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Efficient Synthesis of Taurine and Structurally Diverse Substituted Taurines from Aziridines

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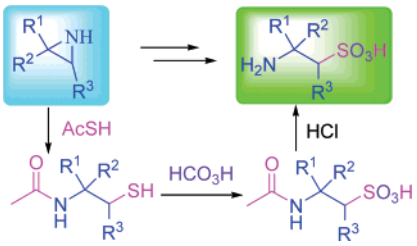

Taurine and substituted taurines were synthesized efficiently from aziridines via ring-opening reaction with thioacetic acid, oxidation with performic acid, and hydrolysis in hydrochloric acid. The current method shows more benefit in purification and efficiency in the preparation of taurine and structurally diverse 2-substituted, 2,2-disubstituted, and 1,2-, 2,2-, and 2,*N*-alkylene taurines.

Aminoalkanesulfonic acids, especially taurine and substituted taurines, are not only very important sulfur analogues of naturally occurring aminocarboxylic acids, but also one class of important naturally occurring amino acids,[1] which have been found in many mammalian tissues[2] and in marine algae, fish, and shellfish.[3] They are involved in various physiological processes.[4] On the other hand, their derivatives, such as sulfonopeptides, have been widely used as enzyme inhibitors during the last two decades because of their tetrahedrally structural properties.[1] Aminoalkanesulfonic acids have played more important roles in biological chemistry and medicinal chemistry recently. Thus, an efficient synthetic method of structurally diverse aminoalkanesulfonic acids is still desired. 1-Substituted taurines have been synthesized from β-amino secondary alcohols via the peroxy acid oxidation of their thioacetates[5] and the amine ring-opening reaction of episulfides, oxidation with performic acid, and subsequent hydrogenolysis.[6] 2-Substituted taurines have been synthesized effectively via the reduction of 2-nitroalkanesulfonic acids,[7] from β-amino primary alcohols via the sulfite displacement of their methanesulfonates[8,9] or via the peroxy acid oxidation of their thioacetates,[9] and via the sulfite ring-opening of aziridines.[10] 1,1-Disubstituted taurines have been synthesized via the ammonia ring-opening reaction of episulfides and subsequent oxidation with performic acid.[11] 1,2-Disubstituted taurines have been synthesized via the amino-sulfonation of olefins and subsequent hydrolysis[12] and the amine ring-opening reaction of episulfides and subsequent oxidation with performic acid.[6] Herein, we present an expeditious and practical method for the synthesis of 2-mono- and 1,2- and 2,2-disubstituted taurines from aziridines.

In our ongoing program aimed at the synthesis of structurally diverse aminoalkanesulfonic acids, we have developed some general methods to prepare 1-mono- and 1,1-disubstituted taurines effectively from episulfides.[6,11] We also found that 2-substituted taurines could be synthesized from aziridines via the nucleophilic ring-opening reaction with sodium sulfite.[10] However, purification is a tedious process to remove inorganic salts in the sodium sulfite substitution method, especially for large scaled preparations. We hoped to develop an efficient and practical method to synthesize structurally diverse substituted taurines, especially 2-mono- and 2,2-disubstituted taurines, from various aziridines without the tedious purification. In order to avoid inconvenience in purification in the final step, we sought methods to remove inorganic salts prior to the final step or without any inorganic salts in the whole prepararion. Peroxy acid oxidation of vicinal aminoalkyl isothiocyanates and vicinal amino primary mercaptans or their thioacetates should be an alternative method to prepare 2-mono- and 2,2-disubstituted taurines without the tedious purification.

We first selected (*S*)-2-benzylaziridine (**1a**) to prepare vicinal aminoalkyl isothiocyanate via the nucleophilic ring-opening reaction with potassium isothiocyanate. Unfortunately, no reaction occurs even under the catalysis of BF_3·Et_2O (Table 1, entries 1 and 2). We then attempted to prepare vicinal amino primary mercaptan from (*S*)-2-benzylaziridine (**1a**) via the nucleophilic ring-opening reaction with potassium thioacetate and subsequent in situ basic hydrolysis of thioacetates during workup (Scheme 1). Because amino mercaptans could be partially oxidized to disulfides in air, the ring-opening products were extracted from aqueous solution and oxidized directly to the substituted taurines. However, potassium thioacetate under-

