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Taurine isothiocyanate: a versatile intermediate for the preparation of ureas, thioureas, and guanidines. Taurine-derived cyclodextrins

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Abstract

A versatile and expeditious synthesis of taurine-derived thioureas, ureas, and guanidines using taurine isothiocyanate as the key intermediate is reported. Thioureas were obtained by a one-pot two-step procedure starting from taurine by the isothiocyanation reaction with thiophosgene in aqueous THF, followed by coupling with aliphatic and aromatic amines. Desulfurization of thiourea derivatives with yellow mercury(II) oxide gave access to either taurine-containing ureas or guanidines in a one-pot three-step fashion. This methodology was successfully applied to the preparation of a cyclodextrin-derived thiourea and guanidine with a taurine residue in their structures.

Keywords: Taurine; Isothiocyanate; Thioureas; Ureas; Guanidines; Cyclodextrin

Taurine, or 2-aminoethanesulfonic acid, is a natural β-sulfoaminoacid that is not incorporated into proteins, but is particularly abundant as a free amino acid in all mammalian electrically excitable tissues such as heart, brain, retina, and skeletal muscles.[1,2] Although it was isolated from the animal tissues more than two hundred years ago, its biological activities and beneficial effects have been recently rediscovered.[1,3] Taurine is involved in brain and retina development, neurotransmission, osmoregulation, and immunomodulation;[1,2,4,5] numerous studies show that taurine also exerts an antioxidant activity by scavenging reactive oxygen species (ROS) such as endogenously generated hypochlorous acid,[6] nitric oxide or H_2O_2.[7]

Although the exact antioxidant mechanism still remains unclear, the promising in vivo and in vitro studies suggest that this sulfoaminoacid might be considered as a potential drug to ameliorate the oxidative stress[8,9] in diseases such as diabetes.[10,11] Furthermore, taurine has been described to play a protective role in spinal cord injury[12] and a detoxificant role against some toxins such as heavy metals[13] or against vitamin A excess.[14]

The exceptional properties showed by taurine have prompted the researchers to prepare a plethora of derivatives[3,15–17] among which acamprosate (calcium 3-acetylaminopropane-1-sulfonate) has a predominant place, as it has recently been approved for the clinical treatment of alcoholism.[18,19] Other taurine derivatives such as taltrimide and tauromustine are commercialized as anti-convulsant and anti-cancer agents,[3] respectively. Some different applications of taurine derivatives comprise nanosensors,[20] organogelators[21] or water-soluble dyes.[22]

In this context, we now describe a novel methodology for the easy and practical preparation of taurine-derived thioureas, ureas, and guanidines, families of compounds with both synthetic and biological interests.[23–26] Despite the vast amount of taurine derivatives described so far,[3,27] reports on the synthesis of thioureas, ureas, and guanidines are very scarce,[28,29] and never involving taurine isothiocyanate or isocyanate.

We have used the sodium salt of taurine isothiocyanate as the key and versatile intermediate for the preparation of these compounds. There is only one report for the

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preparation of the potassium salt of taurine isothiocyanate, used as an intermediate in the synthesis of thiazolines;[30] however, the procedure described by the authors turns out to be quite tedious and expensive, and consists of sequential treatment of taurine with DBU, carbon disulfide, *N*,*N*′-diisopropylcarbodiimide, and potassium thiocyanate in an acetonitrile–pyridine mixture. Furthermore, no characterization data for the title compound are included. Bültmann and co-workers reported[31] the use of the sodium salt of taurine isothiocyanate **2** as a potential P_2-purinoceptor antagonist; this compound was synthesized from taurine by the addition of thiophosgene, but neither experimental nor spectroscopy data are included.

