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Efficient synthesis of *N*-protected 1-substituted homotaurines from a xanthate and olefins

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ABSTRACT

A series of *N*-protected 1-substituted homotaurines was synthesized efficiently from various olefins with *O*-ethyl *S*-2-phthalimidomethylxanthate as a sulfur-aminomethylation reagent via a radical addition and subsequent performic acid oxidation. The current method is a convenient and practical method for the synthesis of 1-substituted homotaurines with high yields and short synthetic route.

1. Introduction

Homotaurine, 3-amino-1-propanesulfonic acid, was a candidate drug for treating Alzheimer's disease (AD) due to its great biological activities of neuroprotective and amyloid antagonist.[1] However, it has failed in clinical treatment of Alzheimer's disease. On the other hand, homotaurine and substituted homotaurines are structural analogs and mimetics of γ-aminobutryic acid (GABA), which is of great importance as a specific inhibitor of impulse transmission in the central nervous system.[2] Thus, several methods for synthesis of substituted homotaurines have been developed.

Several 1-substituted homotaurines have been synthesized till now. For instance, 1-carboxyhomotaurine was prepared from methyl 2,4-dibromobutanoate via displacement with thiolacetic acid, oxidation with performic acid, and subsequent substitution with sodium azide, acidic hydrolysis, and hydrogenation.[3] 1-Substituted homotaurines were also synthesized from α,β-unsaturated nitriles via the Michael addition with thiolacetic acid, reduction with lithium aluminum hydride, and oxidation with performic acid.[4] 2-Methylhomotaurine was first synthesized as competitive antagonists of the GABA receptor via addition of methacrolein with sodium bisulfite and subsequent reductive amination.[5] 2-Phenylhomotaurine was prepared from phenyl styrenesulfonate via addition of nitromethane and subsequent catalytic hydrogenation and hydrolysis.[6] 2-(4-Chlorophenyl) homotaurine was considered as important antagonist of GABA and was synthesized from 1-(4-chlorophenyl)acrylonitrile via addition with sodium bisulfite and subsequent reduction,[7] via the oxygen-catalyzed radical addition of bisulfite to 2-(4-chlorophenyl)allylamine or their *N*-phthalyl derivatives.[8] 3-Carboxyhomotaurine was prepared via hydrolysis of 2-(2,5-dioxoimidazolidin-4-yl)ethanesulfonic acid[9] or via oxidation of homocysteine with peroxy acid.[10] 3-Substituted homotaurines were synthesized via the Horner–Wadsworth–Emmons reaction of *N*-protected α-aminoalkanals and ethyl (diethoxyphosphoryl) methanesulfonate and subsequent hydrogenation and deprotection.[11] Ring-opening reactions of substituted propane-1,3-sultones with ammonia or with sodium azide followed by reduction were applied for synthesis of variously substituted homotaurines.[12] 3-Nitroalkanesulfonic acids, the precursors of 1,3-disubstituted homotaurines, were obtained via addition of arylmethanesulfonates to nitroolefins in the presence of *n*-butyl lithium.[13] In addition, a cyclic substituted homotaurine, considered as a 1,3-disubstituted homotaurine, was synthesized via Diels–Alder reaction of cyclopentadiene and *N*-sulfinyl carbamate and subsequent basic hydrolysis and performic acid oxidation.[14] Recently, *cis*- and *trans*-2-aminomethylcyclopropane-1-sulfonic acids were synthesized via diazoester addition to olefins as a key step and were applied as conformationally restricted GABA analogs as pharmacological tools to study GABA receptor subtypes.[2,15]

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Although several synthetic methods have been developed for the preparation of substituted homotaurines, most methods are not general and practical.[3–15] Recently, we focus on the synthesis of substituted homotaurines. 1-Substituted homotaurines were prepared from α,β-unsaturated nitriles[4] and different substituted homotaurines were synthesized from α,β-unsaturated 2-alkenamides.[16] However, commercially available α,β-unsaturated nitriles and 2-alkenamides are limited, restricting the application of these two methods. Very recently, we prepared various 1-substituted taurines from *N*-allylphthalimide and various xanthates.[17] Abundant olefins are commercially available. Thus, we hope to use diverse olefins as starting materials to synthesize *N*-protected 1-substituted homotaurines via a radical addition with *O*-ethyl *S*-2-phthalimidomethylxanthate as an efficient sulfur-aminomethylation reagent and performic acid oxidation. The *N*-protected 1-substituted homotaurines are useful building blocks for synthesis of sulfonopeptides and potential GABA receptors. Herein, we present our efficient synthesis of 1-substituted homotaurines.

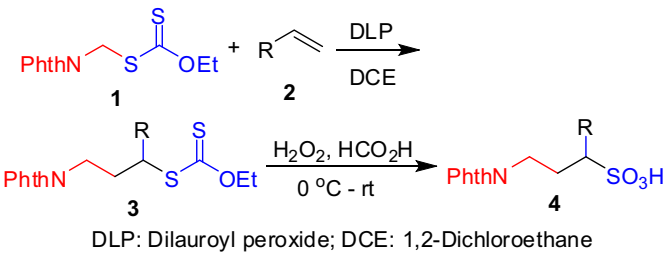
2. Results and discussion

In our investigation, *O*-ethyl *S*-2-phthalimidomethylxanthate (**1**) was selected as a useful sulfur-aminomethylation reagent to olefins and prepared via the displacement of potassium *O*-ethyl xanthate with *N*-chloromethylphthalimide, which was synthesized from phthalimide via condensation with formaldehyde and subsequent chlorination with thionyl chloride.[18] *O*-Ethyl *S*-2-phthalimidomethylxanthate (**1**) reacted with various simple olefins **2a**–**f** under the catalysis of dilauroyl peroxide (DLP) as a radical initiator in refluxing dichloroethane (DCE) to afford *O*-ethyl *S*-1-phthalimidoalkan-3-yl xanthate derivatives **3a**–**f** in satisfactory to good yields (Table 1, entries 1–6) (Scheme 1). For these simple olefins, no big difference was observed in yields except for olefin **2a**, which shows a relatively lower yield possibly because of the loss of olefin **2a** when refluxed in the condenser during reaction due to its lower boiling point (Table 1, entry 1). However, the reaction of xanthate **1** and styrene (**2g**) did not produce the desired product, instead, polystyrene was observed (Table 1, entry 7). We also tried to use BPO (benzoyl peroxide) and AIBN (azodiisobutyronitrile) as radical initiators in the reaction of styrene. However, no desired adduct was observed as well. Xanthate **1** was recovered in 91% and 96%, respectively, and polystyrene was observed in each of cases. The results indicate that it is a competitive reaction between the radical addition and

Table 1
Synthesis of *N*-phthalyl 1-substituted homotaurines **4**

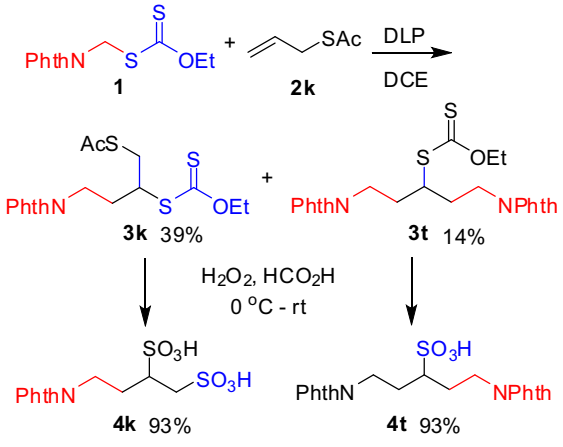
Entry	Olefin	R	**3** Yield (%)	**4** Yield (%)
1	**2a**	*n*-Bu	62	92
2	**2b**	*n*-Hex	73	90
3	**2c**	$^{c}HexCH_2$	79	92
4	**2d**	$Ph(CH_2)_3$	74	91
5	**2e**	$Ph(CH_2)_2$	83	91
6	**2f**	$PhCH_2$	73	90
7	**2g**	Ph	—	—
8	**2h**	CH_2OH	63	93
9	**2i**	CH_2OPh	95	87
10	**2j**	CH_2OAc	84	91 (**4h**)
11	**2k**	CH_2SAc	39	93[b]
12	**2l**	CH_2NPhth	84	90
13	**2m**	CH_2NHCbz	74	90
14	**2n**	CH_2NHBoc	74	89[c]
15	**2o**	CH_2NHBn	—[a]	—
16	**2r**	CO_2Et	—	—
17	**2s**	$CONH_2$	—	—

[a] Bis(phthalimidomethy1) disulfide was obtained in 53% yield.
[b] 4-Phthalimidobutane-1,2-disulfonic acid was obtained in 93% yield.
[c] 1-Amino-4-phthalimidobutane-2-sulfonic acid was obtained in 89% yield.