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(1) For a recent review, see: Xu, J. X. *Chin. J. Org. Chem.* **2003**, *23*, 1.
(2) For a review, see: Timothy, C.; Birdsall, N. D. *Alt. Med. Rev.* **1998**, *3*, 128.
(3) Wickberg, B. *Acta Chem. Scand.* **1957**, *11*, 506.
(4) For a review, see: Huxtable, R. J. *Physiol. Rev.* **1992**, *72*, 101.
(5) (a) Brouwer, A. J.; Monnee, M. C. F.; Liskamp, R. M. J. *Synthesis* **2000**, 1579. (b) Lowik, D. W. P. M.; Liskamp, R. M. J. *Eur. J. Org. Chem.* **2000**, 1219. (c) Xu, J. X.; Xu, S. *Synthesis* **2004**, 276. (d) Xu, J. X.; Xu, S.; Zhang, Q. H. *Heteratom Chem.* **2005**, *16*, 466.
(6) Huang, J. X.; Wang, F.; Du, D. M.; Xu, J. X. *Synthesis*, **2005**, 2122.
(7) Gold, M. H.; Skebelsky, M.; Lang, G. *J. Org. Chem.* **1951**, *16*, 1500.
(8) (a) Higashiura, H.; Morino, H.; Matsuura, H.; Toyomaki, Y.; Ienaga, K. *J. Chem. Soc., Perkin. Trans. 1* **1989**, 1479. (b) Braghiroli, D.; Di Bella, M. *Tetrahedron: Asymmetry* **1996**, *7*, 2145. (c) Braghiroli, D.; Di Bella, M. *Tetrahedron Lett.* **1996**, *37*, 7319.
(9) (a) Higashiura, K.; Ienaga, K. *J. Org. Chem.* **1992**, *57*, 764. (b) Moree, W. J.; van der Marel, G. A.; Liskamp, R. M. J. *Tetrahedron Lett.* **1992**, *33*, 6389. (c) Moree, W. J.; van der Marel, G. A.; Liskamp, R. M. J. *J. Org. Chem.* **1995**, *60*, 5157. (d) Monnee, M. C. F.; Marijne, M. F.; Brouwer, A. J.; Liskamp, R. M. J. *Tetrahedron Lett.* **2000**, *41*, 7991.
(10) Xu, J. X. *Tetrahedron: Asymmetry* **2002**, *13*, 1129.
(11) Huang, J. X.; Du, D.-M.; Xu, J. X. *Synthesis* **2006**, 315.
(12) Cordero, F. M.; Cacciarini, M.; Machetti, F.; De Sarlo, F. *Eur. J. Org. Chem.* **2002**, 1407.

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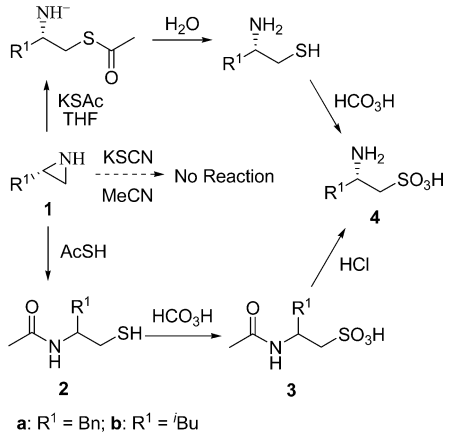
TABLE 1. Optimizing Reaction Conditions for Synthesis of 2-Substituted Taurines[a]

entry	aziridine	solvent	nucleophile	reaction conditions in the ring-opening[b]	overall yield, %[c]
1	**1a**	MeCN	KSCN	RT to reflux for 12 h	-
2	**1a**	MeCN, BF_3•Et_2O	KSCN	reflux for 12 h	-
3	**1a**	MeCN	AcSK	reflux for 12 h	-[d]
4	**1a**	EtOH/H_2O, 95:5 (v/v)	AcSK	reflux for 12 h	Trace[e]
5	**1a**	THF	AcSK	reflux for 12 h	40
6	**1a**	THF/H_2O, 95:5 (v/v)	AcSK	reflux for 12 h	40
7	**1a**	THF/H_2O, 95:5 (v/v)	AcSK	RT for 1d	55
8	**1a**	THF	AcSH	reflux for 12 h	61
9	**1a**	THF	AcSH	RT for 2d	87[f]
10	**1a**	benzene	AcSH	RT for 2d	91
11	**1b**	THF	AcSH	reflux for 12 h	64
12	**1b**	benzene	AcSH	RT for 2d	90

