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Full Paper

Use of Ethyl (Benzothiazol-2-ylsulfonyl)acetate for Malonic Ester-type Syntheses of Carboxylic Acids and Esters*

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A new methodology for the synthesis of substituted carboxylic acids is described. Alkylation of either ethyl (benzothiazol-2-ylsulfonyl)acetate or ethyl 2-(benzothiazol-2-ylsulfonyl)propionate was achieved with alkyl halides and 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) in dichloromethane solution. These products were then desulfinated and hydrolysed in one-pot under mild conditions to give substituted acetic acids in good-to-excellent yields.

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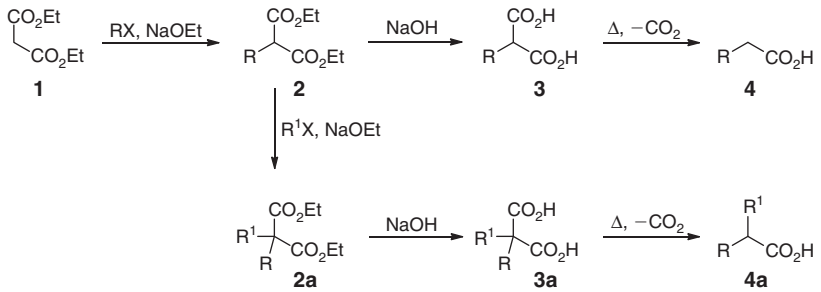
Introduction

A classical method for the preparation of mono- and di-substituted carboxylic acids is the malonic ester synthesis.[1] In this approach, diethyl malonate **1** is alkylated with an alkyl halide (or dialkylated with the same or a different alkyl halide), and the resulting diester **2** or **2a** is subjected to hydrolysis to afford the substituted malonic acid **3** or **3a**. The diacid **3** or **3a** can then be decarboxylated to give the carboxylic acid product **4** or **4a** (Scheme 1).

Prolonged reaction times and high temperatures (as high as 180–190°C[2]) are required to achieve the final decarboxylation reaction of **3** or **3a** to give **4** or **4a**, accordingly, severely restricting the scope of this methodology. Because of this limitation, we considered a potentially milder approach, whereby an ester of (benzothiazol-2-ylsulfonyl)acetic acid is singly- or dialkylated to give the substituted ester **5** (Scheme 2). Benzothiazol-2-sulfones, such as **5**, participate readily in intramolecular Smiles-type rearrangement reactions[3] with oxygen as nucleophile, as evident in the modified Julia (Julia–Kocienski) olefination[4,5] and our recently described epoxide deoxygenation reaction.[6] We believe that benzothiazol-2-sulfones, such as **5**, can also undergo intermolecular attack of a nucleophile at C2, leading to an intermediate (ethoxycarbonyl)alkyl sulfinate **6**. β-Carbonyl sulfinates, such as **6**, have a fleeting existence, rapidly losing SO_2 to give the carbonyl compound,[7–9] and so we expect that **6**, if formed, would rapidly desulfinate under very mild conditions, at significantly lower temperatures than those typically required for the decarboxylation of malonic acids. This approach would be complementary to the malonate ester synthesis of carboxylic acids and would significantly broaden its scope. This concept was experimentally examined and details of this new approach are provided herein.

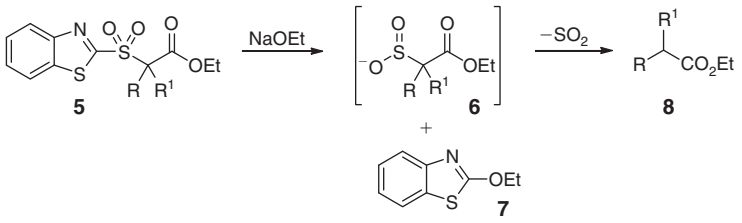
Results and Discussion

The syntheses of β-sulfonyl esters **11a** and **11b** using methods modified from Blakemore and co-workers[10] are shown in

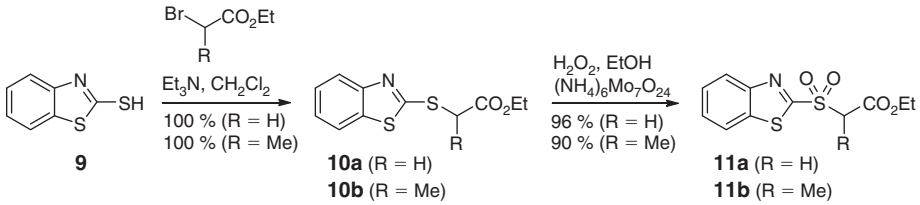


Scheme 1. Malonic ester synthesis of carboxylic acids.

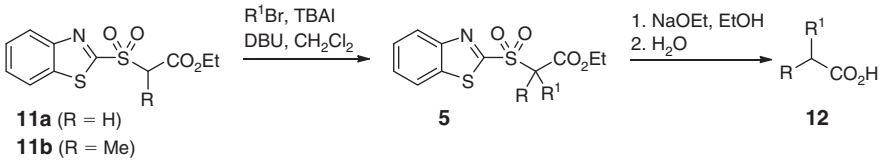
*Dedicated to the memory of Roger F. C. Brown (1931–2013), Ph.D. supervisor of RPM.



Scheme 2. Proposed formation of α-substituted acetate esters from ethyl (benzothiazol-2-ylsulfonyl) acetates.



Scheme 3. Alkylation of 2-mercaptobenzothiazole (**9**) with α-bromo esters to yield thioethers **10**, and oxidation of **10** to produce the corresponding sulfones **11**.