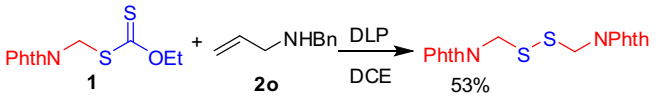
Scheme 1. Synthesis of *N*-phthalyl 1-substituted homotaurines.

polymerization and the competitive reaction is dependent on the structure of olefins rather than initiators. To synthesize 1-substituted homotaurines with different functionalized side-chains, a series of functionalized olefins was attempted. Both allylic alcohol (**2h**) and its derivatives, allyl phenyl ether (**2i**) and allyl acetate (**2j**), gave rise to the desired *S*-1-phthalimidoalkan-3-yl xanthate derivatives **3h**–**j** in good to excellent yields (Table 1, entries 8–10). Although the oxygen-containing olefins **2h**–**j** generally gave rise to the corresponding products in relative higher yields compared with simple olefins **2a**–**f**, allylic alcohol (**2h**) generated the corresponding product **3h** in a relatively lower yield possibly because the active proton in the allylic alcohol can trap some radical intermediates in the reaction system (Table 1, entry 8). Moreover, allyl thioacetate (**2k**) gave rise to the desired product **3k** in 39% yield with a symmetric byproduct *O*-ethyl *S*-1,5-diphthalimidopentan-3-yl xanthate (**3t**) in 14% yield under the same reaction conditions. The symmetric *O*-ethyl *S*-1,5-diphthalimidopentan-3-yl xanthate (**3t**) was assumed to be generated via a tandem radical addition–elimination–addition process (Scheme 2). For nitrogen-functionalized olefins, *N*-allylphthalimide (**2l**), benzyl and *tert*-butyl *N*-allylcarbamates (**2m** and **2n**) produced the corresponding xanthates **3l**–**n** in good yields (Table 1, entries 13–15). However, *N*-allylbenzylamine (**2o**) did not give rise to the corresponding desired product. Instead, it generated bis(phthalimidomethyl) disulfide in 53% yield due to aminolysis of the xanthate **1** with *N*-allylbenzylamine (**2o**), affording phthalimidomethy1 thiol, which was further oxidized to bis(phthalimidomethyl) disulfide under reaction conditions (Table 1, entry 15) (Scheme 3). For electron-deficient olefins, ethyl acrylate (**2r**) and acrylamide (**2s**), only polymerization occurred under the same reaction conditions (Table 1, entries 17 and 18).



Scheme 2. Synthesis of *N*-phthalyl 1-substituted homotaurines from allyl thioacetate.

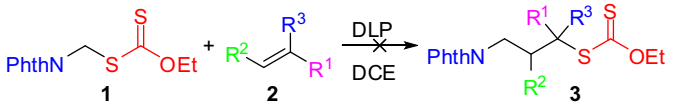
Most xanthates **3** were oxidized to the corresponding *N*-phthalyl 1-substituted homotaurines **4** with performic acid in excellent yields (Table 1) (Schemes 1 and 2). However, the xanthate **3j** produced homotaurine **4h** in 91% yield, instead of **4j**, due to the



Scheme 3. Reaction of *O*-ethyl *S*-2-phthalimidomethylxanthate (**1**) and *N*-allylbenzylamine (**2o**).

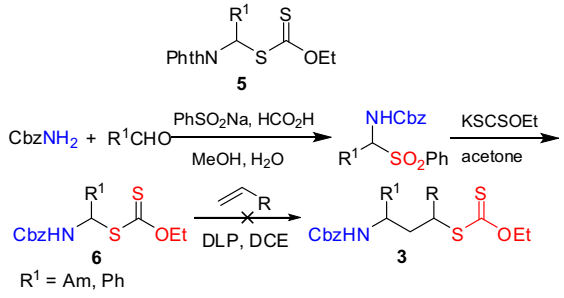
in situ hydrolysis of the acetate group in its side-chain during the acidic oxidation conditions (Table 1, entry 10). The xanthate **3k** gave rise to 4-phthalimidobutane-1,2-disulfonic acid (**4k**) in 93% yield because the thioacetate group in its side-chain was also oxidized in the same time under the oxidation conditions as expected (Table 1, entry 11). 4-Phthalimidobutane-1,2-disulfonic acid (**4k**) can be considered as both 3-aminoalkanesulfonic acid (1-substituted homotaurine) and 4-aminoalkanesulfonic acid. The symmetric *O*-ethyl *S*-1,5-diphthalimidopentan-3-yl xanthate (**3t**) produced 1,5-diphthalimidopentan-3-sulfonic acid (**4t**) in 93% yield (Scheme 2).

After success in the synthesis of 1-substituted homotaurine from terminal olefins, we hoped to extend the current method to prepare 1,1- and 1,2-disubstituted homotaurines with 1,1- and 1,2-disubstituted olefins as starting materials. To attempt the synthesis of 1,2- and 1,1-disubstituted homotaurines, *O*-ethyl *S*-2-phthalimidomethylxanthate (**1**) was reacted with 1,2-disubstituted olefin 5-decene (**2u**), and 1,1-disubstituted olefins 5,5-dimethyl-1-hexene (**2v**), 2-phenyl-1-propene (**2w**), and 1,1-diphenylethene (**2x**). Unfortunately, no desired radical addition occurred in each of cases due to steric hindrance of disubstituted olefins (Scheme 4). Furthermore, we also tried to synthesize 1,3-disubstituted homotaurines with the current method. Attempt to synthesis of xanthates **5** failed. However, xanthates **6** were prepared via the displacement of potassium *O*-ethyl xanthate with corresponding sulfones, which were synthesized from benzyl carbamate and aldehydes according to the reported method.[19] Unfortunately, they did not undergo the radical addition with selected olefins **2b** and **2e**, either, due to steric hindrance of xanthates **6** (Scheme 5). The results indicate that the radical addition is very sensitive to steric hindrance of both xanthates and olefins.



u) R^1 = Bu; R^2 = Bu; R^3 = H v) R^1 = Me; R^2 = H; R^3 = *t*-BuCH_2
w) R^1 = Me; R^2 = H; R^3 = Ph x) R^1 = Ph; R^2 = H; R^3 = Ph

Scheme 4. Attempt to synthesize of disubstituted homotaurines.



Scheme 5. Attempt to synthesize of disubstituted homotaurines.

3. Conclusion

In summary, we have developed a convenient and practical protocol for the synthesis of 1-substituted homotaurines with diverse side-chains via the radical addition of *O*-ethyl *S*-2-phthalimidomethylxanthate to various olefins with different functionalized groups and subsequent performic acid oxidation. Compared with previous methods, the current approach applies commercially available diverse olefins and one synthetic xanthate as starting materials. Thus, it shows higher efficiency for synthesis of 1-substituted homotaurines.

4. Experimental section

4.1. General

Melting points were determined with a Yanaco MP-500 melting point apparatus and are uncorrected. ^{1}H NMR spectra were recorded at Bruker AV 400 (400 MHz) in $CDCl_3$, D_2O, or DMSO-d_6 with TMS, DOH, or DMSO-d_6 as the internal standards, respectively. ^{13}C NMR spectra were recorded at 100.6 MHz in $CDCl_3$, DMSO-d_6, or D_2O (with HCO_2H as an internal standard at 163.3 ppm). IR spectra were determined directly on a Nicolet AVATAR 330 FT-IR spectrometer. HRMS spectra were recorded with an Agilent LC/MSD TOF mass spectrometer. TLC analysis was performed on glass pre-coated silica gel YT257-85 (10–40 μm) plate. Spots were visualized with UV light or iodine. Column chromatography was performed on silica gel zcx II (200–300 mesh) with silica gel (200–300 mesh).