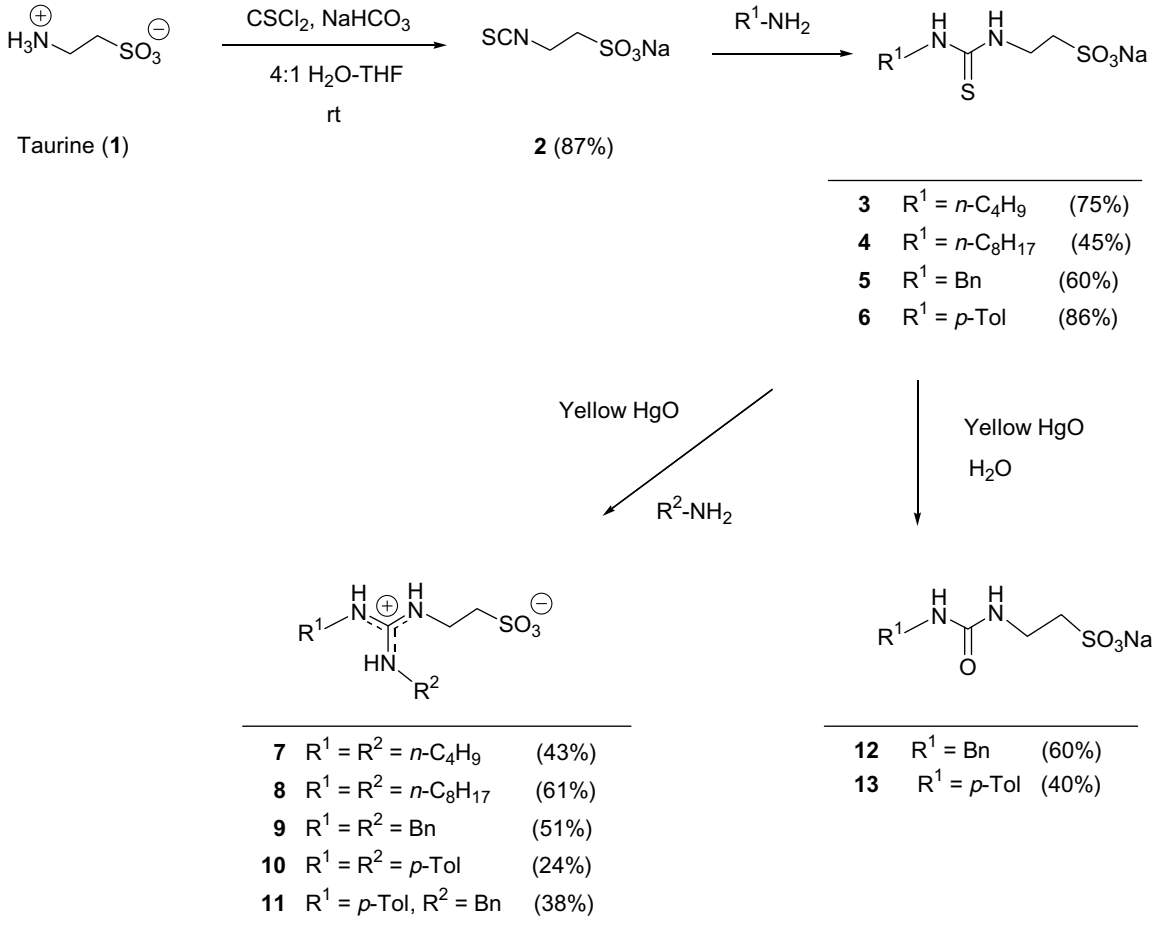
On the contrary, we have prepared crystalline isothiocyanate **2**[32] in quite an effective and operative fashion by the treatment of taurine with thiophosgene in aqueous THF in the presence of $NaHCO_3$ as a mild base (Scheme 1), using similar conditions as those reported by us for the preparation of glycopyranosyl isothiocyanates.[33] Purification by column chromatography afforded compound **2** in an 87% yield, and remarkably, the reaction could be performed in a multi-gram scale.

Compound **2** could be in situ transformed into thioureas **3**–**6** by the addition of both aliphatic and aromatic amines to the reaction medium, without the necessity of first isolating or purifying the isothiocyanate; these thioureas were obtained in a 45–86% yield for the two steps after column chromatography.[34]

