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A facile generation of C–S bonds via one-pot, odourless and efficient thia-Michael addition reactions using alkyl, aryl or allyl halides, thiourea and electron-deficient alkenes in wet polyethylene glycol (PEG 200) under mild reaction conditions

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ABSTRACT

An efficient and odourless synthesis of thia-Michael adducts by the reaction of various organic halides (primary, secondary, tertiary, allylic, and benzylic), structurally diverse electron-deficient alkenes (ketones, esters, and acrylonitrile) and thiourea in the presence of sodium carbonate in wet polyethylene glycol (PEG 200) at 30–35 °C has been developed. This protocol is also a highly useful method for large-scale operation.

1. Introduction

New approaches to C–S bond formation, especially under safe and eco-friendly conditions, which can lead to the discovery of new, green and more efficient synthetic protocols for preparation of industrial and biologically active organo-sulfur compounds, have attracted a great deal of attention.[1] Synthetically, sulfur–carbon bonds can be introduced by a variety of methods[2] within which thia-Michael addition plays an important role. In addition, sulfur functionality in thioethers can be readily converted into other useful functional groups such as sulfoxides or sulfones, placing further importance on the synthesis of the resulting sulfur-containing compounds. Moreover, the conjugate addition of thiols to α,β-unsaturated carbonyl groups provides a root to preparation of β-sulfido carbonyl derivatives, which are starting materials for the generation of β-acylvinyl cation[3] and homoenolate anion equivalents.[4] These reactions have multiple applications in the synthesis of biologically active molecules, including calcium antagonist dilthiazem.[5] On the other hand, sulfur functionality in the thia-Michael adducts can be readily removed by oxidative[3] or reductive[6] means, thus conversion of conjugated olefins to the corresponding thia-Michael adducts provides an applicable strategy for chemoselective protection of the olefinic double bond in their structure during chemical reactions.

A great deal of attention has been paid mainly to introducing new acidic and basic catalysts for conjugate addition of thiols to electron-deficient olefins in organic solvents.[7] Due to environmental issues, new studies for the development of reactions in non-hazardous media such as ionic liquids,[8] water,[9] solvent-free conditions[10] and polyethylene glycol[11] in the presence of mild and environmentally more compatible catalysts or even in the absence of any catalyst were carried out over recent years. Although, some of these studies led to the introduction of efficient new methods under more eco-friendly conditions, the use of highly volatile and foul-smelling thiols is still a main drawback, which could lead to serious environmental and safety problems and thus restricts any scale up operation.

Recently efficient methods for odourless thia-Michael addition reactions have been reported in the literature. This has been achieved by using trimethylsilyl substituted thiophenols and benzyl mercaptans,[12] or replacement of thiols with thiol equivalent compounds such as dialkyl disulfides,[13] 3-[bis(alkylthio)methylene]pentane-2,4-diones,[14] and 2-[bis(alkylthio)methylene]-3-oxo-*N*-*O*-tolylbutanamides.[15]

However, the above mentioned methods suffer from one of a number of drawbacks such as multi-step synthesis is needed for the preparation of thiol equivalents, expensive catalysts, hazardous materials and the use of organic solvents. In addition, in some of them, strongly basic conditions and long reaction times are required.

These drawbacks encouraged us to report a new environmentally friendly methodology using non-thiolic precursors, environmentally benign media and mild reaction conditions in an odourless process.

Recently, readily available *S*-alkylisothiouronium salts were reacted with electron-deficient olefins in the presence of a strong base such as NaOH to produce the corresponding thia-Michael adducts.[16]

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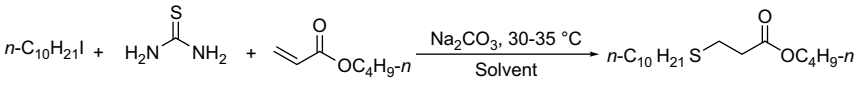
Table 1
Effect of the media upon the reaction of 1-iododecane, thiourea and *n*-butyl acrylate in the presence of Na_2CO_3 at 30–35 °C



Entry	Solvent	Time (h)	Isolated yields (%)
1	Water[a]	24	0
2	Aqueous solution of β-cyclodextrin[b]	24	0
3	Wet PEG (200)	12	86

[a] Water (3 mL).
[b] β-Cyclodextrin (10 mol %) in 3 mL of water.

