2 H, CH_2CN), 4.84 (t, *J* = 8 Hz, 1 H, CH), 7.31–7.40 (m, 5 H, ArH).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 25.5, 30.4, 43.6, 116.9, 127.4, 128.7, 129.1, 137.5, 193.9.

***S*-1-(2-Chlorophenyl)-2-cyanoethyl Thioacetate (2d)**

Yield: 819 mg (68.3%); yellowish crystals; mp 89−90 °C; R_f = 0.55 (PE–EtOAc, 8:1).

IR (KBr): 2248 (CN), 1697 (C=O) cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.42 (s, 3 H, CH_3CO), 3.08 (dd, *J* = 6.0, 17.0 Hz, 1 H, CH_2CN), 3.14 (dd, *J* = 7.2, 17.0 Hz, 1 H, CH_2CN), 5.34 (dd, *J* = 6.0, 7.2 Hz, 1 H, CHS), 7.31–7.49 (m, 4 H, ArH).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 24.7, 30.7, 41.1, 117.0, 127.9, 129.7, 130.2, 130.6, 133.5, 135.2, 193.7.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{11}H_{11}ClNOS$: 240.0250; found: 240.0251.

***S*-1-(3-Chlorophenyl)-2-cyanoethyl Thioacetate (2e)**

Yield: 809 mg (67.5%); yellowish crystals; mp 65–67 °C; R_f = 0.50 (PE–EtOAc, 8:1).

IR (KBr): 2251 (CN), 1696 (C=O) cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.39 (s, 3 H, CH_3CO), 3.00 (dd, *J* = 7.3, 17.0 Hz, 1 H, CH_2CN), 3.05 (dd, *J* = 6.4, 17.0 Hz, 1 H, CH_2CN), 4.80 (dd, *J* = 6.4, 7.3 Hz, 1 H, CHS), 7.24–7.34 (m, 4 H, ArH).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 25.3, 30.5, 43.1, 116.6, 125.7, 127.7, 129.0, 130.4, 135.0, 139.6, 193.4.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{11}H_{11}ClNOS$: 240.0250; found: 240.0253.

***S*-1-(4-Chlorophenyl)-2-cyanoethyl Thioacetate (2f)**

Yield: 791 (66.0%); yellowish crystals; mp 82–83 °C; R_f = 0.55 (PE–EtOAc, 8:1).

IR (KBr): 2251 (CN), 1691 (C=O) cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.38 (s, 3 H, CH_3CO), 3.00 (dd, *J* = 7.4, 17.0 Hz, 1 H, CH_2CN), 3.04 (dd, *J* = 6.2, 17.0 Hz, 1 H, CH_2CN), 4.80 (dd, *J* = 6.2, 7.4 Hz, 1 H, CHS), 7.28–7.37 (m, 4 H, ArH).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 25.4, 30.5, 43.0, 116.7, 128.9, 129.4, 134.7, 136.1, 193.6.

HRMS (ESI): *m*/*z* [M + K]$^+$ calcd for $C_{11}H_{10}ClKNOS$: 277.9809; found: 277.9795.

***S*-2-Cyano-1-(4-methylphenyl)cyanoethyl Thioacetate (2g)**

Yield: 342 mg (31.2%); yellow crystals; mp 68–69 °C; R_f = 0.60 (PE–EtOAc, 8:1).

IR (KBr): 2254 (CN), 1693 (C=O) cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.37 (s, 3 H, CH_3), 2.39 (s, 3 H, CH_3), 3.00 (dd, *J* = 7.2, 17.0 Hz, 1 H, CH_2CN), 3.05 (dd, *J* = 6.5, 17.0 Hz, 1 H, CH_2CN), 4.83 (dd, *J* = 6.5, 7.2 Hz, 1 H, CHS), 7.20 (d, *J* = 8.1 Hz, 2 H, ArH), 7.25 (d, *J* = 8.1 Hz, 2 H, ArH).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 21.1, 25.6, 30.4, 43.5, 117.0, 127.3, 129.8, 134.4, 138.6, 194.1.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{12}H_{14}NOS$: 220.0796; found: 220.0789.