4.2. Synthesis of *O*-ethyl *S*-2-phthalimidomethylxanthate (1)

A mixture of phthalimide (41.14 g, 0.30 mol) and distilled water (100 mL) was stirred for 10 min at room temperature. After addition of formaldehyde solution (40%, 27 mL, 0.36 mol), the resulting solution was refluxed for 1.5 h. After cooling to 0–5 °C, the resulting precipitate was collected by filtration, washed with cold water (0–5 °C, 200 mL) and dried in air to give the corresponding *N*-hydroxymethylphthalimide (51.01 g, 96% yield).

A solution of thionyl chloride (23.0 mL, 37.7 g, 0.32 mol) in dichloromethane (50 mL) was slowly added to a mixture of the resulting *N*-hydroxymethylphthalimide and dichloromethane (550 mL) and *N*,*N*-dimethylformamide (350 mL) during 30 min at room temperature with stirring. The resulting mixture was further stirred for 2 h at room temperature. After cooling to 0 °C, water (200 mL) was added slowly. And the solution was neutralized to pH 6.7–7.0 by using saturated aqueous $NaHCO_3$ solution. The organic layer was separated and then was dried over anhydrous magnesium sulfate. After evaporation of the solvent under the reduced pressure, the residue was washed with *n*-hexane (100 mL) to give *N*-chloromethylphthalimide (51.4 g, 93% yield).

N-Chloromethylphthalimide (51.0 g, 0.26 mol) was dissolved in acetone (500 mL) and potassium *O*-ethyl xanthate (43.9 g, 274 mmol) was added portionwise in an ice water bath under stirring. The resulting solution was further stirred for 10 h at room temperature. After removal of the solvent, the residue was dissolved in dichloromethane. The resulting solution was washed with water and dried over sodium sulfate. After removal of the solvent under the reduced pressure, pale yellow solid was obtained and recrystallized from ethyl acetate to afford the xanthate **1** as colorless crystals 67.2 g, 92% yield, mp: 99–100 °C. Lit.[20] mp: 94–95 °C. ^{1}H NMR ($CDCl_3$, 400 MHz) (δ, ppm) 1.47 (t, J=7.1 Hz, 3H, CH_3), 4.68 (q, J=7.1 Hz, 2H, CH_2), 5.34 (s, 2H, CH_2), 7.75 (dd, J=5.5, 3.1 Hz, 2H, ArH), 7.88 (dd, J=5.5, 3.1 Hz, 2H, ArH). ^{13}C NMR ($CDCl_3$, 100 MHz) (δ, ppm) 13.7, 41.2, 70.5, 123.6, 131.8, 134.4, 166.6, 210.2.

4.3. General procedure for synthesis of *O*-ethyl *S*-3-phthalimidoalkyl xanthates 3

A mixture of xanthate **1** (562 mg, 2 mmol) and an olefin (3 mmol) in 1,2-dichloroethane (1.5 mL) was degassed by vacuumized, then filled with nitrogen. The solution was then heated to reflux and dilauroyl peroxide (DLP) (1.25–10 mol %, 10–80 mg) was added per hour. The

reaction was monitored by TLC until complete disappearance of the xanthate. After evaporation of the solvent, the residue was chromatographed on a silica gel column to yield the addition product **3**.

*4.3.1. O-Ethyl S-1-phthalimidoheptan-3-yl dithiocarbonate (**3a**).* The reaction was complete after addition of 35 mol % of DLP. Yellow oil; yield: 488 mg, 62%. ^{1}H NMR ($CDCl_3$, 400 MHz) (δ, ppm) 0.91 (t, J=7.2 Hz, 3H, CH_3), 1.38 (t, J=7.1 Hz, 3H, CH_3), 1.21–1.56 (m, 4H, $2CH_2$), 1.68 (dddd, J=14.4, 8.5, 5.6, 4.9 Hz, 1H in CH_2), 1.82 (dddd, J=14.4, 10.1, 5.6, 5.2 Hz, 1H in CH_2), 2.05 (dddd, J=14.1, 7.2, 6.9, 6.9 Hz, 1H in CH_2), 2.08 (dddd, J=14.1, 7.5, 7.2, 7.2 Hz, 1H in CH_2), 3.72 (dddd, J=7.6, 7.2, 6.9, 5.6 Hz, 1H, CH), 3.81 (ddd, J=13.7, 7.2, 7.2 Hz, 1H in CH_2), 3.85 (ddd, J=13.7, 7.5, 7.5 Hz, 1H in CH_2), 4.65 (q, J=7.1 Hz, 2H, CH_2), 7.72 (dd, J=5.5, 3.1 Hz, 2H, ArH), 7.85 (dd, J=5.5, 3.1 Hz, 2H, ArH). ^{13}C NMR ($CDCl_3$, 100 MHz) (δ, ppm) 13.7, 13.9, 22.5, 28.9, 33.2, 33.4, 35.7, 48.7, 69.7, 123.2, 132.1, 133.9, 168.2, 214.2. IR (ν_{max}, cm^{-1}) 1772, 1713, 1216, 1049. HRMS (ESI) calcd for $C_{18}H_{23}NNaO_3S_2$ $[M+Na]^+$ m/z 388.1017; found 388.1018.

*4.3.2. O-Ethyl S-1-phthalimidononan-3-yl dithiocarbonate (**3b**).* The reaction was complete after addition of 15 mol % of DLP. Yellow oil; yield: 534 mg, 73%. ^{1}H NMR ($CDCl_3$, 400 MHz) (δ, ppm) 0.88 (t, J=7.0 Hz, 3H, CH_3), 1.38 (t, J=7.1 Hz, 3H, CH_3), 1.20–1.50 (m, 8H, $4CH_2$), 1.67 (dddd, J=15.1, 9.7, 5.6, 4.8 Hz, 1H in CH_2), 1.80 (dddd, J=15.1, 10.5, 5.6, 5.4 Hz, 1H in CH_2), 2.06 (dddd, J=14.3, 7.5, 6.8, 6.8 Hz, 1H in CH_2), 2.08 (dddd, J=14.3, 7.5, 7.3, 7.3 Hz, 1H in CH_2), 3.72 (dddd, J=8.0, 6.8, 5.6, 5.6 Hz, 1H, CH), 3.80 (ddd, J=13.8, 7.3, 6.8 Hz, 1H in CH_2), 3.85 (ddd, J=13.8, 7.5, 7.3 Hz, 1H in CH_2), 4.60 (q, J=7.1 Hz, 2H, CH_2), 7.72 (dd, J=5.5, 3.1 Hz, 2H, ArH), 7.85 (dd, J=5.5, 3.1 Hz, 2H, ArH). ^{13}C NMR ($CDCl_3$, 100 MHz) (δ, ppm) 13.7, 14.0, 22.5, 26.7, 29.0, 31.6, 33.2, 33.5, 35.7, 48.7, 69.7, 123.2, 132.1, 133.9, 168.2, 214.2. IR (ν_{max}, cm^{-1}) 1772, 1713, 1215, 1050. HRMS (ESI) calcd for $C_{20}H_{28}NO_3S_2$ $[M+H]^+$ m/z 394.1511; found 394.1500.

*4.3.3. S-1-Cyclohexyl-4-phthalimidobutan-2-yl O-ethyl dithiocarbonate (**3c**).* The reaction was complete after addition of 15 mol % of DLP. Yellow oil; yield: 641 mg, 79%. ^{1}H NMR ($CDCl_3$, 400 MHz) (δ, ppm) 1.13–1.76 (m, 13H in cyclohexylmethylene), 1.39 (t, J=7.1 Hz, 3H, CH_3), 2.06 (dddd, J=14.8, 13.8, 7.7, 6.4 Hz, 1H in CH_2), 2.08 (dddd, J=14.8, 13.2, 7.6, 7.0 Hz, 1H in CH_2), 3.72–3.87 (m, 3H, CH_2 & CH), 4.60 (q, J=7.1 Hz, 2H, CH_2), 7.72 (dd, J=5.5, 3.1 Hz, 2H, ArH), 7.85 (dd, J=5.5, 3.1 Hz, 2H, ArH). ^{13}C NMR ($CDCl_3$, 100 MHz) (δ, ppm) 13.7, 26.0, 26.2, 26.4, 32.7, 33.6, 34.2, 34.9, 35.6, 41.0, 46.2, 69.7, 123.1, 132.1, 133.9, 168.2, 214.2. IR (ν_{max}, cm^{-1}) 1772, 1714, 1214, 1049. HRMS (ESI) calcd for $C_{21}H_{28}NO_3S_2$ $[M+H]^+$ m/z 406.1511; found 406.1503.