2. Results and discussion

Polyethylene glycols (PEGs) and their derivatives are known to be inexpensive, thermally stable, recoverable, non-toxic and environmentally benign media for chemical reactions and which posses negligible vapour pressure.[17]

In line with our interest for introducing organic reactions conducted in green media, such as water[18] and ionic liquids,[19] now in this article we introduce a method for C–S bond generation via an odourless thia-Michael addition reaction using alkyl halides, thiourea and electron-deficient alkenes in the wet PEG 200 as a green media.

In order to optimize the reaction conditions, we initiated our study by using 1-iododecane (2.4 mmol), thiourea (3 mmol), *n*-butyl acrylate (2 mmol), water (0.15 mL) and sodium carbonate (3 mmol) as a model reaction at 30–35 °C in PEG 200 (3 mL). The reaction proceeded well and the desired Michael adduct was isolated in 86% yield after 12 h. In order to show the vital role of PEG in this reaction, we have also studied the same reaction in water and also in aqueous solution of β-cyclodextrin at 30–35 °C (Table 1). These reactions completely failed and starting materials were isolated intact from the reaction mixtures.

The optimized reaction conditions were then applied to the reaction of structurally diverse α,β-unsaturated compounds with different alkyl halides in the presence of thiourea and Na_2CO_3 at 30–35 °C. All the reactions proceeded well and the desired products were obtained in good to excellent yields (Table 2).

As it is evident from the results presented in Table 2, by this method, primary halides (iodides, bromides) under the reaction conditions have been easily converted to the related thia-Michael adducts within appropriate reaction times in good to excellent yields (Table 2, entries 1–17). Methyl mercaptan is highly volatile at ambient temperature and has a very strong foul smell. Thus, its unsatisfactory applications in the thia-Michael addition reactions were limited to only a few reports.[35] However, under our reaction conditions the reactions including methyl iodide gave good results and the corresponding β-sulfido derivatives were produced in 77–85% yields (Table 2, entries 14–17). Allylic and benzylic halides under similar reaction conditions have produced the thia-Michael derivatives within appropriate reaction times in good to excellent yields (Table 2, entries 18–34). We have also investigated the applicability of the method for the preparation of other thia-Michael adducts using secondary halides. Under the optimized conditions, cyclopentyl bromide was cleanly reacted with electron-deficient alkenes and produced the required thia-Michael adducts after 24 h (Table 2, entries 39–42). Also, the reactions of *iso*-propyl bromide proceeded smoothly, albeit slowly and the corresponding β-sulfido derivatives were isolated in good to excellent yields after 36 h (Table 2, entries 35–38). To extend the applicability of the method to tertiary halides, the reaction of *tert*-butyl bromide was also studied. The reaction proceeded and after 72 h, the corresponding thia-Michael adducts were produced in 50–73% yields (Table 2, entries 43–46).

This protocol is easily applicable for large-scale operation. For this aim, the reaction of *n*-butyl acrylate with 1-bromooctane and thiourea in wet PEG in the presence of Na_2CO_3 as a model reaction was studied. Our observation showed that the reaction was easily scaled up to several grams of the substrates without affecting the rate and the yield of the reaction (Table 2, entry 8).

We have also proposed a general pathway for the reaction as presented in Scheme 1.

3. Conclusion

In conclusion, we have introduced an efficient, versatile and odourless protocol for direct preparation of thia-Michael adducts from non-thiolic precursors under mild and eco-friendly conditions. In this protocol, a mixture of an alkyl halide (primary, secondary, tertiary, allylic or benzylic), thiourea, a conjugated olefin (ketones, esters, nitriles) and sodium carbonate in wet PEG 200 cleanly produced the related thia-Michael adducts in good to excellent yields. This protocol is easily applicable for large-scale operation. Moreover, this method is important because it provides a short pathway to achieve the corresponding thia-Michael adducts of non-commercially available thiols.