Scheme 4. Mono- and dialkylation of the sulfone esters **11**, and solvolysis/desulfination of **5** followed by hydrolysis to yield dialkyl acetic acids **12**.

Table 1. Yields of alkylated sulfone esters 5 from 11 and yields of carboxylic acids 12 following alkaline hydrolysis of 5

Entry[A]	Starting sulfone	R	R^1	Yield of sulfone ester **5** [%]	Yield of carboxylic acid **12** [%]
a[B]	**11a**	H	Hexyl	38	80
b[C]	**11a**	Hexyl	Hexyl	53	81
c[D,E]	**11a**	Dodecyl	Dodecyl	67	63
d[E]	**11a**	Benzyl	Benzyl	68	42
e[E]	**11a**	Allyl	Allyl	55	84
f[E]	**5a**	Hexyl	Dodecyl	24	–
g[E]	**5a**	Hexyl	Benzyl	84	82
h[F]	**11b**	Me	Hexyl	82	84
i	**11b**	Me	Benzyl	85	95
j	**11b**	Me	Dodecyl	81	34
k	**11b**	Me	Allyl	83	83
l	**11b**	Me	Isopropyl	18	100

[A]Five equivalents of DBU was used in all cases; 4 equiv. of alkyl bromide and 0.05 equiv. of TBAI were used in most cases.
[B]One equivalent of iodohexane was used.
[C]Eight equivalents of iodohexane was used.
[D]Eight equivalents of KI was used instead of TBAI.
[E]Eight equivalents of alkyl bromide was used.
[F]Four equivalents of iodohexane was used.

Scheme 3. Alkylation of 2-mercaptobenzothiazole (**9**) with either ethyl bromoacetate or ethyl 2-bromopropanoate gave the corresponding thioethers **10a** and **10b** in quantitative yields. Oxidation of **10a** and **10b** to the corresponding sulfones **11a** and **11b** was accomplished in high yields using aqueous hydrogen peroxide in ethanol solution in the presence of a catalytic amount of ammonium molybdate.

Alkylation of sulfonyl esters **11a**, **11b**, and **5a** (**5**: R = H, R^1 = Hexyl) with an excess of either alkyl bromide or alkyl iodide was performed in dichloromethane solution at room temperature, using 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) as base (Scheme 4, Table 1). In the examples using alkyl bromides, a catalytic amount of tetrabutylammonium iodide was also added. As reported by other groups,[11] selective monoalkylation of α-sulfonylacetates is difficult to achieve in acceptable yields. This was confirmed in our case for the alkylation of **11a** using one molar equivalent of iodohexane (Table 1, entry a); the adduct was obtained in only 38 % yield. In

other cases, the use of excess alkyl halide gave the disubstituted products **5** in good-to-excellent yields (Table 1, entries b–e). Similarly, alkylation of **5a** and **11b** with an excess of alkyl halides gave the disubstituted products **5** in very good yields (Table 1, entries f–k). However, alkylation with the secondary halide, isopropyl bromide, gave a very poor yield (18 %) of the product (Table 1, entry l).

Treatment of the sulfone esters **5** with sodium ethoxide in ethanol gave the expected ethyl esters **8** (Scheme 2). These could be isolated if desired. However, performing the subsequent hydrolysis step without isolation of the intermediate esters was more efficient, by simply adding water to the sodium ethoxide solution. Extraction of the carboxylic acid product from the reaction mixture then facilitated purification of the final product **12**. Yields for this step were generally very good, except for these cases (Table 1, entries f and j) in which pronounced emulsion formation during extraction with base led to product loss.

Conclusions

We have developed a new route to synthesising substituted carboxylic acids and esters. Mono- or dialkylation of ethyl (benzothiazol-2-ylsulfonyl)acetate or ethyl 2-(benzothiazol-2-ylsulfonyl)propionate occurs readily, and these products can undergo solvolysis with sodium ethoxide, followed by hydrolysis within a single reaction process to give substituted carboxylic acids. Unlike the classical malonate ester synthesis of carboxylic acids, our method does not employ the elevated temperatures required for decarboxylation of malonic acid intermediates.

Experimental

Ethanol was dried over 3-Å molecular sieves. Light petroleum (LP, bp 40–60°C) was distilled before use. NMR spectra were recorded on 300, 400, and 500 MHz Bruker spectrometers. Chemical shifts are reported in parts per million (ppm) on a δ scale, relative to the solvent peak ($CDCl_3$: δ_H 7.24, δ_C 77.0). Coupling constants (*J*) are reported in hertz and peak multiplicities described as singlet (s), doublet (d), triplet (t), quartet (q), quintet (quin), and multiplet (m). High-resolution (HR) electrospray ionisation (ESI) accurate mass spectrometry (MS) measurements were recorded in positive and negative modes on a quadrupole time-of-flight instrument (Bruker) equipped with an ESI source. Accurate mass measurements were carried out with external calibration using sodium formate as reference calibrant and/or Agilent tune mix (MW >500). Low- and high-resolution electron impact ionisation mass measurements were recorded using perfluorokerosene-H as reference calibrant. TLC plates were visualised under UV illumination and $KMnO_4$ solution.

