An Improved and Green Preparation of 3-(Alkylthio)propionic Acids

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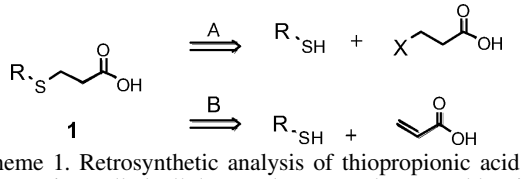
An efficient, facile microwave-assisted synthesis has been developed for the preparation of unsymmetrical sulfide derivatives from 3-mercaptopropionic acid and a wide variety of alkyl, allyl or aryl chlorides or bromides. The synthesis performed in ethanol at 80 or 120 °C using sodium hydroxide as a base, selectively without an offensive smell, generates 3-(alkylthio)propionic acids in good yields. Effects of reaction components, temperature, and the heating technique on the formation of the product and side-products were studied.

Key words: Thio-alkylation, Microwave-assisted Synthesis, Unsymmetrical Sulfide, β-(Alkylthio)carboxylic Acid

Introduction

3-(Alkylthio)propionic acids **1** are industrially interesting compounds. They have been used as additives in various applications [1 – 6] to improve resistance toward heat [2] and oxidants [3], as well as to increase lubrication [4], antibacterial, and detergent properties [1] of various materials. Derivatives with small molecular masses have also been studied in antiviral [7] and other biological [8] applications as close analogues of cysteine and methionine and, therefore, they are potential starting compounds for drug development studies.

The alkylation of a thiol group is a well-known synthetic procedure. The syntheses of **1** have usually been performed by S_N2 displacement of a halide group with a thiol group or by a polar addition of an alkanethiol to an α,β-unsaturated carboxylic acid (Scheme 1) [9]. Typically, substitutions of this kind need rather harsh reaction conditions, and often a stoichiometric amount of a base, *e. g*. NaOH [10], sodium alkoxide [11], or KOH [12], to activate the sulphur nucleophile. Modern versions of nucleophilic substitution by a thiol include a palladium-catalyzed reaction with an alkyl halide in the presence of phosphine additives and Et_3N [13] or Na_2CO_3 [14], *S*-alkylation (thioalkylation) in an ionic liquid by using K_2CO_3 [15], or using a phase transfer catalyst [16] or a hydrotalcite clay [17]. Usually, an equimolar amount of a base is needed to bind the leaving group, *e. g*. a halide anion. In addition, it is known that thiols tend to form side products with a repulsive odor like volatile sulfides and disulfides (Scheme 2) under basic reaction conditions [9].



Scheme 1. Retrosynthetic analysis of thiopropionic acid **1**, where R is an alkyl, allyl, or aryl group and *X* a good leaving group, as *e. g*. Cl or Br.

This paper reports an improved, rapid and almost odorless synthesis of **1** starting from 3-mercaptopropionic acid and a wide variety of halides R*X* (R = alkyl, allyl, or aryl; *X* = Cl, or Br) by using microwave activation.

Results and Discussion

The reaction of a β-halo-substituted carboxylic acid with an alkyl thiol using solid NaOH in ethanol was our starting point toward propionic acid derivatives **1** (Scheme 1, route A) [18]. The substitution of 3-chloropropionic acid (**2**) by a slight excess of butanethiol (**3**) in refluxing ethanol for 1 h gave a crude product from which the desired product **4** was easy to isolate. The formation of non-toxic sodium halide as a side product was the primary reason to select NaOH as the base. However, the reaction mixture contained some malodorous by-products, *S*-dibutylsulfide (**5**) and *S*,*S*′-dibutyldisulfide (**6**) and an ester **7** identified by GC-MS and ^{1}H NMR methods (Scheme 2). In order to improve

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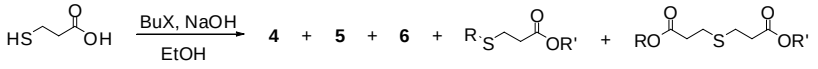
Table 1. The effect of the reaction temperature on the microwave-assisted synthesis of 3-(butylthio)propionic acid (**4**).