[a] Reaction was carried out in 10 mmol scale of aziridine with 20 mmol of nucleophile. [b] Ring-opening product was oxidized with performic acid for 1d and hydrolyzed in hydrochloric acid overnight. [c] Overall yield from the aziridine in each of cases. [d] Adduct of thioacetate to acetonitrile [AcSC(=NH)Me] was obtained as a major product in the ring-opening reaction. [e] Ethanol ring-opening product 1-ethoxy-3-phenyl-2-propylamine was obtained as a major product in the ring-opening reaction. [f] No obvious improvement in the yield (from 87% to 88%) was observed when the oxidation time was extended to 2 and 3 d.

SCHEME 1. Synthesis of Substituted Taurines



went an addition with the solvent acetonitrile as previously reported[13] when the reaction was conducted in polar acetonitrile (Table 1, entry 3). The ethanol ring-opening product was obtained as a major product when the reaction was carried out in a mixture of ethanol and water as solvents (Table 1, entry 4). The desired product **4a** was obtained in about 40% yields in a mixture of THF and water or in THF as solvents (Table 1, entries 5 and 6). The yield was improved to 55% when the reaction temperature was decreased to RT (Table 1, entry 7) (Scheme 1).

Because of difficult extraction of amino mercaptans from aqueous solution and low yields of the desired products, finally, we attempted to prepare vicinal *N*-acetylamino primary mercaptans from aziridines via the nucleophilic ring-opening reaction with thioacetic acid. In this way, we could avoid the use of any inorganic salt in the whole synthetic procedure. It is well-known that the direct ring-opening product vicinal amino mercaptan thioacetates favor an acyl shift to generate *N*-acetylaminomercaptans,[14] which could be partially oxidized to disulfide derivatives in air. To avoid separation and identification of these intermediates, the ring-opened products could be oxidized directly and hydrolyzed to substituted taurines because all of these intermediates could be converted to the final desired products in these treatments. We first conducted the acidic ring-opening reaction of (*S*)-2-benzylaziridine (**1a**) and (*S*)-2-isobutylaziridine (**1b**) in THF and subsequent oxidation with performic acid and hydrolysis in hydrochloric acid. The desired substituted taurines **4a** and **4b** were obtained in yields of 61 and 64%, respectively (Table 1, entries 8 and 11). However, some viscous byproducts were generated from the acidic ring-opening reaction of THF and the subsequent oxidation. The yield was improved by decreasing the temperature in the ring-opening reaction (Table 1, entry 9). The yields were further improved when the ring-opening reaction was conducted in benzene (Table 1, entries 10 and 12). Although this procedure includes multistep reactions, intermediates in the procedure can be used directly without any purification. Furthermore, extraction and chromatographic separation were avoided so that the workup in the whole procedure is very simple. The current method shows more benefit than the nucleophilic ring-opening reaction with sodium sulfite in the purification (removal of inorganic salts).[10] To determine efficiency in each of steps, we also separated, purified, and characterized the intermediates in the synthesis of substituted taurines **4a** and **4b**. The results indicate that almost quantitative yields were obtained in the oxidation and hydrolysis steps for each of the reactions, and the ring-opening steps are the yield-determining steps (see Experimental Section).

After successful preparation of (*S*)-2-benzyltaurine (**4a**) and (*S*)-2-isobutyltaurine (**4b**), we hoped to develop this procedure as a general, efficient, and practical method to synthesize structurally diverse substituted taurines. A series of aziridines, including 2-substituted, 2,2-disubstituted, bridged, and spiro cyclic aziridines, were prepared from vicinal amino alcohols via the Wenker reaction.[10,15] Following this same procedure, we synthesized taurine, 2-substituted, 2,2-disubstituted, and 1,2-, 2,2-, and 2,*N*-alkylene taurines in satisfactory to good total yields (Scheme 2 and Table 2).

For aziridines with poor solubility in benzene, the ring-opening reaction was conducted in polar solvent THF or a mixture of benzene and diethyl ether.