*Ethyl 2-(Benzo[d]thiazol-2-ylthio)acetate (**10a**)*

Ethyl bromoacetate (8.0 mL, 12.0 g, 72.0 mmol) and triethylamine (30.0 mL, 21.2 g, 210 mmol) were added to a solution of 2-mercaptobenzothiazole (**9**) (10.0 g, 60.0 mmol) in dichloromethane (250 mL). The reaction mixture was stirred for 14 h at room temperature under argon. The reaction mixture was evaporated under vacuum and the residue was extracted in diethyl ether (100 mL) and filtered off. The mixture was evaporated under vacuum to afford **10a** as a yellow oil, which slowly solidified upon storage in the fridge (15.0 g, 100 %). R_F 0.21 (5 % ethyl acetate (EtOAc) in LP). δ_H ($CDCl_3$, 300 MHz) 7.82 (1H, ddd, *J* 6.2, 1.3, 0.6, ArH), 7.72 (1H, ddd, *J* 6.0, 1.3, 0.6, ArH), 7.41–7.36 (1H, m, ArH), 7.30–7.25 (1H, m, ArH), 4.22 (2H, q, *J* 7.1, CH_2CH_3), 4.15 (2H, s, SCH_2), 1.27 (3H, t, *J* 7.1, CH_2CH_3) (^{1}H NMR spectrum is in agreement with that described by Blakemore et al.[10]).

*Ethyl 2-(Benzo[d]thiazol-2-ylthio)propanoate (**10b**)*

Ethyl bromopropanoate (9.4 mL, 13.0 g, 72.0 mmol) and triethylamine (30.0 mL, 21.2 g, 210 mmol) were added to a solution of 2-mercaptobenzothiazole (**9**) (10.0 g, 60.0 mmol) in dichloromethane (250 mL). The reaction mixture was stirred for 14 h at room temperature under argon. The reaction mixture was evaporated under vacuum and the residue was extracted in diethyl ether (100 mL) and filtered off. The mixture was evaporated under vacuum to afford **10b** as an orange oil, which slowly solidified upon storage in the fridge (16.0 g, 100 %). R_F 0.55 (10 % EtOAc in LP). δ_H ($CDCl_3$, 300 MHz) 7.86 (1H, ddd, *J* 6.2, 1.3, 0.6, ArH), 7.73 (1H, ddd, *J* 6.0, 1.3, 0.6, ArH), 7.43–7.37 (1H, m, ArH), 7.31–7.26 (1H, m, ArH), 4.68 (1H, q, *J* 7.3, SC*H*), 4.27–4.16 (2H, m, CH_2CH_3), 1.70 (3H, d, *J* 7.3, $CHCH_3$), 1.25 (3H, t, *J* 7.1, CH_2CH_3). δ_C ($CDCl_3$, 75 MHz) 171.5, 164.2, 152.9, 135.4, 126.0, 124.4, 121.7, 120.9, 61.7, 45.0, 17.9, 14.0 (NMR spectra are in agreement with those described by Kuroda et al.[12]).

*Ethyl 2-(Benzo[d]thiazol-2-ylsulfonyl)acetate (**11a**)*

Ammonium molybdate (3.5 g, 2.8 mmol) and aqueous hydrogen peroxide 30 % (21.5 mL, 25.4 g, 0.22 mol) were added to a solution of **10a** (14.2 g, 56.0 mmol) in ethanol (50 mL) at 0°C. The reaction mixture was stirred for 48 h at room temperature then evaporated under vacuum. The residue was extracted in ethyl acetate (250 mL) and washed with water (2 × 50 mL) and brine (50 mL), then dried over anhydrous Na_2SO_4, filtered, and evaporated under vacuum to afford **11a** as a green solid (15.3 g, 96 %), mp 58°C (lit. 58–59°C[10]). R_F 0.45 (35 % EtOAc in LP). δ_H ($CDCl_3$, 300 MHz) 8.18 (1H, ddd, *J* 5.2, 2.2, 0.8, ArH), 7.98 (1H, ddd, *J* 5.0, 1.5, 0.9, ArH), 7.64–7.54 (2H, m, ArH), 4.54 (2H, s, SO_2CH_2), 4.14 (2H, q, *J* 7.1, CH_2CH_3), 1.27 (3H, t, *J* 7.2, CH_2CH_3) (^{1}H NMR spectrum is in agreement with that described by Blakemore et al.[10]).

*Ethyl 2-(Benzo[d]thiazol-2-ylsulfonyl)propanoate (**11b**)*

Ammonium molybdate (3.7 g, 3.0 mmol) and aqueous hydrogen peroxide 30 % (23.0 mL, 27.2 g, 0.22 mol) were added to a solution of **10b** (16.0 g, 59.9 mmol) in ethanol (50 mL) at 0°C. The reaction mixture was stirred for 48 h at room temperature then evaporated under vacuum. The residue was extracted in ethyl acetate (250 mL) and washed with water (2 × 50 mL) and brine (50 mL), then dried over anhydrous Na_2SO_4, filtered, and evaporated under vacuum to afford **11b** as a green solid (15.1 g, 90 %), mp 51–53°C. R_F 0.56 (35 % EtOAc in LP). δ_H ($CDCl_3$, 500 MHz) 8.20 (1H, dt, *J* 6.1, 0.6, ArH), 7.99 (1H, dt, *J* 6.3, 0.7, ArH), 7.68–7.55 (2H, m, ArH), 4.58 (1H, q, *J* 7.3, SC*H*), 4.16–4.07 (2H, m, CH_2CH_3), 1.75 (3H, d, *J* 7.4, $CHCH_3$), 1.07 (3H, t, *J* 7.2, CH_2CH_3). δ_C ($CDCl_3$, 125 MHz) 165.1, 164.4, 152.5, 137.0, 128.2, 127.7, 125.5, 122.2, 64.3, 62.6, 13.6, 10.8. *m/z* (ESI–MS) 322 $[M + Na]^+$. HRMS Anal. Calc. for $C_{12}H_{13}NNaO_4S_2^+$ 322.0184. Found: 322.0176.