Synthesis of 1-Substituted Homotaurines 4b–g; General Procedure

To a suspension of $LiAlH_4$ (304 mg, 8 mmol) in anhydrous Et_2O (20 mL) in an ice–water bath, was added a solution of *S*-cyanoethyl thioacetate **2** (1 mmol) in anhydrous Et_2O (10 mL) dropwise. After the resulting solution was stirred in the ice-water bath for 12 h, the excess $LiAlH_4$ was quenched by adding H_2O (5 mL). The mixture was filtered through Celite and the filter cake was washed with CH_2Cl_2 (3 × 25 mL) and EtOAc (3 × 25 mL). The combined liquid phase was separated and the organic phase was dried over sodium sulfate and evaporated in vacuo to obtain a malodorous yellow oil, which was dissolved in anhydrous formic acid (4 mL). To the solution was added H_2O_2 (30% in H_2O, 1 mL). The resulting solution was stirred for 12 h to complete the reaction and decompose the excess H_2O_2. After removal of the solvents, a yellow odorless oil residue was obtained that was crystallized from a mixture of EtOH and Et_2O to give the corresponding 1-substituted homotaurine as colorless crystals.

1-Aminobutane-3-sulfonic Acid (4b)

Yield: 83 mg (54.0%); colorless crystals; mp 290–292 °C.

IR (KBr): 3448 (C=O), 1215 and 1169 (SO_2) cm^{-1}.

^{1}H NMR (400 MHz, D_2O): δ = 1.25 (d, *J* = 6.9 Hz, 3 H, CH_3), 1.80 (dddd, *J* = 6.4, 7.3, 9.1, 14.0 Hz, 1 H, CH_2), 2.12 (dddd, *J* = 6.2, 6.5, 9.3, 14.0 Hz, 1 H, CH_2), 2.95 (ddq, *J* = 6.2, 7.3, 6.9 Hz, 1 H, CHS), 3.09 (ddd, *J* = 6.4, 9.3, 12.8 Hz, 1 H, CH_2N), 3.10 (ddd, *J* = 6.5, 9.1, 12.8 Hz, 1 H, CH_2N).

^{13}C NMR (100 MHz, D_2O/HCOOH): δ = 15.1, 29.1, 37.8, 53.5.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_4H_{12}NO_3S$: 154.0538; found: 154.0535.

3-Amino-1-phenylpropane-1-sulfonic Acid (4c)

Yield: 135 mg (62.5%); colorless crystals; mp 313–314 °C.

IR (KBr): 3407 (OH, NH), 1238 and 1177 (SO_2) cm^{-1}.

^{1}H NMR (400 MHz, D_2O): δ = 2.35 (dddd, *J* = 5.2, 10.4, 10.6, 13.7 Hz, 1 H, CH_2), 2.50 (dddd, *J* = 4.8, 6.3, 10.8, 13.7 Hz, 1 H, CH_2), 2.76 (ddd, *J* = 5.2, 10.8, 12.2 Hz, 1 H, CH_2N), 2.93 (ddd, *J* = 6.3, 10.6, 12.2 Hz, 1 H, CH_2N), 4.03 (dd, *J* = 4.8, 10.4 Hz, 1 H, CHS), 7.34 (s, 5 H, ArH).

^{13}C NMR (100 MHz, D_2O): δ = 28.3, 37.5, 63.4, 128.7, 128.9, 129.1, 134.4.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_9H_{14}NO_3S$: 216.0694; found: 216.0691.

3-Amino-1-(2-chlorophenyl)propane-1-sulfonic Acid (4d)
Yield: 188 mg (75.2%); colorless crystals; mp 332–333 °C.

IR (KBr): 3437 (OH, NH), 1224 and 1175 (SO_2) cm^{-1}.