The results indicate that the acidic ring-opening reaction of aziridines with thioacetic acid shows the same regioselectivity

(13) Gauthier, J. Y.; Lebel, H. *Phosphorus Sulfur Silicon Relat. Elem.* **1994**, *95*, *96*, 325.

(14) (a) Kuhn, R.; Quadbeck, G. *Chem. Ber.* **1951**, *84*, 844. (b) Hsu, J.-L.; Fang, J.-M. *J. Org. Chem.* **2001**, *66*, 8573.

(15) (a) Wenker, H. *J. Am. Chem. Soc.* **1935**, *57*, 2328. (b) Leighton, P. A.; Perkins, W. A.; Renquist, M. I. *J. Am. Chem. Soc.* **1947**, *69*, 1540.

SCHEME 2. Synthesis of Taurine and Substituted Taurines from Aziridines and Thioacetic Acid

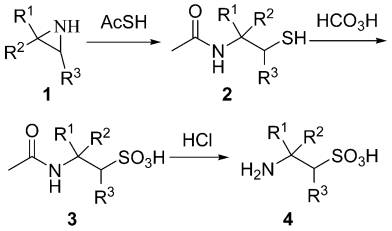
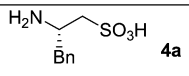
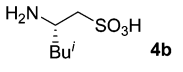
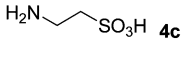
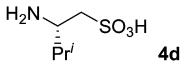
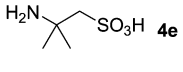
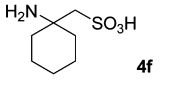
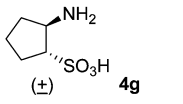
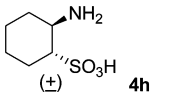
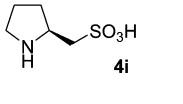


TABLE 2. Synthesis of Taurine and Substituted Taurines

Entry	Aziridine	Taurine	Total Yield (%)[a]
1	 **1a**	 **4a**	91
2	 **1b**	 **4b**	90
3	 **1c**	 **4c**	97[b]
4	 **1d**	 **4d**	70[b]
5	 **1e**	 **4e**	89
6	 **1f**	 **4f**	87
7	 **1g**	 **4g**	78[b]
8	 **1h**	 **4h**	78[b]
9	 **1i**	 **4i**	71[c]

[a] Total yield from aziridine. Ring-opening reaction was conducted in benzene. [b] Ring-opening reaction was conducted in THF. [c] Ring-opening reaction was conducted in benzene and diethyl ether (1:1, v/v).

in that the ring-opening occurs specifically at the less substituted carbon atom in unsymmetric aziridines, following the rule summarized previously by us.[16] For bridged bicyclic aziridines **1g** and **1h**, *trans*-2-aminocycloalkanesulfonic acids **4g** and **4h** were obtained due to the S_N2 substitution in the acidic ring-opening reaction. For optically pure aziridines, optically pure taurines were obtained without racemerization through the whole synthetic process on the basis of specific rotation comparison.

In summary, taurine and structurally diverse taurines, including linear 2-substituted and 2,2-disubstituted taurines and cyclic 1,2-, 2,2-, and 2,*N*-alkylene taurines, were synthesized expeditiously from various aziridines via the nucleophilic ring-opening reaction with thioacetic acid, subsequent oxidation with performic acid, and deacetylation in refluxing hydrochloric acid. Although most of the aziridines are not commercially available, they could be prepared easily via the Wenker method from commercially available vicinal amino alcohols. The current method is a highly efficient and convenient way for both laboratory and industrial large-scale preparation of highly pure and structurally diverse taurines, including optically pure substituted taurines.

(16) Ma, L. G.; Xu, J. X. *Chem. Prog.* **2004**, *16*, 220.

Experimental Section

General Procedure for the Ring-Opening Reaction of Aziridines with Thiolacetic Acid. To a solution of aziridine (10 mmol) in 50 mL of benzene [or THF for aziridines **1c**, **1d**, **1g**, **1h**, 1:1 (v/v) mixture of benzene and diethyl ether for the aziridine **1i**] was added thioacetic acid (1.522 g, 20 mmol). The resulting mixture was stirred at room temperature (about 10 °C) for 36 to 48 h. After removal of the solvent, oily or crystalline product *N*-acetylamino mercaptan was obtained and was used directly in the next step. Further purification on silica gel column chromatography with chloroform and methanol (1:1, v/v) as an eluent afforded pure *N*-acetylamino mercaptan.