*General Alkylation Procedure for the Preparation of **5***

DBU (5 equiv.) was added to a solution of either **11a** or **11b** (1 equiv.) in dichloromethane (5–10 mL). After stirring the

yellow solution for 10 min at room temperature under argon, the alkyl iodide was added (when alkyl bromide was used, 0.05 equiv. Tetrabutylammonium iodide (TBAI) was added). The reaction mixture was stirred for 14–48 h then dichloromethane (150 mL) was added and the solution was washed with 5 % HCl (3 × 50 mL), then dried over anhydrous Na_2SO_4, filtered, and evaporated under vacuum to give the crude product **5**.

*Ethyl 2-(Benzo[d]thiazol-2-ylsulfonyl)octanoate (**5a**)*

The product was purified by silica flash column chromatography (10 % EtOAc/LP) to afford **5a** as a colourless oil (38 % yield). R_F 0.22 (10 % EtOAc in LP). δ_H ($CDCl_3$, 500 MHz) 8.22 (1H, dt, *J* 6.6, 0.7, ArH), 8.00 (1H, dt, *J* 6.6, 0.6, ArH), 7.65–7.57 (2H, m, ArH), 4.40 (1H, dd, *J* 10.0, 5.2, SC*H*), 4.15 (2H, q, *J* 7.1, OCH_2CH_3), 2.25–2.19 (2H, m, $CH_2(CH_2)_4CH_3$), 1.42–1.20 (8H, m, $(CH_2)_4CH_3$), 1.10 (3H, t, *J* 7.2, OCH_2CH_3), 0.84 (3H, t, *J* 7.0, $(CH_2)_5CH_3$). δ_C ($CDCl_3$, 125 MHz) 164.9, 164.4, 152.6, 137.1, 128.2, 127.7, 125.7, 122.3, 69.8, 62.6, 31.3, 28.6, 26.8, 26.0, 22.4, 13.9, 13.8. *m/z* (ESI–MS) 392 $[M + Na]^+$. HRMS Anal. Calc. for $C_{17}H_{23}NNaO_4S_2^+$ 392.0966. Found: 392.0950.

*Ethyl 2-(Benzo[d]thiazol-2-ylsulfonyl)-2-hexyloctanoate (**5b**)*

The product was purified by silica flash column chromatography (10 % EtOAc/LP) to afford **5b** as a yellow oil (53 % yield). R_F 0.36 (10 % EtOAc in LP). δ_H ($CDCl_3$, 300 MHz) 8.22 (1H, dt, *J* 5.3, 0.6, ArH), 7.98 (1H, dt, *J* 5.0, 1.5, ArH), 7.64–7.54 (2H, m, ArH), 4.10 (2H, q, *J* 7.1, OCH_2CH_3), 2.35–2.13 (4H, m, 2 × $CH_2(CH_2)_4CH_3$), 1.33–1.28 (16H, m, 2 × $(CH_2)_4CH_3$), 1.10 (3H, t, *J* 7.1, OCH_2CH_3), 0.86 (6H, t, *J* 6.7, 2 × $(CH_2)_5CH_3$). δ_C ($CDCl_3$, 75 MHz) 167.4, 164.3, 152.6, 137.5, 128.0, 127.5, 125.8, 122.1, 78.1, 62.4, 31.4, 30.3, 29.6, 24.0, 22.5, 14.0, 13.7. *m/z* (ESI–MS) 476 $[M + Na]^+$. HRMS Anal. Calc. for $C_{23}H_{35}NNaO_4S_2^+$ 476.1905. Found: 476.1908.

*Ethyl 2-(Benzo[d]thiazol-2-ylsulfonyl)-2-dodecyltetradecanoate (**5c**)*

The product was purified by silica flash column chromatography (3–10 % EtOAc/LP) to afford **5c** as a yellow oil (67 % yield). R_F 0.44 (10 % EtOAc in LP). δ_H ($CDCl_3$, 300 MHz) 8.21 (1H, dd, *J* 5.2, 1.4, ArH), 7.97 (1H, dd, *J* 5.1, 1.3, ArH), 7.62–7.53 (2H, m, ArH), 4.10 (2H, q, *J* 7.1, OCH_2CH_3), 2.29–2.14 (4H, m, 2 × $CH_2(CH_2)_{10}CH_3$), 1.38–1.18 (40H, m, 2 × $(CH_2)_{10}CH_3$), 1.10 (3H, t, *J* 7.1, OCH_2CH_3), 0.85 (6H, t, *J* 6.4, 2 × $(CH_2)_{11}CH_3$). δ_C ($CDCl_3$, 75 MHz) 167.4, 164.3, 152.6, 137.5, 128.0, 127.4, 125.7, 122.0, 78.1, 62.4, 31.9, 30.3, 29.9, 29.60, 29.55, 29.5, 29.3, 29.2, 24.0, 22.6, 14.1, 13.7. *m/z* (ESI–MS) 644 $[M + Na]^+$. HRMS Anal. Calc. for $C_{35}H_{59}NNaO_4S_2^+$ 644.3783. Found: 644.3764.

*Ethyl 2-(Benzo[d]thiazol-2-ylsulfonyl)-2-benzyl-3-phenylpropanoate (**5d**)*

The product was purified by silica flash column chromatography (5–20 % EtOAc/LP) to afford **5d** as a colourless semisolid (68 % yield). R_F 0.27 (10 % EtOAc in LP). δ_H ($CDCl_3$, 500 MHz) 8.19 (1H, dt, *J* 6.6, 0.7, ArH), 7.94 (1H, dt, *J* 7.3, 0.9, ArH), 7.63–7.55 (2H, m, ArH), 7.27–7.20 (10H, m, BzH), 4.20 (2H, q, *J* 7.1, OCH_2CH_3), 3.82 (2H, d, *J* 14.4, 2 × CH_aPh), 3.68 (2H, d, *J* 14.4, 2 × CH_bPh), 1.13 (3H, t, *J* 7.2, OCH_2CH_3). δ_C ($CDCl_3$, 125 MHz) 166.9, 166.0, 152.2, 137.3, 134.0, 131.0, 128.0, 127.8, 127.3, 127.2, 125.5, 121.9, 79.4, 62.6, 38.6, 13.5. *m/z* (ESI–MS) 488 $[M + Na]^+$. HRMS Anal. Calc. for $C_{25}H_{23}NNaO_4S_2^+$ 488.0966. Found: 476.0956.