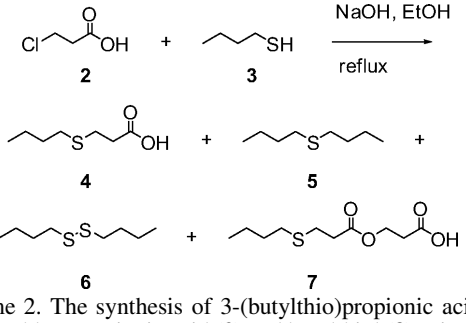
8

9: R, R' = Bu
10: R = H, R' = Bu

11: R, R' = Et
12: R = Et, R' = Bu
13: R, R' = Bu

	Reactant/reagent (equiv.)				Time	Components in the reaction mixture (%)[a]					Isolated
Entry	BuX[b]	X	NaOH	T (°C)	(min)	**4**	**5**	**9**	**10** – **13**	**3**	yield of **4** (%)
1	1.1	Cl	2.0	70	10						0[c]
2	1.1	Cl	2.0	80	10	100					77
3	1.1	Cl	2.0	100	10	98			2 (**11**)		77
4	1.1	Cl	2.0	120	10	> 98		< 1	< 1 (**11**)		84
5	1.1	Cl	2.0	140	10	93	2	4	< 1 (**11**)	1	83
6	1.1	Cl	2.0	160	10	75	7	14	< 1 (**11**)	3	69
7	1.1	Br	2.0	70	10	97	1	2			60
8	1.1	Br	2.0	80	10	96	1	3			72
9	1.1	Br	2.0	100	10	87	2	11			78
10	1.1	Br	2.0	120	10	54	13	30	3 (**10**)	< 1	59
11	1.1	Br	2.0	160	10	21	17	22	34 (**10**), 4 (**11**)	2	no purification

[a] Compounds were identified by GC-MS (EI) [21, 22]. Percentages are based on GC analysis (FID). The formation of *S*,*S*′-dibutyldisulfide (**6**) was not detected. [b] If not specified otherwise, in this paper "butyl" always refers to "*n*-butyl". c) Only the starting material **8** was recovered.



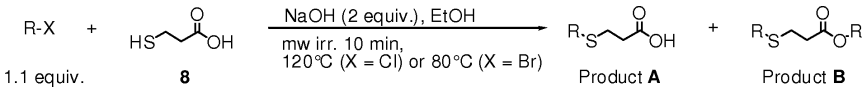
Scheme 2. The synthesis of 3-(butylthio)propionic acid (**4**) from 3-chloropropionic acid (**2**) and butylthiol (**3**) using conventional heating. Side products **5**, **6**, and **7** were verified by GC-MS and ^{1}H NMR [20 – 22].

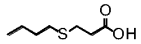
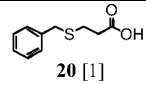
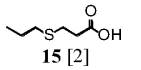
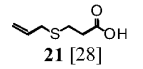
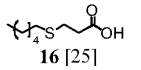
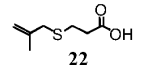
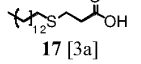
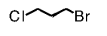
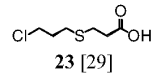
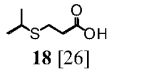
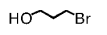
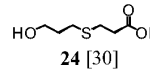
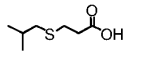
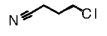
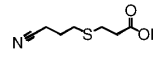
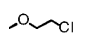
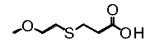
the fair yield (67 %), the reaction was repeated by using 1.5 equivalents of **3**. However, the use of excess thiol increased the formation of **5**, **6**, and **7**. Similar results were obtained also in the reaction of **2** with other alkanethiols [19]. Obviously, there is a competition between the thiol and the carboxylate function of **2** toward the halide substituted carbon. Thus, the substitution by a soft nucleophile like thiol is a thermodynamically favorable process and therefore, microwave-assistance is suitable for this reaction.

Under microwave irradiation at 70 °C for 10 min, the analogous reaction between **2** and **3** (Scheme 2) produced besides 3-(butylthio)propionic acid (**4**) some sulfide **5** and ester **7**. In order to prevent the formation of the sulfides **5** and **6**, the functionality of the starting compounds was simply interchanged so that 3-mercaptopropionic acid (**8**) and alkyl halides were used instead. This change also multiplied the variety of commercially available starting materials. The deprotonation of the carboxylic acid required the use of an additional equivalent of sodium hydroxide [23]. The microwave-assisted reaction of **8** with butyl chloride at 70 °C did not yield any *S*-alkylated product (Table 1, entry 1). However, when the reaction temperature was raised to 80 °C, the reaction made a dramatic progress (Table 1, entry 2). A series of microwave-assisted experiments was carried out at various temperatures as shown in Table 1.