4. Experimental

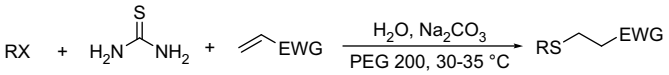
4.1. General

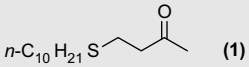
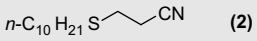
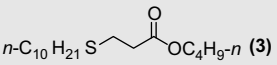
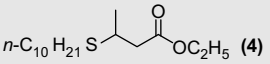
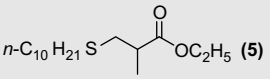
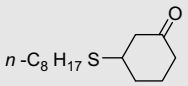
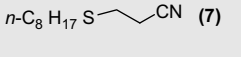
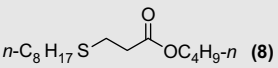
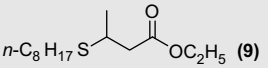
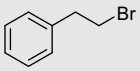
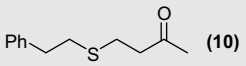
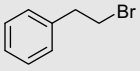
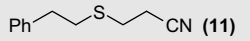
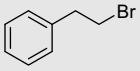
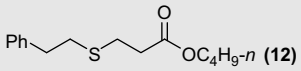
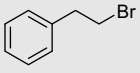
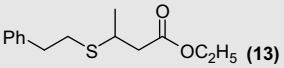
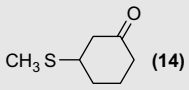
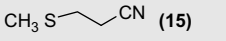
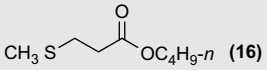
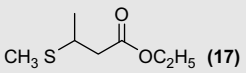
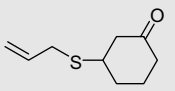
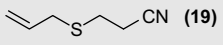
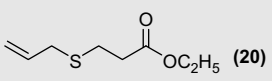
Chemicals were purchased from Merck, Fluka and Acros Chemical Companies. IR spectra were run on a Shimadzu FT-IR 8300 spectrophotometer. ^{1}H NMR and ^{13}C NMR spectra were recorded in $CDCl_3$ using a Bruker Avance DPX instrument (^{1}H NMR 250 MHz, ^{13}C NMR 62.5 MHz). Chemical shifts are reported in parts per million (δ) downfield from TMS. Coupling constants (J) are in hertz. The mass spectra were recorded on a Shimadzu GC–MS QP 1000 EX instrument. Elemental analyses were run on a Thermo Finnigan Flash EA-1112 series. Thin-layer chromatography was carried out on silica gel 254 analytical sheets obtained from Fluka. Column chromatography was performed on Merck Kiesel gel (70–230 mesh).

4.2. General procedure for one-pot preparation of thia-Michael adducts using alkyl halides, thiourea, electron-deficient alkenes and sodium carbonate in wet PEG 200 at 30–35 °C

To a solution of thiourea (3 mmol), an electron-deficient alkene (2 mmol), an alkyl halide (2.4 mmol) and H_2O (0.15 mL) in PEG 200 (3 mL), Na_2CO_3 (3 mmol) was added. The mixture was stirred magnetically at 30–35 °C and the progress of the reaction was

Table 2
One-pot thia-Michael addition using alkyl halides, thiourea and Michael acceptors in the presence of Na_2CO_3 in PEG 200 at 30–35 °C