*Ethyl 2-Allyl-2-(benzo[d]thiazol-2-ylsulfonyl)pent-4-enoate (**5e**)*

The product was purified by silica flash column chromatography (20 % EtOAc/LP) to afford **5e** as a colourless oil (55 % yield). R_F 0.24 (10 % EtOAc in LP). δ_H ($CDCl_3$, 300 MHz) 8.19 (1H, ddd, *J* 5.1, 2.2, 1.4, ArH), 7.96 (1H, ddd, *J* 4.9, 1.6, 0.7, ArH), 7.61–7.51 (2H, m, ArH), 5.92–5.78 (2H, m, 2 × $CH_2CH{=}CH_2$), 5.21–5.12 (4H, m, 2 × $CH_2CH{=}CH_2$), 4.08 (2H, q, *J* 7.1, OCH_2CH_3), 3.13–2.98 (4H, m, 2 × $CH_2CH{=}CH_2$), 1.04 (3H, t, *J* 7.1, OCH_2CH_3). δ_C ($CDCl_3$, 75 MHz) 166.2, 163.8, 152.5, 137.2, 130.6, 128.1, 127.5, 125.6, 122.0, 120.5, 76.4, 62.6, 34.8, 13.5. *m/z* (ESI–MS) 388 $[M + Na]^+$. HRMS Anal. Calc. for $C_{17}H_{19}NNaO_4S_2^+$ 388.0653. Found: 388.0651.

*Ethyl 2-(Benzo[d]thiazol-2-ylsulfonyl)-2-hexyltetradecanoate (**5f**)*

The product was purified by silica flash column chromatography (3–10 % EtOAc/LP) to afford **5f** as a colourless oil (24 % yield). R_F 0.49 (10 % EtOAc in LP). δ_H ($CDCl_3$, 500 MHz) 8.22 (1H, dd, *J* 6.7, 0.8, ArH), 7.98 (1H, dd, *J* 6.2, 1.2, ArH), 7.62–7.55 (2H, m, ArH), 4.10 (2H, q, *J* 7.1, OCH_2CH_3), 2.32–2.27 (2H, m, $CH_2(CH_2)_4CH_3$), 2.21–2.15 (2H, m, $CH_2(CH_2)_{10}CH_3$), 1.39–1.18 (28H, m, $(CH_2)_4CH_3$ and $(CH_2)_{10}CH_3$), 1.10 (3H, t, *J* 7.1, OCH_2CH_3), 0.86 (6H, t, *J* 6.4, $(CH_2)_5CH_3$ and $(CH_2)_{11}CH_3$). δ_C ($CDCl_3$, 125 MHz) 167.4, 164.3, 152.6, 137.5, 128.0, 127.5, 125.7, 122.0, 78.1, 62.4, 31.9, 31.4, 30.3, 29.9, 29.62 (2 × C), 29.56, 29.49, 29.3, 29.2, 24.00, 23.97, 22.7, 22.5, 14.1, 14.0, 13.7. *m/z* (ESI–MS) 560 $[M + Na]^+$. HRMS Anal. Calc. for $C_{29}H_{47}NNaO_4S_2^+$ 560.2844. Found: 560.2825.

*Ethyl 2-(Benzo[d]thiazol-2-ylsulfonyl)-2-benzyloctanoate (**5g**)*

The product was purified by silica flash column chromatography (5–10 % EtOAc/LP) to afford **5g** as a colourless oil (84 % yield). R_F 0.34 (10 % EtOAc in LP). δ_H ($CDCl_3$, 500 MHz) 8.23 (1H, dd, *J* 6.1, 1.3, ArH), 8.00 (1H, dd, *J* 6.2, 1.4, ArH), 7.64–7.57 (2H, m, ArH), 7.24–7.14 (5H, m, BzH), 4.17–4.06 (2H, m, OCH_2CH_3), 3.82 (1H, d, *J* 13.8, CH_aPh), 3.57 (1H, d, *J* 13.8, CH_bPh), 2.20–2.14 (1H, m, $CH_AH_B(CH_2)_4CH_3$), 2.11–2.05 (1H, m, $CH_AH_B(CH_2)_4CH_3$), 1.62–1.57 (2H, m, $CH_2CH_2(CH_2)_3CH_3$), 1.25–1.20 (6H, m, $(CH_2)_3CH_3$), 1.07 (3H, t, *J* 7.2, OCH_2CH_3), 0.83 (3H, t, *J* 7.0, $(CH_2)_5CH_3$). δ_C ($CDCl_3$, 125 MHz) 167.1, 164.9, 152.6, 137.5, 134.1, 130.4, 128.4, 128.1, 127.7, 127.4, 125.8, 122.1, 79.0, 62.5, 38.0, 31.3, 30.9, 29.9, 24.3, 22.5, 14.0, 13.6. *m/z* (ESI–MS) 482 $[M + Na]^+$. HRMS Anal. Calc. for $C_{24}H_{29}NNaO_4S_2^+$ 482.1436. Found: 482.1422.