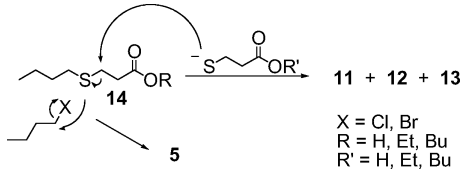
The results in Table 1 show the influence of the reaction temperature on the selectivity of *S*-alkylation. The reaction of **8** with butyl chloride at 80 °C solely yielded the product **4**. Reaction temperatures higher than 100 °C had only a minor effect on the total yield but induced the formation of side products. The reaction of butyl bromide was cleanest at the lowest reaction temperature (70 or 80 °C). In addition, substitutions of butyl bromide (Table 1, entries 7 – 11) yielded more ester side products **9** and **10** than those of the corresponding chloride (Table 1, entries 4 – 6). Thereby, the isolated yields of **4** from the reactions with butyl bromide were systematically lower than with the corresponding chloride. Amazingly, the substitution reactions at high temperatures with mercaptopropionic acid (**8**) still yielded some sulfide **5** (Table 1, entries 5 – 11). This cannot be explained by a direct reaction between the reactants. We believe that sulfide **5** can be formed by the cleavage of the C–S bond in compound **14** [24] forced either by heat or by the attack of the thiolate an-

Table 2. Products and yields of microwave-assisted syntheses of 3-(alkylthio)propionic acid derivatives under basic conditions in ethanol.



Entry	R–X	Product **A**	Yield of **A** (%)[a]	Ratio **A** : **B**[b]	Entry	R–X	Product **A**	Yield of **A** (%)[a]	Ratio **A** : **B**[b]
1		 **4** [1]	89	99 : 1	8		 **20** [1]	72	79 : 21
2		 **15** [2]	94	99 : 1	9		 **21** [28]	85	94 : 6
3		 **16** [25]	94	99 : 1	10		 **22**	85	96 : 4
4		 **17** [3a]	77	99 : 1	11		 **23** [29]	90	95 : 5
5		 **18** [26]	97	99 : 1	12		 **24** [30]	57	90 : 10
6		 **19** [27]	90	99 : 1	13		 **25**	82	98 : 2
7		**19** [27]	72	96 : 4[c]	14		 **26**	90	99 : 1

[a] Isolated yield; [b] the ratio of the acid (**A**) *vs*. its ester (**B**) as based on ^{1}H NMR. The amount of the ester (**B**) was calculated from the integral value of OCH_2 triplet at 4.2 – 4.5 ppm; [c] *tert*-butyl ester of **19**.



Scheme 3. A possible path for the formation of side products in the microwave-assisted thio-alkylation of mercaptopropionic acid (**8**).

ion at the β-position of **14** (Scheme 3). The formation of butanethiol (**3**) in high temperature reactions supports the former assumption (Table 1, entries 5, 6, 10, 11). However, the formation of thio(bis)propionic acid derivatives **11** – **13** speaks for the nucleophilic substitution at the β-carbon. Ethyl esters **11** and **12** were formed in the esterification reaction with the solvent.

Based on the results presented in Table 1, the optimum reaction temperature for the microwave-assisted preparation of 3-(alkylthio)propionic acids **1** was 120 and 80 °C for various chlorides and bromides, respectively. Temperature profiles of *S*-alkylations were similar for both halides reaching the set temperature in 20 s by an initial irradiation power of 100 – 200 W. After 2 min the irradiation was continued with the power of 15 – 25 W for the rest of the reaction. *S*-Alkylation of **8** with simple primary and secondary halides selectively yielded the desired product **A** (Table 2, entries 1 – 6). Aryl, allyl and tertiary alkyl halides can form stable carbocations and, therefore, favour the S_N1-type reaction with a nucleophile resulting in the increasing formation of the ester **B** (Table 2, entries 7 – 10).