*4.3.4. O-Ethyl S-6-phenyl-1-phthalimidohexan-3-yl dithiocarbonate (**3d**).* The reaction was complete after addition of 30 mol % of DLP. Yellow oil; yield: 633 mg, 74%. ^{1}H NMR ($CDCl_3$, 400 MHz) (δ, ppm) 1.36 (t, J=7.1 Hz, 3H, CH_3), 1.52–1.65 (m, 4H, $2CH_2$), 2.04 (dddd, J=14.3, 6.8, 6.8, 6.8 Hz, 1H in CH_2), 2.07 (dddd, J=14.3, 7.3, 7.3, 7.3 Hz, 1H in CH_2), 2.61 (ddd, J=13.7, 7.2, 7.2 Hz, 1H in CH_2), 2.68 (ddd, J=13.7, 7.6, 7.6 Hz, 1H in CH_2), 3.70–3.86 (m, 3H, CH_2 & CH), 4.57 (dq, J=11.6, 7.1 Hz, 1H in CH_2), 4.60 (dq, J=11.6, 7.1 Hz, 1H in CH_2), 7.15–7.18 (m, 3H, ArH), 7.18 (dd, J=7.5, 6.4 Hz, 2H, ArH), 7.71 (dd, J=5.5, 3.1 Hz, 2H, ArH), 7.84 (dd, J=5.5, 3.1 Hz, 2H, ArH). ^{13}C NMR ($CDCl_3$, 100 MHz) (δ, ppm) 13.7, 28.4, 33.1, 33.4, 35.5, 35.6, 48.6, 69.8, 123.2, 125.8, 128.2, 128.3, 132.1, 133.9, 141.8, 168.2, 214.0. IR (ν_{max}, cm^{-1}) 3060, 3025, 1772, 1712, 1217, 1050. HRMS (ESI) calcd for $C_{23}H_{26}NO_3S_2$ $[M+H]^+$ m/z 428.1354; found 428.1349.

*4.3.5. O-Ethyl S-5-phenyl-1-phthalimidopentan-3-yl dithiocarbonate (**3e**).* The reaction was complete after addition of 17.5 mol % of DLP. Yellow oil; yield: 686 mg, 83%. ^{1}H NMR ($CDCl_3$, 400 MHz) (δ, ppm) 1.37 (t, J=7.1 Hz, 3H, CH_3), 1.98 (dddd, J=14.4, 7.3, 7.1, 6.9 Hz, 1H in CH_2), 2.08–2.18 (m, 3H, 1H in CH_2 & CH_2), 2.72 (ddd, J=13.6, 10.0, 6.0 Hz, 1H in CH_2), 2.81 (ddd, J=13.6, 10.4, 5.6 Hz, 1H in CH_2), 3.75 (dddd, J=8.4, 7.1, 6.9, 5.3 Hz, 1H, CH), 3.80 (ddd, J=13.8, 6.9, 6.9 Hz, 1H in CH_2), 3.85 (ddd, J=13.8, 7.3, 7.3 Hz, 1H in CH_2), 4.59 (dq, J=10.3, 7.1 Hz, 1H in CH_2), 4.61 (dq, J=10.3, 7.1 Hz, 1H in CH_2), 7.15–7.20 (m, 3H, ArH), 7.26 (dd, J=7.3, 5.8 Hz, 2H, ArH), 7.72 (dd, J=5.5, 3.1 Hz, 2H, ArH), 7.85 (dd, J=5.5, 3.1 Hz, 2H, ArH). ^{13}C NMR ($CDCl_3$, 100 MHz) (δ, ppm) 13.7, 33.1, 33.3, 33.5, 35.6, 48.2, 69.9, 123.2, 126.0, 128.3, 128.4, 132.1, 133.9, 141.1, 168.2, 213.7. IR (ν_{max}, cm^{-1}) 3059, 3025, 1772, 1712, 1218, 1050. HRMS (ESI) calcd for $C_{22}H_{24}NO_3S_2$ $[M+H]^+$ m/z 414.1198; found 414.1197.

*4.3.6. O-Ethyl S-4-phenyl-1-phthalimidobutan-3-yl dithiocarbonate (**3f**).* The reaction was complete after addition of 32.5 mol % of DLP. Yellow oil; yield: 583 mg, 73%. ^{1}H NMR ($CDCl_3$, 400 MHz) (δ, ppm) 1.36 (t, J=7.1 Hz, 3H, CH_3), 2.02 (dddd, J=14.1, 7.2, 7.2, 6.9 Hz, 1H in CH_2), 2.07 (dddd, J=14.1, 7.2, 7.2, 6.6 Hz, 1H in CH_2), 3.02 (dd, J=13.8, 6.9 Hz, 1H in CH_2), 3.08 (dd, J=13.8, 6.9 Hz, 1H in CH_2), 3.77 (ddd, J=13.8, 7.2, 6.6 Hz, 1H in CH_2), 3.86 (ddd, J=13.8, 7.2, 6.9 Hz, 1H in CH_2), 3.95 (dddd, J=7.2, 7.2, 6.9, 6.9 Hz, 1H, CH), 4.55 (dq, J=10.7, 7.1 Hz, 1H in CH_2), 4.58 (dq, J=10.7, 7.1 Hz, 1H in CH_2), 7.17–7.22 (m, 1H, ArH), 7.24–7.27 (m, 4H, ArH), 7.71 (dd, J=5.5, 3.1 Hz, 2H, ArH), 7.83 (dd, J=5.5, 3.1 Hz, 2H, ArH). ^{13}C NMR ($CDCl_3$, 100 MHz) (δ, ppm) 13.7, 32.0, 35.7, 40.1, 49.6, 69.8, 123.2, 126.7, 128.3, 129.3, 132.0, 133.9, 137.9, 168.1, 213.5. IR (ν_{max}, cm^{-1}) 3054, 3027, 1771, 1712, 1218, 1049. HRMS (ESI) calcd for $C_{21}H_{22}NO_3S_2$ $[M+H]^+$ m/z 400.1041; found 400.1043.

*4.3.7. O-Ethyl S-1-hydroxy-4-phthalimidobutan-2-yl dithiocarbonate (**3h**).* The reaction was complete after addition of 25 mol % of DLP. Yellow oil; yield: 427 mg, 63%. ^{1}H NMR ($CDCl_3$, 400 MHz) (δ, ppm) 1.39 (t, J=7.1 Hz, 3H, CH_3), 2.07 (dddd, J=14.0, 7.1, 7.1, 6.3 Hz, 1H in CH_2), 2.10 (s, 1H, OH), 2.24 (dddd, J=14.0, 7.1, 7.1, 6.3 Hz, 1H in CH_2), 3.82–3.94 (m, 5H, $2CH_2$ & CH), 4.61 (q, J=7.1 Hz, 2H, CH_2), 7.72 (dd, J=5.1, 3.6 Hz, 2H, ArH), 7.85 (dd, J=5.1, 3.6 Hz, 2H, ArH). ^{13}C NMR ($CDCl_3$, 100 MHz) (δ, ppm) 13.7, 29.7, 35.7, 50.6, 64.2, 70.2, 123.3, 132.0, 134.0, 168.2, 213.4. IR (ν_{max}, cm^{-1}) 3463, 1771, 1710, 1219, 1050. HRMS (ESI) calcd for $C_{15}H_{17}NNaO_4S_2$ $[M+Na]^+$ m/z 362.0497; found 362.0493.