(*S*)-*N*-(1-Mercaptomethyl-2-phenylethyl)acetamide (2a). Colorless crystals, yield 90%, mp 166−169 °C, lit.[17] mp 70−71 °C; $[\alpha]_D^{20} = -45.9$ (*c* 1.13, $CHCl_3$), Lit.[17] $[\alpha]_D^{20} = -18.8$ (*c* 1, $CHCl_3$); IR ν (cm^{-1}): 1708 (C═O); ^{1}H NMR (200 MHz, $CDCl_3$) δ: 1.94 (s, 3H), 2.75−2.85 (m, 1H), 2.89−3.01 (m, 2H), 2.98 (s, br, 1H), 3.55−3.65 (m, 1H), 4.36−4.46 (m, 1H), 6.52 (d, $J = 8.0$ Hz, 1H), 7.17−7.33 (m, 5H); ^{13}C NMR (50.0 MHz, $CDCl_3$) δ: 23.2, 38.6, 42.8, 50.3, 126.7, 128.6, 129.2, 137.2, 170.4.

(*S*)-*N*-(1-Mercaptomethyl-3-methylbutyl)acetamide (2b). Yellow oil, yield 87%, $[\alpha]_D^{20} = -41.7$ (*c* 1.30, $CDCl_3$); IR ν (cm^{-1}): 1645.6 (C═O); ^{1}H NMR (200 MHz, $CDCl_3$) δ: 0.92 (d, $J = 6.4$ Hz, 3H), 0.93 (d, $J = 6.6$ Hz, 3H), 1.32−1.40 (m, 2H), 1.55−1.68 (m, 1H), 2.00 (s, 3H), 3.46−3.55 (m, 1H), 3.62−3.70 (m, 1H), 3.74 (s, br, 1H), 4.00−4.11 (m, 1H), 6.29 (d, $J = 8.2$ Hz, 1H). ^{13}C NMR (50.0 MHz, $CDCl_3$) δ: 22.1, 22.9, 23.2, 24.8, 40.0, 49.8, 65.5, 171.2. MS (ESI) *m/z*: 176 $[M + H]^+$; HRMS (ESI) Cacld. for $C_8H_{17}NOS$ $[M + H]^+$ 176.1104; Found 176.1108.

General Procedure for the Oxidation of *N*-Acetylamino Mercaptans with Performic Acid. H_2O_2 (30%) (15 mL) was dissolved in 88% formic acid (35 mL) at 0 °C, and the mixture was stirred at 0 °C for 1 h to afford performic acid. The *N*-acetylamino mercaptan in 88% formic acid (5 mL) was carefully added dropwise to the performic acid solution. The resulting solution was allowed to warm to room temperature and stirred for 1 d. After removal of the solvent, viscous oily or crystalline *N*-acetylaminoalkanesulfonic acid was obtained and was used directly in the next step. Further purification via crystallization from methanol or washing with diethyl ether afforded pure *N*-acetylaminoalkanesulfonic acid.

(*S*)-2-Acetylamino-3-phenylpropane-1-sulfonic Acid (3a). Colorless crystals, yield 99%, mp 195−8 °C; $[\alpha]_D^{20} = +9.0$ (*c* 1.34, CH_3OH); IR ν (cm^{-1}): 1679 (C═O), 1127 (SO_2), 1023 (SO_2); ^{1}H NMR (200 MHz, D_2O) δ: 1.65 (s, 3H), 2.50−2.62 (m, 1H), 2.80−2.98 (m, 3H), 4.20−4.36 (m, 1H), 7.09−7.13 (m, 5H). ^{13}C NMR (50.0 MHz, HCO_2H) δ: 19.2, 38.9, 51.5, 52.5, 127.2, 128.6, 129.2, 135.4, 176.6; MS (ESI) *m/z*: 256 $[M - H]^-$; Anal. Calcd for $C_{11}H_{15}NO_4S \cdot 2HCO_2H \cdot 2/3H_2O$ (361.37): C, 43.21; H, 5.67; N, 3.88. Found: C, 43.02; H, 5.25; N, 4.30.