In order to see what would happen between the reaction components when the S_N2-type substitution is an unfavourable process, the alkylation with a hindered halide, tertiary butyl chloride, was carried out (Table 2, entry 7). As expected, the main product was not the *tert*-butyl adduct of **8**. We believe that *tert*-butyl chloride under basic conditions formed the elimination product 2-methylpropene which subsequently reacted with **8** yielding *iso*-butylthiopropionic acid (**19**). Indeed, the formation of gaseous 2-methylpropene was detected by GC-MS during the reaction. This would explain the moderate yield of the reaction (72 %). The same reaction was repeated also at 80 and 100 °C producing even lower yields of **19**. The preparation of functionalized 3-(alkylthio)propionic acids was stud-

ied by using the corresponding halides (Table 2, entries 11 – 14).

Simultaneous bromo and chloro substitution in the alkyl chain directed the *S*-alkylation to take place with good selectivity at the bromo substituted end, yielding compound **23**. The latter is an excellent starting compound for further 3-(alkylthio)propionic acid derivatives. A similar trend was also observed in *S*-alkylation with other double-substituted compounds. Substitution occurred at the end carrying the good leaving group (Table 2, entries 12 – 14). The relatively low isolated yield of 3-(2-hydroxypropylthio)propionic acid (**24**) (57 %) is explained by its high water-solubility. It was found later in the course of this study that ethyl acetate probably could be used in place of dichloromethane in the isolation of all products in Table 2 (ethyl acetate was tested in the extraction of compounds **17** – **24**). This would be a further improvement towards greener chemistry.

Conclusion

In summary, the presented microwave-assisted *S*-alkylation of 3-mercaptopropionic acid by alkyl, allyl, or aryl halides is a simple, efficient, and green method to prepare various 3-(alkylthio)propionic acids. The improved method minimized the formation of toxic side products. Interchange of the functionality of the reactive components increased the chemoselectivity of *S*-alkylation towards the desired product and simultaneously decreased the formation of odorous by-product. The amount of side products could be further diminished by optimizing the reaction temperature according to the leaving group. The optimum reaction temperatures for chlorides and bromides were 120 and 80 °C, respectively. The use of microwave activation was superior to conventional heating. Besides the shortening of the reaction time from 1 h to 10 min, the purity and yield of 3-(alkylthio)propionic acids were improved.

Experimental Section

All commercially available reagents (Aldrich, Fluka, Merck) were used as purchased. ^{1}H and ^{13}C nuclear magnetic resonance spectra were recorded on a Bruker DPX 200 spectrometer and are reported in ppm from internal tetramethylsilane (TMS) or solvent residue ($CDCl_3$, δ_H = 7.26 ppm, δ_C = 77.16 ppm). Gas chromatograms were recorded on a Perkin Elmer Autosystem XL using a CP-SIL 19 CB column equipped with an FI detector. EI mass spectra (GC-MS) were recorded at 70 eV ionization energies using a HP 5973 mass spectrometer and a HP 6890 series GC system with a DB-624 column. High resolution mass spectra (ESI-MS) were recorded either at negative $[M–H]^-$ or positive $[M+Na]^+$ modes on a Micromass LCT mass spectrometer equipped with a TOF detector, *N*-(*N*-butyl)benzenesulfonamide being used as a lock mass. The purity of the products was determined to be > 95 % by ^{1}H NMR and GC. Microwave-assisted syntheses were performed in Biotage's SmithCreator™ or Initiator™ microwave reactors with a single mode cavity in closed vials with a standard aluminum open-top seal with a septum and equipped with a teflon-coated stirring bar.

Typical procedure

3-Mercaptopropionic acid (**8**) (1.00 g, 9.4 mmol) and 2 mL of ethanol (absolute) were placed into a 7 mL reactor vial. Halide (1.1 equiv.), NaOH (0.75 g, 18.8 mmol) and an additional 1 mL of absolute ethanol were added to the solution followed by a microwave irradiation period of 10 min within the temperature appointed (80 °C for bromides or 120 °C for chlorides). After the reaction was quenched by 20 mL of 2 M HCl, the reaction mixture was extracted with 20 mL of dichloromethane or ethyl acetate. The separated water phase was washed with an additional 20 mL of dichloromethane or ethyl acetate. Organic fractions were combined, dried (Na_2SO_4), filtered, and concentrated.