*4.3.8. O-Ethyl S-1-phenoxy-4-phthalimidobutan-2-yl dithiocarbonate (**3i**).* The reaction was complete after addition of 20 mol % of DLP. Yellow oil; yield: 789 mg, 95%. ^{1}H NMR ($CDCl_3$, 400 MHz) (δ, ppm) 1.38 (t, J=7.1 Hz, 3H, CH_3), 2.16 (dddd, J=14.4, 7.4, 6.9, 6.9 Hz, 1H in CH_2), 2.42 (dddd, J=14.4, 6.9, 6.9, 6.4 Hz, 1H in CH_2), 3.89 (t, J=6.9 Hz, 2H, CH_2), 4.12 (dd, J=11.5, 5.5 Hz, 1H in CH_2), 4.19 (dd, J=11.5, 5.5 Hz, 1H in CH_2), 4.35–4.40 (m, 1H, CH), 4.60 (q, J=7.1 Hz, 2H, CH_2), 6.89–6.95 (m, 3H, ArH), 7.23–7.27 (m, 2H, ArH), 7.73 (dd, J=5.5, 3.1 Hz, 2H, ArH), 7.85 (dd, J=5.5, 3.1 Hz, 2H, ArH). ^{13}C NMR ($CDCl_3$, 100 MHz) (δ, ppm) 13.7, 29.7, 35.7, 47.5, 68.8, 70.2, 114.6, 121.2, 123.2, 129.4, 132.0, 133.9, 158.3, 168.2, 213.4. IR (ν_{max}, cm^{-1}) 3059, 1772, 1712, 1227, 1050. HRMS (ESI) calcd for $C_{21}H_{22}NO_4S_2$ $[M+H]^+$ m/z 416.0990; found 416.0995.

*4.3.9. S-1-Acetoxy-4-phthalimidobutan-2-yl O-ethyl dithiocarbonate (**3j**).*[21] The reaction was complete after addition of 6.25 mol % of DLP. Yellow oil; yield: 641 mg, 84%. ^{1}H NMR ($CDCl_3$, 400 MHz) (δ, ppm) 1.40 (t, J=7.1 Hz, 3H, CH_3), 2.08 (s, 3H, CH_3), 2.05 (dddd, J=14.1, 7.7, 7.2, 6.8 Hz, 1H in CH_2), 2.19 (dddd, J=14.1, 7.2, 6.8, 6.8 Hz, 1H in CH_2), 3.83 (ddd, J=13.9, 7.2, 7.2 Hz, 1H in CH_2), 3.88 (ddd, J=13.9, 6.8, 6.8 Hz, 1H in CH_2), 3.99 (dddd, J=6.9, 6.9, 5.7, 4.7 Hz, 1H, CH), 4.28 (dd, J=11.5, 5.7 Hz, 1H in CH_2), 4.42 (dd, J=11.5, 4.7 Hz, 1H in CH_2), 4.62 (q, J=7.1 Hz, 2H, CH_2), 7.73 (dd, J=5.5, 3.1 Hz, 2H, ArH), 7.85 (dd, J=5.5, 3.1 Hz, 2H, ArH). ^{13}C NMR ($CDCl_3$, 100 MHz) (δ, ppm) 13.6, 20.7, 29.7, 35.5, 46.9, 65.0, 70.2, 123.2, 132.0, 134.0, 168.1, 170.5, 212.6.

*4.3.10. S-1-Acetylthio-4-phthalimidobutan-2-yl O-ethyl dithiocarbonate (**3k**).* The reaction was complete after addition of 25 mol % of DLP. Pale yellow solid; mp: 59–61 °C; yield: 310 mg, 39%. ^{1}H NMR ($CDCl_3$, 400 MHz) (δ, ppm) 1.40 (t, J=7.1 Hz, 3H, CH_3), 2.03 (dddd, J=14.2, 7.7, 6.8, 6.8 Hz, 1H in CH_2), 2.14 (dddd, J=14.2, 7.7, 6.4, 6.4 Hz,

1H in CH_2), 2.35 (s, 3H, CH_3), 3.35 (dd, J=14.0, 6.5 Hz, 1H in CH_2), 3.41 (dd, J=14.0, 5.7 Hz, 1H in CH_2), 3.75–3.99 (m, 3H, CH_2 & CH), 4.62 (q, J=7.1 Hz, 2H, CH_2), 7.72 (dd, J=5.6, 3.2 Hz, 2H, ArH), 7.85 (dd, J=5.6, 3.2 Hz, 2H, ArH). ^{13}C NMR ($CDCl_3$, 100 MHz) (δ, ppm) 13.6, 30.5, 31.4, 33.0, 35.6, 48.2, 70.2, 123.2, 132.0, 134.0, 168.1, 194.6, 212.6. IR (ν_{max}, cm^{-1}) 1772, 1712, 1219, 1047. HRMS (ESI) calcd for $C_{17}H_{19}NNaO_4S_3$ $[M+Na]^+$ m/z 420.0374; found 420.0370.

*4.3.11. O-Ethyl S-1,4-diphthalimidobutan-2-yl dithiocarbonate (**3l**).* The reaction was complete after addition of 25 mol % of DLP. Pale yellow solid; mp: 154–155 °C; yield: 787 mg, 84%. ^{1}H NMR ($CDCl_3$, 400 MHz) (δ, ppm) 1.39 (t, J=7.2 Hz, 3H, CH_3), 2.06 (dddd, J=14.6, 8.0, 7.0, 6.5 Hz, 1H in CH_2), 2.15 (dddd, J=14.6, 8.8, 8.0, 6.0 Hz, 1H in CH_2), 3.87 (ddd, J=13.9, 8.0, 6.0 Hz, 1H in CH_2), 3.95 (ddd, J=13.9, 7.0, 6.0 Hz, 1H in CH_2), 4.01 (dd, J=14.0, 7.8 Hz, 1H in CH_2), 4.08 (dd, J=14.0, 8.0 Hz, 1H in CH_2), 4.15 (dddd, J=8.8, 8.0, 7.8, 6.5 Hz, 1H, CH), 4.56 (dq, J=10.8, 7.2 Hz, 1H in CH_2), 4.59 (dq, J=10.8, 7.2 Hz, 1H in CH_2), 7.72 (dd, J=5.2, 3.4 Hz, 2H, ArH), 7.84 (dd, J=5.2, 3.4 Hz, 4H, ArH). ^{13}C NMR ($CDCl_3$, 100 MHz) (δ, ppm) 13.6, 30.5, 35.6, 40.7, 47.1, 70.3, 123.3, 123.5, 131.8, 132.1, 133.9, 134.1, 168.1, 212.1. IR (ν_{max}, cm^{-1}) 1772, 1713, 1221, 1047. HRMS (ESI) calcd for $C_{23}H_{21}N_2O_5S_2$ $[M+Na]^+$ m/z: 491.0711; found 491.0718.

*4.3.12. S-1-Benzoxycarbonylamino-4-phthalimidobutan-2-yl O-ethyl dithiocarbonate (**3m**).* The reaction was complete after addition of 25 mol % of DLP. Yellow oil; yield: 699 mg, 74%. ^{1}H NMR ($CDCl_3$, 400 MHz) (δ, ppm) 1.38 (t, J=7.1 Hz, 3H, CH_3), 2.00 (dddd, J=14.1, 7.8, 7.3, 7.3 Hz, 1H in CH_2), 2.13 (dddd, J=14.1, 7.6, 6.5, 6.5 Hz, 1H in CH_2), 3.56 (dd, J=14.4, 6.5 Hz, 1H in CH_2), 3.63 (dd, J=14.4, 5.8 Hz, 1H in CH_2), 3.77–3.93 (m, 3H, CH_2 & CH), 4.59 (q, J=7.1 Hz, 2H, CH_2), 5.10 (s, 2H, CH_2), 5.10 (s, 1H, NH), 7.28–7.37 (m, 5H, ArH), 7.72 (dd, J=5.5, 3.1 Hz, 2H, ArH), 7.84 (dd, J=5.5, 3.1 Hz, 2H, ArH). ^{13}C NMR ($CDCl_3$, 100 MHz) (δ, ppm) 13.6, 30.3, 35.5, 43.9, 49.1, 66.9, 70.3, 123.2, 128.0, 128.1, 128.5, 132.0, 133.9, 156.5, 168.2, 212.9. IR (ν_{max}, cm^{-1}) 3356, 3059, 3031, 1772, 1710, 1522, 1224, 1048. HRMS (ESI) calcd for $C_{23}H_{25}N_2O_5S_2$ $[M+H]^+$ m/z 473.1205; found 473.1208.