Entry	Alkyl halide	Electron-deficient alkene	Product	Time (h)	Isolated yield (%)[Ref]
1	n-$C_{10}H_{21}I$	Methyl vinyl ketone	 **(1)**	12	75[20]
2	n-$C_{10}H_{21}I$	Acrylonitrile	 **(2)**	12	89[21]
3	n-$C_{10}H_{21}I$	n-Butyl acrylate	 **(3)**	12	86
4	n-$C_{10}H_{21}I$	Ethyl crotonate	 **(4)**	12	83
5	n-$C_{10}H_{21}I$	Ethyl methacrylate	 **(5)**	12	83
6	n-$C_8H_{17}Br$	2-Cyclohexenone	 **(6)**	11	84[22]
7	n-$C_8H_{17}Br$	Acrylonitrile	 **(7)**	11	90[23]
8	n-$C_8H_{17}Br$	n-Butyl acrylate	 **(8)**	11	87
9	n-$C_8H_{17}Br$	Ethyl crotonate	 **(9)**	11	88
10		Methyl vinyl ketone	 **(10)**	6	85[24]
11		Acrylonitrile	 **(11)**	6	88
12		n-Butyl acrylate	 **(12)**	6	88
13		Ethyl crotonate	 **(13)**	6	86
14	CH_3I	2-Cyclohexenone	 **(14)**	4	77[16]
15	CH_3I	Acrylonitrile	 **(15)**	4	81[16]
16	CH_3I	n-Butyl acrylate	 **(16)**	4	85[25]
17	CH_3I	Ethyl crotonate	 **(17)**	4	83
18		2-Cyclohexenone	 **(18)**	3	75[16]
19		Acrylonitrile	 **(19)**	3	85[16]
20		Ethyl acrylate	 **(20)**	3	89[26]

(*continued on next page*)

Table 2 (*continued*)

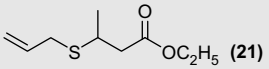
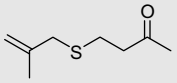
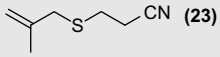
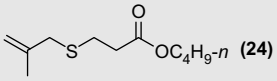
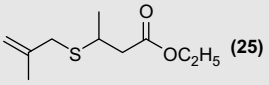
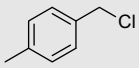
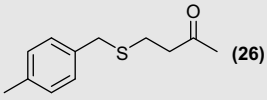
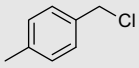
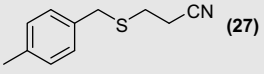
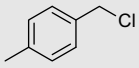
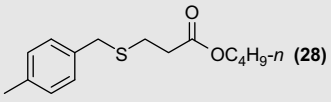
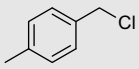
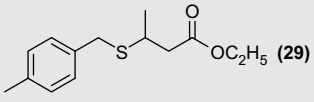
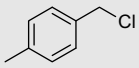
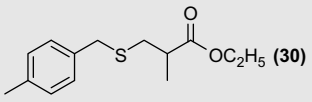
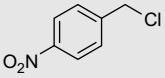
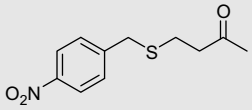
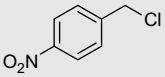
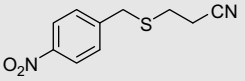
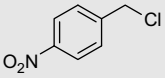
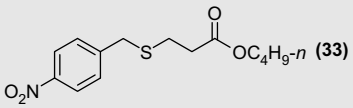
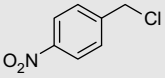
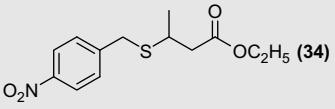
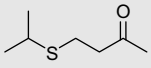
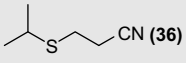
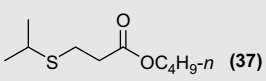
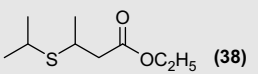
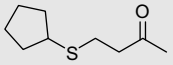
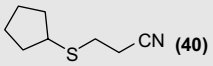
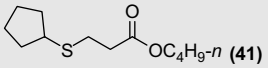
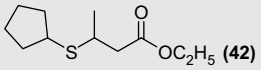
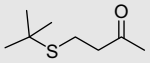
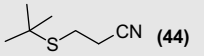
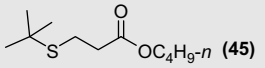
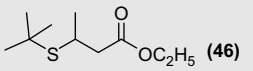
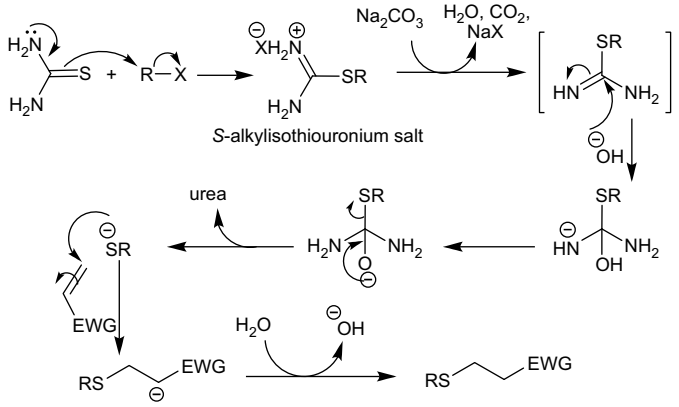
Entry	Alkyl halide	Electron-deficient alkene	Product	Time (h)	Isolated yield (%)[Ref]
21		Ethyl crotonate	 **(21)**	3	85
22		Methyl vinyl ketone	 **(22)**	5	77
23		Acrylonitrile	 **(23)**	5	85[27]
24		*n*-Butyl acrylate	 **(24)**	5	87
25		Ethyl crotonate	 **(25)**	5	87
26		Methyl vinyl ketone	 **(26)**	2.5	82[28]
27		Acrylonitrile	 **(27)**	2.5	90
28		*n*-Butyl acrylate	 **(28)**	2.5	87
29		Ethyl crotonate	 **(29)**	2.5	88
30		Ethyl methacrylate	 **(30)**	2.5	85
31		Methyl vinyl ketone	 **(31)**	7	68[29]
32		Acrylonitrile	 **(32)**	7	85
33		*n*-Butyl acrylate	 **(33)**	7	80
34		Ethyl crotonate	 **(34)**	7	80
35		Methyl vinyl ketone	 **(35)**	36	70[30]
36		Acrylonitrile	 **(36)**	36	85[31]
37		*n*-Butyl acrylate	 **(37)**	36	86
38		Ethyl crotonate	 **(38)**	36	82