*3-(Butylthio)propionic acid (**4**)* [1]

Yield 89 % (colorless oil, 1.36 g, 8.4 mmol). – ^{1}H NMR (200 MHz, $CDCl_3$): δ = 10.73 (br. s, 1 H, OH), 2.9 – 2.6 (m, 4 H, SCH_2CH_2CO), 2.55 (t, J = 7.3 Hz, 2 H, $CH_3(CH_2)_3CH_2S$), 1.75 – 1.30 (m, 4 H, $CH_3CH_2CH_2$), 0.92 (t, J = 7.2 Hz, 3 H, CH_3). – ^{13}C NMR (50 MHz, $CDCl_3$): δ = 178.5 (C=O), 34.8, 31.9, 31.6, 26.6, 22.0, 13.7 (CH_3). – HRMS ((–)ESI): *m/z* = 161.0642 (calcd. 161.0636 for $C_7H_{13}O_2S$).

*3-(Propylthio)propionic acid (**15**)* [2]

Yield 94 % (colorless oil, 1.31 g, 8.8 mmol). – ^{1}H NMR (200 MHz, $CDCl_3$): δ = 10.92 (br. s, 1H, OH), 2.9 – 2.6 (m, 4 H, SCH_2CH_2CO), 2.53 (t, J = 7.3 Hz, 2 H, $CH_3CH_2CH_2S$), 1.62 (m, J = 7.3 Hz, 2 H, CH_3CH_2), 0.99 (t, J = 7.3 Hz, 3 H, CH_3). – ^{13}C NMR (50 MHz, $CDCl_3$): δ = 178.5 (C=O), 34.8, 34.2, 26.6, 22.9, 13.5 (CH_3). – HRMS ((–)ESI): *m/z* = 147.0516 (calcd. 147.0480 for $C_6H_{11}O_2S$).

*3-(Hexylthio)propionic acid (**16**)* [25]

Yield 94 % (colorless oil, 1.69 g, 8.9 mmol). – ^{1}H NMR (200 MHz, $CDCl_3$): δ = 11.66 (br. s, 1 H, OH), 2.9 – 2.6 (m, 4 H, SCH_2CH_2CO), 2.54 (t, J = 7.3 Hz, 2 H, $CH_3(CH_2)_4CH_2S$), 1.7 – 1.5 (m, 2 H, CH_2CH_2S), 1.5 – 1.2

(m, 6 H, $CH_3CH_2CH_2CH_2$), 0.89 (t, J = 6.6 Hz, 3 H, CH_3). – ^{13}C NMR (50 MHz, $CDCl_3$): δ = 178.6 (C=O), 34.8, 32.2, 31.4, 29.5, 28.5, 26.6, 22.6, 14.0 (CH_3). – HRMS ((–)ESI): *m/z* = 189.0930 (calcd. 189.0949 for $C_9H_{17}O_2S$).

*3-(Tetradecylthio)propionic acid (**17**)* [3a]

Yield 77 % (white crystals, 2.26 g, 7.5 mmol). – ^{1}H NMR (200 MHz, $CDCl_3$): δ = 10.93 (br. s, 1 H, OH), 2.79 (2dd, J = 2.5, 6.0, and 1.1, 8.1 Hz, 2 H, SCH_2CH_2CO), 2.66 (2dd, J = 1.1, 8.1, and 2.5, 6. 2 H, 0 Hz, SCH_2CH_2CO), 2.53 (t, J = 7.3 Hz, 2 H, $CH_3(CH_2)_{12}CH_2S$), 1.58 (m, J = 7.3 Hz, 2 H, $CH_3(CH_2)_{11}CH_2CH_2S$), 1.45 – 1.15 (m, 22 H, $CH_3(CH_2)_{11}$), 0.88 (t, J = 6.5 Hz, 3 H, CH_3). – ^{13}C NMR (50 MHz, $CDCl_3$): δ = 178.3 (C=O), 34.8, 32.3, 32.1, 29.83, 29.82, 29.79 (2×C), 29.74, 29.66 (2×C), 29.5, 29.4, 29.0, 26.7, 22.8, 14.3 (CH_3). – HRMS ((+)ESI): *m/z* = 325.2162 (calcd. 325.2177 for $C_{17}H_{34}NaO_2S$).