*Ethyl 2-(Benzo[d]thiazol-2-ylsulfonyl)-2-methyloctanoate (**5h**)*

The product was purified by silica flash column chromatography (5–10 % EtOAc/LP) to afford **5h** as a colourless oil (82 % yield). R_F 0.28 (10 % EtOAc in LP). δ_H ($CDCl_3$, 300 MHz) 8.21 (1H, dt, *J* 5.3, 1.5, ArH), 7.97 (1H, dt, *J* 4.9, 0.9, ArH), 7.63–7.53 (2H, m, ArH), 4.26–4.02 (2H, m, OCH_2CH_3), 2.46 (1H, dt, *J* 12.1, 7.5, SO_2CCH_a), 2.05 (1H, dt, *J* 12.2, 7.6, SO_2CCH_b), 1.73 (3H, s, SO_2CCH_3), 1.48–1.19 (8H, m, $(CH_2)_4CH_3$), 1.12 (3H, t, *J* 7.1, OCH_2CH_3), 0.84 (3H, t, *J* 6.8, $(CH_2)_5CH_3$). δ_C ($CDCl_3$, 75 MHz) 167.3, 163.6, 152.7, 137.3,

128.0, 127.5, 125.7, 122.0, 74.5, 62.6, 32.6, 31.3, 29.2, 24.1, 22.4, 16.4, 13.9, 13.7. *m/z* (ESI–MS) 406 $[M + Na]^+$. HRMS Anal. Calc. for $C_{18}H_{25}NNaO_4S_2^+$ 406.1123. Found: 406.1128.

*Ethyl 2-(Benzo[d]thiazol-2-ylsulfonyl)-2-methyl-3-phenylpropanoate (**5i**)*

The product was purified by silica flash column chromatography (5–20 % EtOAc/LP) to afford **5i** as a colourless semisolid (85 % yield). R_F 0.17 (10 % EtOAc in LP). δ_H ($CDCl_3$, 300 MHz) 8.25 (1H, dd, *J* 5.1, 1.6, ArH), 8.00 (1H, dt, *J* 3.3, 1.4, ArH), 7.66–7.57 (2H, m, ArH), 7.26–7.24 (3H, m, BzH), 7.12–7.10 (2H, m, BzH) 4.13 (2H, q, *J* 7.2, OCH_2CH_3), 3.98 (1H, d, *J* 13.2, CH_aPh), 3.35 (1H, d, *J* 13.3, CH_bPh), 1.64 (3H, s, SO_2CCH_3), 1.09 (3H, t, *J* 7.1, OCH_2CH_3). δ_C ($CDCl_3$, 75 MHz) 166.8, 163.4, 152.7, 137.4, 133.6, 131.3, 128.5, 128.2, 127.6, 127.5, 125.8, 122.1, 75.1, 62.7, 38.6, 15.9, 13.7. *m/z* (ESI–MS) 412 $[M + Na]^+$. HRMS Anal. Calc. for $C_{19}H_{19}NNaO_4S_2^+$ 412.0653. Found: 412.0654.

*Ethyl 2-(Benzo[d]thiazol-2-ylsulfonyl)-2-methyltetradecanoate (**5j**)*

The product was purified by silica flash column chromatography (3–20 % EtOAc/LP) to afford **5j** as a colourless oil (81 % yield). R_F 0.47 (10 % EtOAc in LP). δ_H ($CDCl_3$, 500 MHz) 8.18 (1H, dt, *J* 6.5, 0.6, ArH), 7.95 (1H, dt, *J* 6.2, 0.7, ArH), 7.60–7.52 (2H, m, ArH), 4.17–4.07 (2H, m, OCH_2CH_3), 2.46 (1H, dt, *J* 8.3, 4.4, SO_2CCH_a), 2.04 (1H, dt, *J* 8.5, 4.7, SO_2CCH_b), 1.71 (3H, s, SO_2CCH_3), 1.45–1.12 (20H, m, $(CH_2)_{10}CH_3$), 1.09 (3H, t, *J* 7.1, OCH_2CH_3), 0.82 (3H, t, *J* 7.0, $(CH_2)_{11}CH_3$). δ_C ($CDCl_3$, 125 MHz) 167.2, 163.5, 152.6, 137.2, 128.0, 127.4, 125.6, 122.0, 74.4, 62.4, 32.5, 31.7, 29.44, 29.39, 29.3, 29.2, 29.1, 24.1, 22.5, 16.3, 14.0, 13.6. *m/z* (ESI–MS) 490 $[M + Na]^+$. HRMS Anal. Calc. for $C_{24}H_{37}NNaO_4S_2^+$ 490.2062. Found: 490.2063.

*Ethyl 2-(Benzo[d]thiazol-2-ylsulfonyl)-2-methylpent-4-enoate (**5k**)*

The product was purified by silica flash column chromatography (20 % EtOAc/LP) to afford **5k** as a colourless oil (83 % yield). R_F 0.25 (10 % EtOAc in LP). δ_H ($CDCl_3$, 300 MHz) 8.22 (1H, ddd, *J* 5.1, 2.2, 0.8, ArH), 7.98 (1H, ddd, *J* 5.0, 2.2, 1.6, ArH), 7.64–7.57 (2H, m, ArH), 5.69–5.56 (1H, m, $CH=CH_2$), 5.23–5.16 (2H, m, $CH=CH_2$), 4.21–4.02 (2H, m, OCH_2CH_3), 3.29 (1H, dd, *J* 13.5, 6.6, $CH_aCH=CH_2$), 2.79 (1H, dd, *J* 9.7, 7.9, $CH_bCH=CH_2$), 1.72 (3H, s, SO_2CCH_3), 1.11 (3H, t, *J* 7.1, OCH_2CH_3). δ_C ($CDCl_3$, 75 MHz) 166.8, 163.3, 152.7, 137.4, 130.1, 128.1, 127.6, 125.8, 122.1, 121.2, 73.7, 62.7, 37.3, 16.3, 13.7. *m/z* (ESI–MS) 362 $[M + Na]^+$. HRMS Anal. Calc. for $C_{15}H_{17}NNaO_4S_2^+$ 362.0497. Found: 362.0498.