^1H NMR (400 MHz, D_2O): δ = 2.35 (dddd, *J* = 5.1, 10.2, 11.0, 13.7 Hz, 1 H, CH_2), 2.57 (dddd, *J* = 5.1, 5.1, 10.5, 13.7 Hz, 1 H, CH_2), 2.77 (ddd, *J* = 5.0, 10.5, 12.0 Hz, 1 H, CH_2N), 3.02 (ddd, *J* = 5.1, 11.0, 12.0 Hz, 1 H, CH_2N), 4.74 (dd, *J* = 5.1, 10.2 Hz, 1 H, CHS), 7.32 (d, *J* = 8.7 Hz, 2 H, ArH), 7.35 (d, *J* = 8.7 Hz, 2 H, ArH).

^{13}C NMR (100 MHz, D_2O/HCOOH): δ = 29.4, 37.9, 59.1, 128.2, 129.2, 130.4, 130.5, 132.8, 135.5.

HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_9H_{13}ClNO_3S$: 250.0305; found: 250.0313.

3-Amino-1-(3-chlorophenyl)propane-1-sulfonic Acid (4e)
Yield: 187 mg (74.8%); colorless crystals; mp 330–332 °C.

IR (KBr): 3421 (OH, NH), 1196 and 1037 (SO_2) cm^{-1}.

^1H NMR (300 MHz, D_2O): δ = 2.34 (dddd, *J* = 5.2, 10.4, 10.4, 13.7 Hz, 1 H, CH_2), 2.52 (dddd, *J* = 4.8, 6.0, 10.4, 13.7 Hz, 1 H, CH_2), 2.79 (ddd, *J* = 5.2, 10.4, 12.8 Hz, 1 H, CH_2N), 2.96 (ddd, *J* = 6.0, 10.4, 12.8 Hz, 1 H, CH_2N), 4.06 (dd, *J* = 4.8, 10.4 Hz, 1 H, CHS), 7.28–7.42 (m, 4 H, ArH).

^{13}C NMR (75 MHz, D_2O/HCOOH): δ = 23.6, 32.7, 52.7, 122.8, 123.9, 124.2, 125.6, 129.2, 131.8.

HRMS (ESI): *m*/*z* $[M + Na]^+$ calcd for $C_9H_{12}ClNNaO_3S$: 272.0124; found: 272.0124.

3-Amino-1-(4-chlorophenyl)propane-1-sulfonic Acid (4f)
Yield: 214 mg (85.6%); colorless crystals; mp 334–336 °C.

IR (KBr): 3438 (OH, NH), 1194 and 1170 (SO_2) cm^{-1}.

^1H NMR (400 MHz, D_2O): δ = 2.31 (dddd, *J* = 5.3, 10.4, 10.4, 13.7 Hz, 1 H, CH_2), 2.53 (dddd, *J* = 4.9, 6.0, 10.4, 13.7 Hz, 1 H, CH_2), 2.79 (ddd, *J* = 5.3, 10.4, 12.7 Hz, 1 H, CH_2N), 2.96 (ddd, *J* = 6.0, 10.4, 12.7 Hz, 1 H, CH_2N), 4.07 (dd, *J* = 4.9, 10.4 Hz, 1 H, CHS), 7.32 (d, *J* = 8.7 Hz, 2 H, ArH), 7.35 (d, *J* = 8.7 Hz, 2 H, ArH).

^{13}C NMR (100 MHz, D_2O/HCOOH): δ = 28.1, 37.3, 62.5, 127.3, 128.7, 130.4, 133.7.

HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_9H_{13}ClNO_3S$: 250.0305; found: 250.0303.

3-Amino-1-(4-methylphenyl)propane-1-sulfonic Acid (4g)
Yield: 189 mg (82.3%); colorless crystals; mp 350–352 °C.

IR (KBr): 3423 (OH, NH), 1208 and 1170 (SO_2) cm^{-1}.