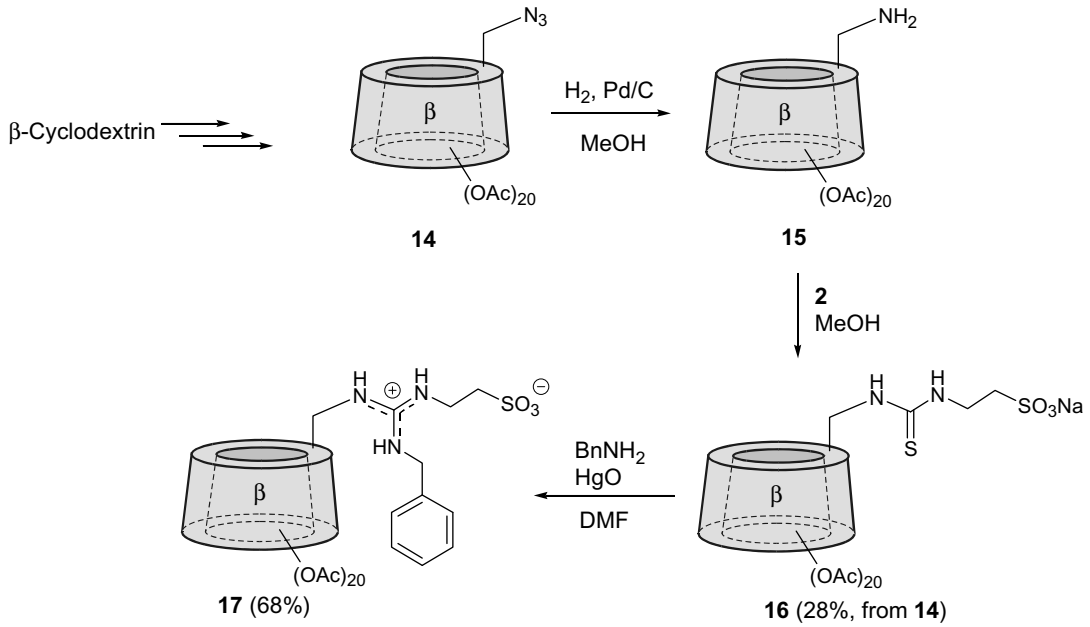
This one-pot procedure could be extended one more step; thus, in situ treatment of crude taurine-containing thioureas with yellow mercury(II) oxide as a desulfurizating agent (Scheme 1), in the presence of aromatic and aliphatic amines afforded guanidines **7**–**11** (24–61%, three steps). It is noteworthy mentioning that zwitterionic guanidines were isolated as solid pure compounds without chromatography. Reaction must proceed through a transient carbodiimide which spontaneously undergoes addition of the amine.[33] It is remarkable that despite using an aqueous medium, the higher nucleophilicity of the amine toward water affords the desired guanidines as the major compounds. An example of a natural taurine-derived guanidine is asterubine, 2-[(dimethylamino)iminomethyl]aminoethanesulfonic acid, isolated from starfish, which displays a plant growth-promoting effect.[35]

Following the same synthetic pathway, the addition of yellow mercury(II) oxide to the crude thioureas **5** and **6**, without the presence of an extra amine, afforded ureas **12** and **13** in a 60% and 40% yield, respectively (Scheme 1).[36]

We decided to extend our methodology to the preparation of taurine-containing cyclodextrins; the latter are macrocyclic oligosaccharides with a truncated-cone structure bearing a hydrophobic cavity capable of forming



Scheme 1.



Scheme 2.

inclusion complexes.[37] This property makes these compounds to be very valuable carbohydrate derivatives in supramolecular chemistry, with interesting practical applications such as drug carriers, catalysts, chiral separations or food additives.[38]

Monoazido derivative **14** is easily available[39] in three steps starting from β-cyclodextrin; this compound can be subjected to Pd-catalyzed hydrogenation to afford transient amine **15** which can be used without further purification for the coupling reaction with taurine isothiocyanate **2** to afford thiourea **16** in a 28% yield from **14**.[40] (Scheme 2). The low yield obtained for compound **16** can be explained considering a partial acetyl migration to the amino group of **15**.

The transformation of **16** into guanidine **17**[41] was achieved by the treatment of the former with yellow mercury(II) oxide in DMF in the presence of benzylamine, in a 68% yield.

In conclusion, we have developed an easy and practical methodology for the preparation of taurine-derived thioureas, ureas, and guanidines, using taurine isothiocyanate as a versatile intermediate. The most highlighting aspect of this procedure is that final compounds can be obtained in a one-pot procedure starting from taurine, without intermediate purifications. The same methodology was successfully applied to the preparation of a cyclodextrin-derived thiourea and guanidine, compounds of interest in the supramolecular chemistry field.