*3-(Isopropylthio)propionic acid (**18**)* [26]

Yield 97 % (colorless oil, 1.34 g, 9.1 mmol). – ^{1}H NMR (200 MHz, $CDCl_3$): δ = 11.54 (br. s, 1 H, OH), 2.96 (m, J = 6.7 Hz, 1 H, CHS), 2.9 – 2.6 (m, 4 H, SCH_2CH_2CO), 1.28 (d, J = 6.7 Hz, 6 H, 2 CH_3). – ^{13}C NMR (50 MHz, $CDCl_3$): δ = 178.5 (C=O), 35.0, 34.8, 25.0, 23.3 ($2CH_3$). – HRMS ((–)ESI): *m/z* = 147.0507 (calcd. 147.0480 for $C_6H_{11}O_2S$).

*3-(Isobutylthio)propionic acid (**19**)* [27]

Yield 90 % (colorless oil, 1.42 g, 8.8 mmol). – ^{1}H NMR (200 MHz, $CDCl_3$): δ = 11.60 (br. s, 1 H, OH), 2.9 – 2.6 (m, 4 H, SCH_2CH_2CO), 2.43 (d, J = 6.8 Hz, 2 H, $CHCH_2S$), 1.80 (m, J = 6.6, 6.8 Hz, 1 H, CH), 0.99 (d, J = 6.6 Hz, 6 H, 2 CH_3). – ^{13}C NMR (50 MHz, $CDCl_3$): δ = 178.6 (C=O), 41.5, 34.9, 28.6, 27.2, 22.0 (2×CH_3). – HRMS ((–)ESI): *m/z* = 161.0625 (calcd. 161.0636 for $C_7H_{13}O_2S$).

*3-(Benzylthio)propionic acid (**20**)* [1]

The reaction was performed as described in the typical procedure above. It was, however, quenched with 10 mL of water and subsequently washed with 10 mL of dichloromethane. The water phase was acidified with 2 M HCl, and extracted with ethyl acetate. The organic fractions were combined, dried (Na_2SO_4), filtered, and concentrated. Yield 72 % (white crystals, 1.33 g, 6.8 mmol). – ^{1}H NMR (200 MHz, $CDCl_3$): δ = 10.23 (br. s, 1 H, OH), 7.4 – 7.1 (m, 5 H (+$CHCl_3$), arom. Hs), 3.72 (s, 2 H, $PhCH_2S$), 2.8 – 2.5 (m, 4 H, SCH_2CH_2CO). – ^{13}C NMR (50 MHz, $CDCl_3$): δ = 178.1 (C=O), 137.9, 128.8 (2× arom. C), 128.6 (2× arom. C), 127.1, 36.3, 34.3, 25.8. – HRMS ((–)ESI): *m/z* = 195.0475 (calcd. 195.0480 for $C_{10}H_{11}O_2S$).

*3-(Prop-2-enylthio)propionic acid (**21**)* [28]

Yield 85 % (colorless oil, 1.16 g, 7.9 mmol). – ^{1}H NMR (200 MHz, $CDCl_3$): δ = 11.73 (br. s, 1 H, OH), 5.9 – 5.6 (1H, m, CH), 5.2 – 5.05 (m, 2 H, CH_2CH), 3.16 (td, J = 1.1, 7.2 Hz, 2 H, $CHCH_2S$), 2.9 – 2.6 (m, 4 H, SCH_2CH_2CO). – ^{13}C NMR (50 MHz, $CDCl_3$): δ = 178.5 (C=O), 134.0, 117.4, 34.8, 34.4, 25.1. – HRMS ((–)ESI): *m/z* = 145.0356 (calcd. 145.0323 for $C_6H_9O_2S$).