*4.3.13. S-1-tert-Butoxycarbonylamino-4-phthalimidobutan-2-yl O-ethyl dithiocarbonate(**3n**).* The reaction was complete after addition of 25 mol % of DLP. Yellow oil; yield: 649 mg, 74%. ^{1}H NMR ($CDCl_3$, 400 MHz) (δ, ppm) 1.40 (t, J=7.1 Hz, 3H, CH_3), 1.43 (s, 9H, $3CH_3$), 2.00 (dddd, J=14.1, 7.8, 7.3, 7.3 Hz, 1H in CH_2), 2.13 (dddd, J=14.1, 7.7, 6.5, 6.5 Hz, 1H in CH_2), 3.45–3.57 (m, 2H, CH_2), 3.78–3.94 (m, 3H, CH_2 & CH), 4.61 (q, J=7.1 Hz, 2H, CH_2), 4.87 (s, br, 1H, NH), 7.72 (dd, J=5.5, 3.1 Hz, 2H, ArH), 7.85 (dd, J=5.5, 3.1 Hz, 2H, ArH). ^{13}C NMR ($CDCl_3$, 100 MHz) (δ, ppm) 13.7, 28.3, 30.4, 35.6, 43.3, 49.3, 70.2, 79.6, 123.2, 132.1, 133.9, 155.9, 168.2, 213.7. IR (ν_{max}, cm^{-1}) 3378, 1772, 1713, 1512, 1220, 1049. HRMS (ESI) calcd for $C_{20}H_{26}N_2NaO_5S_2$ $[M+Na]^+$ m/z 461.1181; found 461.1182.

*4.3.14. S-1,5-Diphthalimidopentan-3-yl O-ethyl dithiocarbonate (**3t**).* The reaction was complete after addition of 25 mol % of DLP. White solid; mp: 90–91 °C; yield: 135 mg, 14%. ^{1}H NMR ($CDCl_3$, 400 MHz) (δ, ppm) 1.33 (t, J=7.1 Hz, 3H, CH_3), 2.08 (dddd, J=14.6, 7.7, 7.1, 7.1 Hz, 2H in $2CH_2$), 2.19 (dddd, J=14.6, 7.1, 6.9, 6.2 Hz, 2H in $2CH_2$), 3.69 (dddd, J=7.7, 7.7, 6.2, 6.2 Hz, 1H, CH), 3.83 (ddd, J=14.1, 7.1, 6.9 Hz, 2H in $2CH_2$), 3.86 (ddd, J=14.1, 7.1, 6.9 Hz, 2H in $2CH_2$), 4.56 (q, J=7.1 Hz, 2H, CH_2), 7.71 (dd, J=5.6, 3.1 Hz, 2H, ArH), 7.78 (dd, J=5.6, 3.1 Hz, 2H, ArH). ^{13}C NMR ($CDCl_3$, 100 MHz) (δ, ppm) 13.6, 32.8, 35.4, 46.0, 70.0, 123.1, 132.0, 134.0, 168.2, 213.2. IR (ν_{max}, cm^{-1}) 1772, 1709, 1221, 1050. HRMS (ESI) calcd for $C_{24}H_{22}N_2NaO_5S_2$ $[M+Na]^+$ m/z 505.0868; found 505.0865.

4.3.15. Bis(phthalimidomethy1) disulfide. Pale yellow solid; mp: 187–190 °C; lit.[22] mp: 194 °C; yield: 407 mg, 53%. ^{1}H NMR ($CDCl_3$, 400 MHz) (δ, ppm) 4.93 (s, 4H, $2CH_2$), 7.75 (dd, J=5.5, 3.1 Hz, 4H, ArH), 7.88 (dd, J=5.5, 3.1 Hz, 4H, ArH). ^{13}C NMR ($CDCl_3$, 100 MHz) (δ, ppm) 43.7, 123.6, 131.9, 134.4, 167.2.

4.4. General procedure for synthesis of *N*-phthyl 1-substituted homotaurines 4

A solution of 30% H_2O_2 (1 mL) was dissolved in 98% formic acid (5 mL) at 0 °C and the mixture was stirred at 0 °C for 1 h to afford peroxyformic acid. Xanthate **3** (1 mmol) was dissolved in 98% formic acid (2 mL), then the solution was added dropwise to the peroxyformic acid solution in an ice water bath. The resulting solution was stirred overnight at room temperature. After removal of the solvent, the residue was purified by column chromatography on silica gel (dichloromethane/methanol: 15/1, v/v) to afford homotaurine **4** in good yield.

*4.4.1. 1-Phthalimidoheptane-3-sulfonic acid (**4a**).* Brown oil; yield: 299 mg, 92%. ^{1}H NMR (D_2O, 400 MHz) (δ, ppm) 0.66 (t, J=7.0 Hz, 3H, CH_3), 1.06–1.29 (m, 4H, $2CH_2$), 1.37–1.45 (m, 1H in CH_2), 1.65–1.75 (m, 2H, CH_2), 1.94 (dddd, J=13.1, 6.6, 6.5, 6.3 Hz, 1H in CH_2), 2.56–2.61 (m, 1H, CH), 3.55 (t, J=7.1 Hz, 2H, CH_2), 7.53–7.60 (m, 4H, ArH). ^{13}C NMR (D_2O, 100 MHz) (δ, ppm) 13.1, 21.9, 28.0, 29.0, 28.3, 35.9, 57.8, 123.2, 130.9, 134.7, 170.0. IR (ν_{max}, cm^{-1}) 1772, 1713, 1170, 1037. HRMS (ESI) calcd for $C_{15}H_{20}NO_5S$ $[M+H]^+$ m/z 326.1062; found 326.1058.

*4.4.2. 1-Phthalimidononan-3-sulfonic acid (**4b**).* Brown oil; yield: 318 mg, 90%. ^{1}H NMR (D_2O, 400 MHz) (δ, ppm) 0.51 (s, 3H, CH_3), 0.85–1.12 (m, 8H, $4CH_2$), 1.31 (s, 1H in CH_2), 1.65 (s, 2H, CH_2), 1.90 (s, 1H in CH_2), 2.52 (s, 1H, CH), 3.54 (s, 2H, CH_2), 7.50–7.53 (m, 4H, ArH). ^{13}C NMR (D_2O, 100 MHz) (δ, ppm) 13.5, 22.0, 26.1, 28.0, 28.5, 29.4, 31.2, 36.1, 51.7, 123.1, 132.1, 134.5, 169.3. IR (ν_{max}, cm^{-1}) 1772, 1713, 1170, 1038. HRMS (ESI) calcd for $C_{17}H_{24}NO_5S$ $[M+H]^+$ m/z 354.1375; found 354.1372.

*4.4.3. 1-Cyclohexyl-4-phthalimidobutane-2-sulfonic acid (**4c**).* Pale yellow oil; yield: 336 mg, 92%. ^{1}H NMR (D_2O, 400 MHz) (δ, ppm) 0.53–1.51 (m, 13H, cyclohexylmethylene), 1.72 (s, 1H in CH_2), 1.93 (s, 1H in CH_2), 2.66 (s, 1H, CH), 3.58 (s, 1H in CH_2), 3.63 (s, 1H in CH_2), 7.61 (s, 4H, ArH). ^{13}C NMR (D_2O, 100 MHz) (δ, ppm) 25.6, 25.9, 26.0, 28.6, 31.8, 33.6, 34.5, 36.3, 37.3, 55.2, 123.2, 132.0, 134.7, 169.9, 214.2. IR (ν_{max}, cm^{-1}) 1773, 1711, 1170, 1041. HRMS (ESI) calcd for $C_{18}H_{23}NNaO_5S$ $[M+Na]^+$ m/z 388.1195; found 388.1188.