*Ethyl 2-(Benzo[d]thiazol-2-ylsulfonyl)-2,3-dimethylbutanoate (**5l**)*

The product was purified by silica flash column chromatography (5–10 % EtOAc/LP) to afford **5l** as a colourless oil (18 % yield). R_F 0.27 (10 % EtOAc in LP). δ_H ($CDCl_3$, 300 MHz) 8.20 (1H, dt, *J* 5.1, 0.7, ArH), 7.97 (1H, dt, *J* 5.0, 1.6, ArH), 7.63–7.53 (2H, m, ArH), 4.27–4.01 (2H, m, OCH_2CH_3), 3.02 (1H, septet, *J* 6.8, $CH(CH_3)_2$), 1.71 (3H, s, SO_2CCH_3), 1.29 (3H, d, *J* 6.7, $CHCH_{3a}$), 1.14 (3H, t, *J* 7.1, OCH_2CH_3), 0.89 (3H, d, *J* 6.8, $CHCH_{3b}$). δ_C ($CDCl_3$, 75 MHz) 168.0, 164.4, 152.5, 137.2, 128.0, 127.5, 125.7, 122.0, 78.9, 62.5, 31.2, 18.8, 17.7, 13.7, 11.1. *m/z* (ESI–MS) 364 $[M + Na]^+$. HRMS Anal. Calc. for $C_{15}H_{19}NNaO_4S_2^+$ 364.0653. Found: 364.0658.

*General Desulfination/Hydrolysis Procedure for the Preparation of **12***

Sodium metal (20 equiv.) was added to a solution of the ester **5** (1 equiv.) in ethanol (5 mL). The solution was stirred for 14 h at room temperature under argon atmosphere. Water (5 mL) was added and the reaction mixture was heated at 30–40°C for 14 h. The solution was evaporated under vacuum and the residue was taken up in 2 M sodium hydroxide solution (100 mL) and washed with dichloromethane (3 × 50 mL). The aqueous layer was acidified with concentrated HCl and extracted with dichloromethane (3 × 50 mL). The organic layer was dried over anhydrous Na_2SO_4, filtered, and evaporated under vacuum to give the carboxylic acid products **12**.

*Octanoic Acid (**12a**)*

Colourless oil (70 mg, 80 %). δ_H ($CDCl_3$, 300 MHz) 2.31 (2H, t, *J* 7.5, CH_2COOH), 1.67–1.55 (2H, m, CH_2CH_2COOH), 1.35–1.21 (8H, m, $(CH_2)_4CH_3$), 0.85 (3H, t, *J* 6.8, CH_3). δ_C ($CDCl_3$, 75 MHz) 180.7, 34.1, 31.6, 29.0, 28.9, 24.6, 22.6, 14.0 (NMR spectra are in agreement with those described by Zweifel et al.[13]).

*2-Hexyloctanoic Acid (**12b**)*

Colourless oil (90 mg, 81 %). δ_H ($CDCl_3$, 300 MHz) 2.35–2.27 (1H, m, CHCOOH), 1.64–1.57 (2H, m, 2 × $CH_aCHCOOH$), 1.48–1.42 (2H, m, 2 × $CH_bCHCOOH$), 1.28–1.23 (16H, m, 2 × $(CH_2)_4CH_3$), 0.86 (6H, t, *J* 13.5, 2 × CH_3). δ_C ($CDCl_3$, 75 MHz) 182.7, 45.5, 32.2, 31.7, 29.2, 27.3, 22.6, 14.0 (NMR spectra are in agreement with those described by Cohen et al.[14]).

*2-Dodecyltetradecanoic Acid (**12c**)*

Colourless solid (117 mg, 63 %). δ_H ($CDCl_3$, 400 MHz) 2.34–2.32 (1H, m, CHCOOH), 1.58–1.55 (2H, m, 2 × $CH_aCHCOOH$), 1.47–1.43 (2H, m, 2 × $CH_bCHCOOH$), 1.38–1.15 (40H, m, 2 × $(CH_2)_{10}CH_3$), 0.86 (6H, t, *J* 6.8, 2 × CH_3). δ_C ($CDCl_3$, 100 MHz) 183.2, 45.6, 32.2, 31.9, 29.7, 29.65, 29.61, 29.57, 29.5, 29.4, 27.4, 22.7, 14.1 (NMR spectra are in agreement with those described by Nishizawa et al.[15]). *m/z* (ESI–MS) 395 $[M - H]^-$. HRMS Anal. Calc. for $C_{26}H_{51}O_2^-$ 395.3889. Found: 395.3899.

*2-Benzyl-3-phenylpropanoic Acid (**12d**)*

Colourless solid (116 mg, 42 %). δ_H ($CDCl_3$, 300 MHz) 7.32–7.16 (10H, m, BzH), 3.03–2.96 (3H, m, CHCOOH and 2 × CH_aPh), 2.86–2.80 (2H, m, 2 × CH_bPh). δ_C ($CDCl_3$, 75 MHz) 180.4, 138.7, 128.9, 128.5, 126.5, 49.2, 37.7 (NMR spectra are in agreement with those described by Koder et al.[16]).