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32. Data for compound **2**: To a solution of taurine (100 mg, 0.799 mmol) in 4:1 water–THF (10 mL) $NaHCO_3$ was added (228 mg, 2.72 mmol) and the mixture was stirred for 15 min at rt. Then, thiophosgene (73 μL, 0.96 mmol) was added and the mixture was stirred for 40 min at rt. The mixture was concentrated to dryness and the residue was purified by column chromatography (CH_2Cl_2→5:1 CH_2Cl_2–MeOH), to give **2** as a solid. mp: 230 °C (desc.); IR ν_{max} 3605, 3518, 2207, 2120, 1609, 1352, 1209, 1053, 806 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6) δ 3.85 (t, 2H, $J_{H,H} = 6.9$ Hz, CH_2NCS), 2.79 (t, 2H, CH_2SO_3Na); ^{13}C NMR (75.5 MHz, DMSO-d_6) δ 127.3 (NCS), 50.1 (CH_2SO_3Na), 41.5 (CH_2NCS); HRLSIMS: $[M+Na]^+$ calcd for $C_3H_4NNa_2O_3S_2$, 211.9428; found, 211.9427.
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34. Selected data for **6**: IR ν_{max} 3449, 1534, 1485, 1262 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6) δ 9.67 (s, 1H, PhN*H*), 7.86 (br t, 1H, $J_{NH,CH} = 5.2$ Hz, N*H*CH_2CH_2), 3.75 (q, 2H, $J_{H,H} = 6.2$ Hz, NHCH_2CH_2), 2.71 (t, 2H, $J_{H,H} = 6.2$ Hz, CH_2SO_3); ^{13}C NMR (75.5 MHz, DMSO-d_6) δ 179.8 (C=S); HRLSIMS: $[M+Na]^+$ calcd for $C_{10}H_{13}N_2Na_2O_3S_2$, 319.0163; found, 319.0159.
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36. Selected data for **12**: IR ν_{max} 3377, 1700, 1630 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6) δ 6.73 (t, 1H, $J_{H,H} = 6.0$ Hz, N*H*Bn), 6.09 (t, 1H, $J_{H,H} = 5.6$ Hz, N*H*CH_2), 3.30 (q, 2H, $J_{H,H} = 6.4$ Hz, CH_2N), 2.56 (t, 2H, CH_2S) ppm; ^{13}C NMR (75.5 MHz, DMSO-d_6) δ 158.0 (CO); HRLSIMS: $[M+Na]^+$ calcd for $C_{10}H_{13}N_2Na_2O_4S$, 303.0391; found, 303.0388.
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40. Data for compound **16**: A suspension of monoazido **14** (80 mg, 0.040 mmol) and 10% Pd/C (25 mg) in MeOH (1.5 mL) was hydrogenated at atmospheric pressure and rt for 3 h. Then, it was filtrated through a Celite pad and the filtrate was concentrated to dryness to give crude **15**, which was used for the next step without further purification. The residue was dissolved in a 2:1 H_2O–THF mixture (3 mL), and to the corresponding solution was added isothiocyanate **2** (7.6 mg, 0.040 mmol). The reaction was kept stirring at rt for 12 h, and then the solvent was eliminated under reduced pressure and the residue was purified by column chromatography (CH_2Cl_2→10:1 CH_2Cl_2–MeOH) to afford **16** (24 mg, 28%, 2 steps). $[\alpha]_D^{25}$ +68 (*c* 1.3, CH_2Cl_2); IR ν_{max} 2926, 2360, 1748, 1653, 1541, 1373, 1236, 1043, 901 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 5.44–5.23 (m, 7H, H-3$^{A–G}$), 5.15 (br s, 1H, NH), 5.10 (d, 1H, $J_{1,2} = 3.7$ Hz, H-1), 5.08 (d, 1H, $J_{1,2} = 3.8$ Hz, H-1), 5.05 (d, 1H, $J_{1,2} = 3.1$ Hz, H-1), 5.10–4.99 (m, 4H, H-1), 4.85 (dd, 1H, $J_{2,3} = 10.6$ Hz, H-2), 4.83 (dd, 1H, $J_{2,3} = 9.0$ Hz, H-2), 4.73 (dd, 1H, $J_{2,3} = 9.9$ Hz, H-2), 4.86–4.73 (m, 4H, H-2), 4.67–4.47 (m, 7H, H-6a$^{B–G}$, NH), 4.42–4.27 (m, 6H, H-6b$^{B–G}$), 4.17–4.08 (m, 6H, H-5$^{B–G}$), 3.93 (m, 1H, H-5^{A}), 3.83 (m, 1H, H-6^{aA}), 3.75–3.64 (m, 10H, H-4$^{A–G}$, H-6b^{A}, CH_2N), 3.11 (m, 2H, CH_2S), 2.15–2.00 (20s, 60H, 20Ac); ^{13}C NMR (125.7 MHz, $CDCl_3$) δ 183.2 (C=S), 171.5–170.2, 169.8–169.2 (20 CO), 97.8–96.2 (C1$^{A–G}$), 77.8–76.5 (C4$^{A–G}$), 72.0–69.0 (C2$^{A–G}$, C3$^{A–G}$, C5$^{A–G}$), 63.2–62.1 (C6$^{B–G}$), 50.2 (*C*H_2S), 45.8 (C6^{A}), 40.4 (*C*H_2N), 20.9–20.7 (20OAc); HRLSIMS: $[M+Na]^+$ calcd for $C_{85}H_{115}N_2Na_2O_{57}S_2$, 2185.5398; found, 2185.5341.
41. Data for compound **17**: To a solution of thiourea **16** (46 mg, 0.021 mmol) in DMF (1 mL) were added benzylamine (2.3 μL, 0.021 mmol) and mercury(II) oxide (18 mg, 0.083 mmol), and the corresponding mixture was vigorously stirred in the darkness for 48 h. Then, it was filtrated through a Celite pad and the filtrate was concentrated to dryness; the residue was purified by column chromatography (CH_2Cl_2→20:1 CH_2Cl_2–MeOH) to afford **17** (32 mg, 68%). $[\alpha]_D^{25}$ +90 (*c* 1.2, CH_2Cl_2); IR ν_{max} 2931, 1748, 1653, 1541, 1373, 1235, 1042, 668 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.36–7.28 (m, 5H, Ar-H), 5.34–5.23 (m, 7H, $J_{2,3} = 9.6$ Hz, H-3$^{A–G}$), 5.12 (d, 1H, $J_{1,2} = 4.0$ Hz, H-1), 5.10 (d, 1H, $J_{1,2} = 4.0$ Hz, H-1), 5.08 (d, 1H, $J_{1,2} = 4.0$ Hz, H-1), 5.06 (d, 2H, $J_{1,2} = 3.8$ Hz, H-1), 5.05 (d, 2H, $J_{1,2} = 3.8$ Hz, H-1), 4.92 (dd, 1H, H-2), 4.83 (dd, 1H, H-2), 4.79 (dd, 1H, H-2), 4.76 (dd, 1H, H-2), 4.74 (dd, 1H, H-2), 4.73 (dd, 2H, H-2), 4.70 (m, 1H, H-6a), 4.57–4.42 (m, 7H, H-6a, CH_2Ph), 4.36–4.20 (m, 5H, $J_{5,6b} = 4.2$ Hz, $J_{6a,6b} = 13.0$ Hz, H-6b), 4.14–3.98 (m, 8H, H-5, H-6b), 3.91 (m, 1H, H-6a^{A}), 3.77–3.60 (m, 10H, H-4, H-6b^{A}, CH_2N), 3.04 (m, 2H, CH_2S), 2.14–1.99 (20s, 60H, 20Ac); ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.2, 171.0, 170.9, 170.8, 170.7, 170.6, 170.5, 170.4, 169.7, 169.6, 169.5, 169.4, (CO), 156.8 (C=N), 136.1, 129.2, 128.8, 127.6 (Ar), 97.3, 97.1, 97.0, 96.8, 96.7, 96.4 (C-1$^{A–G}$), 77.4, 76.5, 76.3 (C-4$^{A–G}$), 71.5–69.3 (21C, C-2$^{A–G}$, C-3$^{A–G}$, C-5$^{A–G}$), 62.6–62.3 (6C, C-6$^{B–G}$), 49.8 (*C*H_2S), 45.8 (*C*H_2Ph), 42.0 (C-6^{A}), 39.8 (*C*H_2N), 20.9 (20 OAc); HRLSIMS: $[M+Na]^+$ calcd for $C_{92}H_{123}N_3NaO_{57}S$, 2236.6437; found, 2236.6619.