*4.4.4. 6-Phenyl-1-phthalimidohexane-3-sulfonic acid (**4d**).* Brown oil; yield: 353 mg, 91%. ^{1}H NMR (D_2O, 400 MHz) (δ, ppm) 1.15–1.40 (m, 3H, 1H in CH_2 & CH_2), 1.51 (dddd, J=13.3, 7.1, 6.8, 6.4 Hz, 1H in CH_2), 1.60–1.68 (m, 1H in CH_2), 1.76 (dddd, J=13.3, 7.1, 6.9, 6.6 Hz, 1H in CH_2), 2.14 (ddd, J=14.5, 7.5, 7.4 Hz, 2H, CH_2), 2.47 (dddd, J=6.9, 6.8, 5.4, 4.9 Hz, 1H, CH), 3.30 (t, J=7.1 Hz, 2H, CH_2), 6.68–6.80 (m, 5H, ArH), 7.27 (s, 4H, ArH). ^{13}C NMR (D_2O, 100 MHz) (δ, ppm) 27.90, 27.91, 29.0, 34.9, 35.8, 57.6, 123.0, 125.5, 128.0, 128.1, 130.9, 134.3, 142.0, 169.1. IR (ν_{max}, cm^{-1}) 3059, 3025, 1772, 1713, 1170, 1037. HRMS (ESI) calcd for $C_{20}H_{22}NO_5S$ $[M+H]^+$ m/z 388.1219; found 388.1215.

*4.4.5. 5-Phenyl-1-phthalimidopentane-3-sulfonic acid (**4e**).* Brown oil; yield: 340 mg, 91%. ^{1}H NMR (D_2O, 400 MHz) (δ, ppm) 1.53–1.68 (m, 2H, CH_2), 1.87–2.04 (m, 2H, CH_2), 2.33–2.41 (m, 1H, CH), 2.48 (s, 2H, CH_2), 3.39–3.51 (m, 2H, CH_2), 6.84 (s, 5H, ArH), 7.33–7.47 (m, 4H, ArH). ^{13}C NMR (D_2O, 100 MHz) (δ, ppm) 27.9, 30.5, 31.8, 35.8, 56.6, 123.2, 125.9, 128.1, 128.4, 130.9, 134.5, 140.9, 169.7. IR (ν_{max}, cm^{-1}) 3060, 3027, 1771, 1710, 1170, 1036. HRMS (ESI) calcd for $C_{19}H_{20}NO_5S$ $[M+H]^+$ m/z 374.1062; found 374.1064.

*4.4.6. 1-Phenyl-4-phthalimidobutane-2-sulfonic acid (**4f**).* Brown oil; yield: 323 mg, 90%. ^{1}H NMR (D_2O, 400 MHz) (δ, ppm) 1.49–1.56

(m, 1H in CH_2), 1.84 (m, 1H in CH_2), 2.20 (dd, J=13.3, 12.4 Hz, 1H in CH_2), 2.63–2.68 (m, 1H, CH), 2.96 (dd, J=13.3, 2.5 Hz, 1H in CH_2), 3.14 (ddd, J=14.2, 4.7, 4.6 Hz, 1H in CH_2), 3.30–3.38 (m, 1H in CH_2), 6.43 (dd, J=7.4, 7.2 Hz, 1H, ArH), 6.56 (dd, J=7.4, 7.2 Hz, 2H, ArH), 6.69 (d, J=7.4 Hz, 2H, ArH), 7.23–7.26 (m, 2H, ArH), 7.40–7.43 (m, 2H, ArH). ^{13}C NMR (D_2O, 100 MHz) (δ, ppm) 27.2, 36.2, 36.8, 59.6, 123.1, 126.2, 128.3, 128.7, 130.6, 134.4, 137.6, 169.6. IR (ν_{max}, cm^{-1}) 3059, 3025, 1770, 1707, 1170, 1029. HRMS (ESI) calcd for $C_{18}H_{18}NO_5S$ $[M+H]^+$ m/z 360.0906; found 360.0906.

*4.4.7. 1-Hydroxyl-4-phthalimidobutane-2-sulfonic acid (**4h**).* White solid, mp: 80–81 °C; yield: 278 mg, 93%. ^{1}H NMR (D_2O, 400 MHz) (δ, ppm) 1.87 (dddd, J=14.1, 7.2, 7.0, 7.0 Hz, 1H in CH_2), 2.04 (dddd, J=14.1, 7.6, 7.6, 5.6 Hz, 1H in CH_2), 2.82 (dddd, J=7.6, 7.2, 6.8, 5.6 Hz, 1H, CH), 3.63–3.67 (m, 2H, CH_2), 3.69 (dd, J=12.0, 6.8 Hz, 1H in CH_2), 3.88 (dd, J=12.0, 5.6 Hz, 1H in CH_2), 7.61 (s, 4H, ArH). ^{13}C NMR (D_2O, 100 MHz) (δ, ppm) 25.8, 35.9, 59.4, 60.4, 123.2, 131.1, 134.6, 170.3. IR (ν_{max}, cm^{-1}) 3435, 1771, 1708, 1180, 1043. HRMS (ESI) calcd for $C_{12}H_{13}NNaO_6S$ $[M+Na]^+$ m/z 322.0361; found 322.0359.

*4.4.8. 1-Phenoxyl-4-phthalimidobutane-2-sulfonic acid (**4i**).* White solid, mp: 291–292 °C; yield: 327 mg, 87%. ^{1}H NMR (D_2O, 400 MHz) (δ, ppm) 1.98–2.08 (m, 1H in CH_2), 2.10–2.20 (m, 1H in CH_2), 3.08–3.17 (m, 1H, CH), 3.54–3.60 (m, 1H in CH_2), 3.64–3.71 (m, 1H in CH_2), 3.95 (dd, J=10.8, 8.3 Hz, 1H in CH_2), 4.29 (dd, J=10.8, 4.0 Hz, 1H in CH_2), 6.54–6.59 (m, 3H, ArH), 6.87–6.91 (m, 2H, ArH), 7.44 (dd, J=5.5, 3.1 Hz, 2H, ArH), 7.52 (dd, J=5.5, 3.1 Hz, 2H, ArH). ^{13}C NMR (D_2O, 100 MHz) (δ, ppm) 26.2, 36.2, 56.4, 65.9, 114.3, 121.3, 123.2, 129.5, 130.8, 134.4, 156.8, 170.1. IR (ν_{max}, cm^{-1}) 3058, 1770, 1711, 1180, 1049. HRMS (ESI) calcd for $C_{18}H_{18}NO_6S$ $[M+H]^+$ m/z 376.0855; found 376.0853.

*4.4.9. 4-Phthalimidobutane-1,2-disulfonic acid (**4k**).* Pale yellow crystals, mp: 175–176 °C; yield: 338 mg, 93%. ^{1}H NMR (D_2O, 400 MHz) (δ, ppm) 2.16 (dddd, J=14.0, 7.4, 6.4, 6.2 Hz, 1H in CH_2), 2.29 (dddd, J=14.0, 7.6, 6.4, 6.2 Hz, 1H in CH_2), 2.92 (dd, J=14.1, 10.8 Hz, 1H in CH_2), 3.20 (m, 1H, CH), 3.30 (dd, J=14.1, 1.6 Hz, 1H in CH_2), 3.79 (ddd, J=12.4, 6.4, 6.2 Hz, 1H in CH_2), 3.87 (ddd, J=12.4, 6.4, 6.2 Hz, 1H in CH_2), 7.69–7.76 (m, 4H, ArH). ^{13}C NMR (D_2O, 100 MHz) (δ, ppm) 28.4, 36.4, 51.3, 54.8, 123.2, 131.4, 134.5, 170.7. IR (ν_{max}, cm^{-1}) 1772, 1709, 1188, 1039. HRMS (ESI) calcd for $C_{12}H_{14}NO_8S_2$ $[M+H]^+$ m/z 364.0161; found 364.0152.

*4.4.10. 1,4-Bisphthalimidobutane-2-sulfonic acid (**4l**).* White solid, mp: 216–217 °C; yield: 386 mg, 90%. ^{1}H NMR (D_2O, 400 MHz) (δ, ppm) 1.77–1.84 (m, 1H in CH_2), 2.16–2.24 (m, 1H in CH_2), 3.06–3.08 (m, 1H, CH), 3.49–3.54 (m, 1H in CH_2), 3.65–3.83 (m, 3H, 1H in CH_2 & CH_2), 7.31–7.35 (m, 4H, ArH), 7.55–7.58 (m, 4H, ArH). ^{13}C NMR (D_2O, 100 MHz) (δ, ppm) 26.8, 36.9, 38.7, 55.3, 122.9, 123.0, 123.1, 134.6, 134.8, 134.9, 169.2, 169.5. IR (ν_{max}, cm^{-1}) 1770, 1712, 1180, 1037. HRMS (ESI) calcd for $C_{20}H_{17}N_2O_7S$ $[M+H]^+$ m/z: 429.0756; found 429.0758.