*3-[(2-Methyl-prop-2-enyl)thio]propionic acid (**22**)*

Yield 85 % (colorless oil, 1.28 g, 8,0 mmol). – ^{1}H NMR (200 MHz, $CDCl_3$): δ = 10.63 (br. s, 1 H, OH), 4.87 (fragmented s, J = 1.4 Hz, 1 H, CH_2C *cis* to CH_3), 4.84 (fragmented s, J = 0.96 Hz, 1 H, CH_2C *cis* to CH_2), 3.14 (fragmented s, J = 0.96 Hz, 2 H, CCH_2S), 2.8 – 2.6 (4H, m, SCH_2CH_2CO), 1.82 (fragmented s, J = 1.4, 0.86 Hz, 3 H, CH_3). – ^{13}C NMR (50 MHz, $CDCl_3$): δ = 178.6 (C=O), 141.0 (quaternary C), 113.6, 39.4, 34.3, 25.3, 20.5 (CH_3). – HRMS ((–)ESI): *m/z* = 159.0499 (calcd. 159.0480 for $C_7H_{11}O_2S$).

*3-(3-Chloropropylthio)propionic acid (**23**)* [29]

The reaction was performed as described in the typical procedure. However, the reaction was quenched by adding 10 mL of water and washed with 10 mL of dichloromethane in order to remove residues of 1-bromo-3-chloropropane. The water phase was acidified with 2 M HCl and extracted with dichloromethane or ethyl acetate. The organic fractions were combined, dried (Na_2SO_4), filtered, and concentrated. Yield 90 % (white crystals, 1.58 g, 8.7 mmol). – ^{1}H NMR (200 MHz, $CDCl_3$): δ = 11.04 (br. s, 1 H, OH), 3.66 (t, J_{av} = 6.4 Hz, 2 H, CH_2Cl), 2.85 – 2.55 (m, 6 H, $CH_2SCH_2CH_2CO$), 2.05 (m, J_{av} = 6.4 Hz, 2 H, $CH_2CH_2CH_2$). – ^{13}C NMR (50 MHz, $CDCl_3$): δ = 178.3 (C=O), 43.4, 34.7, 32.0, 29.1, 26.7. – HRMS ((+)ESI): *m/z* = 205.0062 (calcd. 205.0066 for $C_6H_{11}ClNaO_2S$).

*3-(3-Hydroxypropylthio)propionic acid (**24**)* [30]

Reaction and isolation were performed as described in the typical procedure above except that diethyl ether (4 × 20 mL) was used for extraction and the acidic water phase was saturated with NaCl. Yield 57 % (colorless oil, 0.89 g, 5.4 mmol). – ^{1}H NMR (200 MHz, $CDCl_3$): δ = 3.73 (t, J_{av} = 6.6 Hz, 2 H, $HOCH_2$), 2.90 – 2.55 (m, 6 H, $CH_2SCH_2CH_2CO$), 1.84 (m, J_{av} = 6.6 Hz, 2 H, $CH_2CH_2CH_2$). – ^{13}C NMR (50 MHz, $CDCl_3$): δ = 176.3 (C=O), 61.2, 34.6, 31.7, 28.5, 26.7. – HRMS ((–)ESI): *m/z* = 163.0448 (calcd. 163.0429 for $C_6H_{11}O_3S$).

*3-[(3-Cyanopropyl)thio]propionic acid (**25**)*

The reaction was performed as described in the typical procedure above. However, it was quenched with 10 mL of water and subsequently washed with 10 mL of dichloromethane in order to remove residues of 3-cyanopropyl-1-chloride. The water phase was acidified with 2 M HCl and extracted with CH_2Cl_2 as before. The organic fractions

were combined, dried (Na_2SO_4), filtered and concentrated yielding a colorless oil (1.33 g, 7.7 mmol, 82 %). – ^{1}H NMR (200 MHz, $CDCl_3$): δ = 11.42 (br. s, 1 H, OH), 2.85 – 2.6 (m, 6 H, $CH_2SCH_2CH_2CO$), 2.53 (t, J = 7.0 Hz, 2 H, $CNCH_2$), 1.95 (m, J = 7.0 Hz, 2 H, $CH_2CH_2CH_2$). – ^{13}C NMR (50 MHz, $CDCl_3$): δ = 177.8 (C=O), 119.1 (CN), 34.4, 30.5, 26.3, 24.9, 15.9. – HRMS ((–)ESI): *m/z* = 172.0420 (calcd. 172.0432 for $C_7H_{10}NO_2S$).