^1H NMR (400 MHz, D_2O): δ = 2.16 (s, 3 H, CH_3), 2.25 (dddd, *J* = 5.2, 10.4, 10.4, 13.6 Hz, 1 H, CH_2), 2.41 (dddd, *J* = 4.8, 6.0, 10.4, 13.6 Hz, 1 H, CH_2), 2.66 (ddd, *J* = 5.2, 10.4, 12.4 Hz, 1 H, CH_2N), 2.84 (ddd, *J* = 6.0, 10.4, 12.4 Hz, 1 H, CH_2N), 3.91 (dd, *J* = 4.8, 10.4 Hz, 1 H, CHS),7.10 (d, *J* = 8.1 Hz, 2 H, ArH), 7.16 (d, *J* = 8.1 Hz, 2 H, ArH).

^{13}C NMR (100 MHz, D_2O/HCOOH): δ = 20.8, 28.9, 38.1, 63.6, 129.6, 130.0, 131.9, 139.5.

HRMS (ESI): *m*/*z* $[M + Na]^+$ calcd for $C_{10}H_{15}NNaO_3S$: 252.0670; found: 252.0678.

Synthesis of Homotaurine (4a)
To a suspension of $LiAlH_4$ (304 mg, 8 mmol) in anhydrous Et_2O (20 mL) in an ice–water bath, was added a solution of *S*-2-cyanoethyl thioacetate (**2a**; 129 mg, 1 mmol) in anhydrous Et_2O (10 mL) slowly dropwise. The resulting mixture was stirred in the ice–water bath for 12 h, then the excess $LiAlH_4$ was quenched by adding H_2O. The resulting mixture was filtered through Celite and the filter cake was washed with H_2O (3 × 15 mL) and CH_2Cl_2 (3 × 10 mL). To the liquid phase was added excess Et_3N (3.3 mL, 2.31 g, 23 mmol) in the ice–water bath. Then CbzCl (0.4 mL, 0.51 g, 3 mmol) was added dropwise slowly. After stirring overnight, the mixture was extracted with CH_2Cl_2 (3 × 25 mL) and EtOAc (3 × 25 mL). The combined organic phase was dried over anhydrous sodium sulfate and concentrated in vacuo. The residue was purified by flash column chromatography on silica gel (PE–EtOAc, 3:1) to afford benzyl *N*-(3-mercaptopropyl)carbamate (**5**) as colorless crystals [R_f = 0.13 (silica gel plate; PE–EtOAc, 3:1)].

The product was dissolved in anhydrous formic acid (4 mL). To the solution was added H_2O_2 (30% in H_2O, 1 mL) dropwise. After stirring for 12 h, the solution was evaporated in vacuo to remove solvents to give a yellow oil that was crystallized from a mixture of EtOH and Et_2O to afford pure homotaurine (**4a**).

Benzyl *N*-(3-Mercaptopropyl)carbamate (5)[23]
Yield: 56 mg (25%); colorless crystals; mp 91–92 °C.

^1H NMR (400 MHz, $CDCl_3$): δ = 1.93 (quint, *J* = 6.8 Hz, 2 H, CH_2), 2.73 (t, *J* = 6.8 Hz, 2 H, CH_2S), 3.32 (q, *J* = 6.8 Hz, 2 H, CH_2N), 5.11 (s, 2 H, CH_2), 7.33–7.36 (m, 5 H, ArH).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 29.3, 35.8, 39.6, 66.6, 128.1, 128.4, 136.5, 156.4.

Homotaurine (4a)
Yield: 34 mg (24.3%; two steps, overall yield from **2a**); colorless crystals; mp 293–295 °C (Lit.[24] 294–295 °C).

^1H NMR (400 MHz, D_2O): δ = 2.04 (quint, *J* = 8.0 Hz, 2 H, CH_2), 2.95 (t, *J* = 8.0 Hz, 2 H, CH_2N), 3.09 (t, *J* = 8.0 Hz, 2 H, CH_2SO_3).

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Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synthesis.

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