(*S*)-2-Acetylamino-4-methylpentane-1-sulfonic Acid (3b). Colorless oil, yield 99%, $[\alpha]_D^{20} = -18.2$ (*c* 1.10, CH_3OH); IR ν (cm^{-1}): 1650.2 (C═O), 1171.3 (SO_2), 1037.8 (SO_2); ^{1}H NMR (200 MHz, D_2O) δ: 0.70 (d, $J = 6.8$ Hz, 3H), 0.77 (d, $J = 6.8$ Hz, 3H), 0.98−1.25 (m, 2H), 1.30−1.50 (m, 1H), 1.82 (s, 3H), 3.25−3.53 (m, 1H), 3.70−3.80 (m, 1H), 3.89−4.09 (m, 1H); ^{13}C NMR (75.5 MHz, HCO_2H) δ: 21.1, 21.4, 22.2, 24.3, 39.0, 47.7, 65.8, 175.0; MS

(17) Han, M. S.; Oh, D. J.; Kim, D. H. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 701.

(ESI) *m/z*: 222 $[M - H]^-$; HRMS (ESI) Calcd for $C_8H_{17}NO_4S$ $[M - H]^-$ 222.0806; Found 222.0802.

General Procedure for the Deacetylation of *N*-Acetylaminoalkanesulfonic Acids in Hydrochloric Acid. Crude *N*-acetylaminoalkanesulfonic acid was dissolved in 10% hydrochloric acid (50 mL), and the solution was refluxed overnight. After removal of the solvent, the crude product was recrystallized from a mixture of methanol and chloroform, or methanol and water, to afford the pure product aminoalkanesulfonic acid.

Taurines **4a** and **4b** were obtained in the yield of 99% from purified *N*-acetyltaurines **3a** and **3b**.

(*S*)-2-Amino-4-methylpentane-1-sulfonic Acid (4b). Colorless crystals, mp 343−6 °C (dec); $[\alpha]_D^{20} = +27.3$ (*c* 1.03, HCO_2H); IR υ (cm^{-1}): 1184.7 (SO_2), 1039.9 (SO_2); ^1H NMR (200 MHz, D_2O) δ: 0.81 (d, $J = 5.7$ Hz, 3H), 0.82 (d, $J = 4.8$ Hz, 3H), 1.45−1.63 (m, 3H), 2.98 (dd, $J = 9.6$, 15.0 Hz, 1H), 3.15 (dd, $J = 3.0$, 15.0 Hz, 1H), 3.60 (dd, $J = 3.0$, 9.6 Hz, 1H). ^{13}C NMR (75.5 MHz, HCO_2H) δ: 20.8, 21.5, 23.8, 40.8, 48.1, 51.6; MS (ESI) *m/z*: 182 $(M + H)^+$, 204 $(M + Na)^+$; Anal. Calcd for $C_6H_{15}NO_3S \cdot 1/2HCl$ (199.48): C, 36.13; H, 7.83; N, 7.02. Found: C, 35.99; H, 7.56; N, 7.00.

(1-Amino-cyclohexyl)methanesulfonic Acid (4f). Colorless crystals, mp 331 °C (dec); IR υ (cm^{-1}): 1187.5 (SO_2), 1040.6 (SO_2); ^1H NMR (200 MHz, D_2O) δ: 1.21−1.56 (m, 8H), 1.85−1.96 (m, 2H), 3.22 (s, 2H); ^{13}C NMR (75.5 MHz, HCO_2H) δ: 20.7, 23.7, 33.7, 53.6, 56.9; MS (ESI) *m/z*: 194 $(M + H)^+$; Anal. Calcd for $C_7H_{15}NO_3S$ (193.26): C, 43.50; H, 7.82; N, 7.25. Found: C, 43.19; H, 7.96; N, 7.02.

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Supporting Information Available: Experimental details, additional analytical data, copies of ^{13}C NMR spectra of known substituted taurines, and copies of ^1H and ^{13}C NMR spectra of *N*-acetylamino mercaptans **2a** and **2b**, *N*-acetylaminoalkanesulfonic acids **3a** and **3b**, taurine, and unknown substituted taurines. This material is available free of charge via the Internet at http://pubs.acs.org

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