*3-(2-Methoxyethylthio)propionic acid (**26**)*

Yield 90 % (pale yellow oil, 1.55 g, 8.5 mmol). – ^{1}H NMR (200 MHz, $CDCl_3$): δ = 11.49 (br. s, 1 H, OH), 3.59 (t, J = 6.6 Hz, 2 H, CH_2O), 3.38 (s, 3 H, CH_3), 2.9 – 2.6 (m, 4 H, SCH_2CH_2CO), 2.74 (t, J = 6.6 Hz, 2 H, OCH_2CH_2S). – ^{13}C NMR (50 MHz, $CDCl_3$): δ = 177.5 (C=O), 72.0, 58.5, 34.6, 31.3, 26.9. – HRMS ((–)ESI): *m/z* = 163.0400 (calcd. 163.0395 for $C_6H_{11}O_3S$).

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[21] The product mixture of the reaction between **8** and butyl halide was analyzed by GC-MS (EI). Reactions presented in Table 2 yielded the following identified products: *S*-dibutylsulfide (**5**); *Rt* = 4.6 min; *m/z* (%) = 146 (66) $[M]^+$, 117 (8) $[M–CH_2CH_3]^+$, 103 (16) $[M–CH_2CH_2CH_3]^+$, 90 (29) $[BuSH]^+$, 75 (6), 61 (100) $[CH_2SCH_2]^+$, 56 (96), 47 (13), 41 (52). Butyl 3-mercaptopropanoate (**10**); *Rt* = 6.0 min; *m/z* (%) = 162 (26) $[M]^+$, 160 (15) $[M–2]^+$, 132 (5), 115 (5), 106 (54), 89 (70), 88 (100), 73 (31), 61 (81), 57 (68), 56 (68), 55 (62), 41 (94). *S*,*S*′-Dibutyldisulfide (**6**); *m/z* (%) = 178 (58) $[M]^+$, 122 (41) $[BuSSH]^+$, 87 (9), 57 (100) $[CH_3CH_2CHCH_2]^+$, 41 (65). 3-(Butylthio)propionic acid (**4**); *Rt* = 8.1 min; *m/z* (%) = 162 (58) $[M]^+$, 145 (< 1) $[M–OH]^+$, 133 (2) $[M–CH_3CH_2]^+$, 119 (10) $[M–CH_3CH_2CH_2]^+$, 106 (23), 89 (100) $[BuS^+]^+$, 77 (8), 73 (8), 61 (42), 56 (40) 55 (40), 45 (33), 41 (38). Butyl 3-(butylthio)propanoate (**9**); *Rt* = 9.3 min; *m/z* (%) = 218 (43) $[M]^+$, 162 (33), 145 (33), 129 (8), 116 (48), 106 (40), 89 (100), 74 (54), 61 (77), 57 (76), 55 (73), 47 (21), 45 (87). Ethyl 3-[(3-butoxy-3-oxopropyl) thio]propanoate (**12**); *Rt* = 11.5 min; *m/z* (%) = 262 (2) $[M]^+$, 206 (2), 188 (2), 160 (5), 143 (8), 133 (6), 114 (10), 105 (19), 89 (9), 87 (10), 73 (16), 60 (30), 55 (73), 45 (51), 41 (100). Diethyl 3,3'-thiobispropanoate (**11**); *Rt* = 11.9 min; *m/z* (%) = 234 (1) $[M]^+$, 165 (2), 143 (2), 132 (22), 114 (15), 105 (8), 89 (20), 73 (17), 55 (45), 45 (83), 41 (100). Dibutyl 3,3′-thiobispropanoate (**13**); *Rt* = 13.0 min; *m/z* (%) = 290 (1) $[M]^+$, 217 (1), 188 (3), 161 (1), 143 (5), 132 (4), 114 (8), 105 (13), 89 (9), 73 (8), 57 (36), 55 (44), 41 (100).

[22] Compound **7** formed in the preparation of **4** was identified in the crude product mixture. – ^{1}H NMR: δ = 4.38 ppm (t, J = 6.3 Hz, 2H, $COOCH_2CH_2COOH$). – MS-EI (silylated with HMDS): *m/z* (%) = 306 (4) $[M+Si(CH_3)_3]^+$, 218 (3), 163 (9), 145 (38), 129 (88), 116 (100), 103 (57), 101 (36), 88 (31), 75 (72), 73 (86), 61 (76), 55 (75), 41 (24).

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