*2-Allylpent-4-enoic Acid (**12e**)*

Colourless oil (138 mg, 84 %). δ_H ($CDCl_3$, 300 MHz) 5.82–5.68 (2H, m, 2 × $CH=CH_2$), 5.11–5.02 (4H, m, 2 × $CH=CH_2$), 2.53 (1H, quin, *J* 6.9, CHCOOH), 2.43–2.22 (4H, m, 2 × $CH_2CH=CH_2$). δ_C ($CDCl_3$, 75 MHz) 180.6, 134.9, 117.3, 44.8, 35.4 (^{1}H NMR spectrum is in agreement with that described by Hyun et al.[17]).

*2-Benzyloctanoic Acid (**12g**)*

Colourless semisolid (70 mg, 82 %). δ_H ($CDCl_3$, 300 MHz) 7.30–7.18 (5H, m, BzH), 3.00 (1H, dd, *J* 13.4, 7.8, CH_aPh), 2.81–2.66 (2H, m, CH_bPh and CHCOOH), 1.76–1.59 (1H, m, $CH_aCHCOOH$), 1.59–1.42 (1H, m, $CH_bCHCOOH$), 1.42–1.22 (8H, m,

(CH_2)$_4$$CH_3$), 0.89 (3H, t, *J* 6.6, CH_3). δ_C ($CDCl_3$, 75 MHz) 182.0, 139.1, 128.9, 128.4, 126.4, 47.4, 38.1, 31.7, 31.6, 29.1, 27.1, 22.6, 14.0. *m/z* (ESI–MS) 257 $[M + Na]^+$. HRMS Anal. Calc. for $C_{15}H_{22}NaO_2^+$ 257.1517. Found 257.1506.

*2-Methyloctanoic Acid (**12h**)*

Colourless oil (130 mg, 84 %). δ_H ($CDCl_3$, 400 MHz) 2.43 (1H, sextet, *J* 7.0, C*H*COOH), 1.72–1.62 (1H, m, CH_aCHCOOH), 1.44–1.37 (1H, m, CH_bCHCOOH), 1.35–1.22 (8H, m, (CH_2)$_4$$CH_3$), 1.15 (3H, d, *J* 7.0, CHCH_3), 0.86 (3H, t, *J* 7.2, (CH_2)$_5$CH_3). δ_C ($CDCl_3$, 75 MHz) 183.3, 39.4, 33.5, 31.7, 29.2, 27.1, 22.6, 16.8, 14.0 (^{1}H NMR spectrum is in agreement with that described by Kumagai et al.[18]).

*2-Methyl-3-phenylpropanoic Acid (**12i**)*

Colourless oil (80 mg, 95 %). δ_H ($CDCl_3$, 300 MHz) 7.35–7.22 (5H, m, BzH), 3.13 (1H, dd, *J* 13.1, 6.1, CH_aPh), 2.85–2.68 (2H, m, CH_bPh and C*H*COOH), 1.22 (3H, d, *J* 6.8, CH_3). δ_C ($CDCl_3$, 75 MHz) 182.5, 139.0, 129.0, 128.4, 126.4, 41.2, 39.3, 16.4 (NMR spectra is in agreement with those described by Ueberbacher et al.[19]). *m/z* (ESI–MS) 163 $[M - H]^-$. HRMS Anal. Calc. for $C_{10}H_{11}O_2^-$ 163.0759. Found: 163.0763.

*2-Methyltetradecanoic Acid (**12j**)*

Colourless solid (110 mg, 34 %). δ_H ($CDCl_3$, 300 MHz) 2.43 (1H, sextet, *J* 7.0, C*H*COOH), 1.52–1.51 (1H, m, CH_aCHCOOH), 1.50–1.37 (1H, m, CH_bCHCOOH), 1.36–1.19 (20H, m, (CH_2)$_{10}$$CH_3$), 1.15 (3H, d, *J* 7.0, CHCH_3), 0.86 (3H, t, *J* 6.7, (CH_2)$_{11}$CH_3). δ_C ($CDCl_3$, 75 MHz) 183.5, 39.4, 33.5, 31.9, 29.7, 29.63, 29.59, 29.50, 29.46, 29.3, 27.1, 22.7, 16.8, 14.1. *m/z* (ESI–MS) 241 $[M - H]^-$. HRMS Anal. Calc. for $C_{15}H_{29}O_2^-$ 241.2168. Found: 241.2179.

*2-Methylpent-4-enoic Acid (**12k**)*

Colourless oil (90 mg, 83 %). δ_H ($CDCl_3$, 300 MHz) 5.82–5.69 (1H, m, CH_2C*H*=CH_2), 5.11–5.01 (2H, m, CH_2CH=CH_2), 2.54 (1H, sextet, *J* 6.9, C*H*COOH), 2.47–2.38 (1H, m, CH_aCH=CH_2), 2.24–2.14 (1H, m, CH_bCH=CH_2), 1.17 (3H, d, *J* 6.6, CH_3) (^{1}H NMR spectrum is in agreement with that described by Ueberbacher et al.[19]).

*2,3-Dimethylbutanoic Acid (**12l**)*

Colourless oil (50 mg, 100 %). δ_H ($CDCl_3$, 300 MHz) 2.26 (1H, quin, *J* 7.0, C*H*COOH), 1.93 (1H, sextet, *J* 6.8, C*H*(CH_3)$_2$), 1.11 (3H, d, *J* 7.0, CH_3CHCOOH), 0.95 (3H, d, *J* 6.8, CH_3CHCHCOOH), 0.91 (3H, d, *J* 6.8, CH_3CHCHCOOH) (^{1}H NMR spectrum is in agreement with that described by Kuo et al.[20]).

Supplementary Material

The NMR spectra of all new compounds are available on the Journal's website.

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