*4.4.11. 1-Benzoxycarbonylamino-4-phthalimidobutane-2-sulfonic acid (**4m**).* Pale yellow solid, mp: 206–209 °C; yield: 381 mg, 90%. ^{1}H NMR (D_2O, 400 MHz) (δ, ppm) 1.86–1.89 (m, 1H in CH_2), 1.93–2.01 (m, 1H in CH_2), 2.81–2.93 (m, 1H, CH), 3.20 (dd, J=14.4, 8.2 Hz, 1H in CH_2), 3.48–3.64 (m, 3H, 1H in CH_2 & CH_2), 4.58 (d, J=12.6 Hz, 1H in CH_2), 4.72 (d, J=12.6 Hz, 1H in CH_2), 7.03–7.16 (m, 5H, ArH), 7.49–7.59 (m, 4H, ArH). ^{13}C NMR (D_2O, 100 MHz) (δ, ppm) 26.3, 36.3, 40.5, 57.0, 66.6, 123.2, 123.3, 127.3, 128.0, 128.1, 128.5, 131.0, 134.5, 134.6, 134.7, 136.1, 157.7, 169.9. IR (ν_{max}, cm^{-1}) 3356, 3059, 3031, 1772, 1710, 1179, 1048. HRMS (ESI) calcd for $C_{20}H_{21}N_2O_7S$ $[M+H]^+$ m/z 433.1069; found 433.1066.

*4.4.12. 1-Amino-4-phthalimidobutane-2-sulfonic acid (**4n**).* White solid, mp: 303–305 °C; yield: 265 mg, 89%. ^{1}H NMR (DMSO-d_6, 400 MHz) (δ, ppm) 1.64 (dddd, J=14.3, 7.7, 7.5, 7.5 Hz, 1H in CH_2), 2.14 (dddd, J=14.3, 8.1, 6.1, 6.1 Hz, 1H in CH_2), 2.60–2.66 (m, 1H, CH), 2.92–2.02 (m, 1H in CH_2), 3.04–3.12 (m, 1H in CH_2), 3.37 (s, 1H, OH), 3.63–3.69 (m, 1H in CH_2), 3.74–3.83 (m, 1H in CH_2), 7.72 (s, 2H, NH_2), 7.82–7.88 (m, 4H, ArH). ^{13}C NMR (DMSO-d_6, 100 MHz) (δ, ppm) 27.1, 35.4, 39.5, 53.4, 123.0, 131.7, 134.3, 167.9. IR (ν_{max}, cm^{-1}) 3368, 3025, 1771, 1709, 1180, 1043. HRMS (ESI) calcd for $C_{12}H_{15}N_2O_5S$ $[M+H]^+$ m/z 299.0702; found 299.0704.

*4.4.13. 1,5-Bisphthalimidopentane-3-sulfonic acid (**4t**).* White solid, mp: 167–168 °C; yield: 411 mg, 93%. ^{1}H NMR (D_2O, 400 MHz) (δ, ppm) 1.77 (dddd, J=13.4, 6.5, 6.4, 6.4 Hz, 2H in $2CH_2$), 2.10 (dddd, J=13.4, 7.0, 6.5, 6.4 Hz, 2H in $2CH_2$), 2.65 (dddd, J=6.5, 6.5, 6.4, 6.4 Hz, 1H, CH), 3.59 (ddd, J=14.2, 7.0, 6.4 Hz, 2H in $2CH_2$), 3.59 (ddd, J=14.2, 7.0, 6.4 Hz, 2H in $2CH_2$), 7.43 (dd, J=5.4, 3.0 Hz, 2H, ArH), 7.58 (dd, J=5.4, 3.0 Hz, 2H, ArH). ^{13}C NMR (D_2O, 100 MHz) (δ, ppm) 14.2, 28.3, 35.5, 55.2, 65.8, 123.1, 130.9, 134.6, 135.0, 170.0. IR (ν_{max}, cm^{-1}) 1770, 1709, 1180, 1037. HRMS (ESI) calcd for $C_{21}H_{19}N_2O_7S$ $[M+H]^+$ m/z 443.0913; found 443.0915.

4.5. Synthesis of *O*-ethyl *S*-1-phthalimidoalkyl xanthates 6

To a rapidly stirred suspension of benzyl carbamate (4.65 g, 31 mmol) and sodium benzenesulfinate (10.18 g, 62 mmol) in a mixture of methanol/water (30/60 mL) was added an aldehyde (47 mmol) in one portion, followed by formic acid (4.7 mL). The reaction mixture was vigorously stirred for three days and then filtered. The resulting white solid was filtered and washed with water (50 mL) and ether (50 mL) and then recrystallized from ethyl acetate to furnish sulfone.

The sulfone (5 mmol) was dissolved in acetone (50 mL) and potassium *O*-ethyl xanthate (841 mg, 5.25 mmol, 1.05 equiv) was added portionwise in an ice water bath. The resulting mixture was stirred for 2 h at room temperature. After removal of the solvent, the residue was purified by column chromatography on silica (petroleum ether/ethyl acetate: 5/1 v/v) to afford xanthate **6**.

*4.5.1. Benzyl N-1-(ethoxythiocarbonylthio)hexylcarbamate (**6a**).* Pale yellow oil; yield: 1.56 g, 70%. ^{1}H NMR ($CDCl_3$, 400 MHz) (δ, ppm) 0.88 (t, J=6.9 Hz, 3H, CH_3), 1.39 (t, J=7.1 Hz, 3H, CH_3), 1.29–1.43 (m, 6H, $3CH_2$), 1.91–2.01 (m, 2H, CH_2), 4.59–4.64 (m, 2H, CH_2), 5.12 (s, 2H, CH_2), 5.43 (ddd, J=7.2, 7.2, 7.2 Hz, 1H, CH), 5.48 (br s, 1H, NH), 7.30–7.38 (m, 5H, ArH). ^{13}C NMR ($CDCl_3$, 100 MHz) (δ, ppm) 13.7, 13.9, 22.4, 25.9, 31.1, 34.9, 61.8, 67.1, 69.8, 128.1, 128.2, 128.5, 136.0, 154.8, 212.5. IR (ν_{max}, cm^{-1}) 3313, 3059, 3025, 1701, 1228, 1049. HRMS (ESI) calcd for $C_{17}H_{25}NNaO_3S_2$ $[M+Na]^+$ m/z: 378.1174; found 378.1174.

*4.5.2. Benzyl N-[1-(ethoxythiocarbonylthio)-1-phenylmethyl]carbamate (**6b**).* White solid, mp: 114–115 °C; yield: 1.23 g, 54%. ^{1}H NMR ($CDCl_3$, 400 MHz) (δ, ppm) 1.31 (t, J=7.1 Hz, 3H, CH_3), 4.57 (q, J=7.1 Hz, 2H, CH_2), 5.13 (s, 2H, CH_2), 5.71 (br s, 1H, NH), 6.63 (d, J=8.6 Hz, 1H, CH), 7.29–7.37 (m, 10H, ArH). ^{13}C NMR ($CDCl_3$, 100 MHz) (δ, ppm) 13.5, 62.9, 67.4, 70.0, 126.7, 128.2, 128.3, 128.5, 128.9, 135.8, 137.5, 154.6, 210.6. IR (ν_{max}, cm^{-1}) 3359, 3060, 3025, 1704, 1234, 1045. HRMS (ESI) calcd for $C_{18}H_{19}NKO_3S_2$ $[M+K]^+$ m/z: 400.0443; found. 400.0431.

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Supplementary data

Copies of the ^{1}H NMR and ^{13}C NMR spectra of all key intermediates and final products. These data include MOL files and

InChiKeys of the most important compounds described in this article. Supplementary data associated with this article can be found in the online version, at http://dx.doi.org/10.1016/j.tet.2012.11.074. These data include MOL files and InChiKeys of the most important compounds described in this article.

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