Table 2 (*continued*)

Entry	Alkyl halide	Electron-deficient alkene	Product	Time (h)	Isolated yield (%)[Ref]
39		Methyl vinyl ketone	 **(39)**	24	75[16]
40		Acrylonitrile	 **(40)**	24	86[16]
41		*n*-Butyl acrylate	 **(41)**	24	88
42		Ethyl crotonate	 **(42)**	24	83
43		Methyl vinyl ketone	 **(43)**	72	50[32]
44		Acrylonitrile	 **(44)**	72	70[33]
45		*n*-Butyl acrylate	 **(45)**	72	73
46		Ethyl crotonate	 **(46)**	72	66[34]



Scheme 1.

monitored by TLC or GC until the conjugated alkene was consumed. Then the mixture was diluted with water (3 mL) and extracted with ethyl acetate (5×2 mL), dried over Na_2SO_4 and concentrated. Purification by silica gel chromatography afforded the desired products in 50–90% yields.

*4.2.1. 4-(Decylthio)butan-2-one[20] (**1**)*

Colourless oil; ^{1}H NMR (250 MHz, $CDCl_3$) δ: 2.66 (s, 4H), 2.44 (t, J=7.3 Hz, 2H), 2.10 (s, 3H), 1.56–1.44 (m, 2H), 1.28–1.19 (m, 14H), 0.81–0.78 (m, 3H); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ: 207.0, 43.7, 32.4, 31.9, 30.1, 29.6, 29.5, 29.5, 29.3, 29.2, 28.9, 25.7, 22.7, 14.1; IR (neat): ν (cm^{-1})=1717 (C=O). Anal. Calcd for $C_{14}H_{28}OS$: C, 68.79; H, 11.55; S, 13.12. Found: C, 68.71; H, 11.59; S, 13.17.

*4.2.2. 3-(Decylthio)propanenitrile[21] (**2**)*

Colourless oil; ^{1}H NMR (250 MHz, $CDCl_3$) δ: 2.79–2.71 (m, 2H), 2.65–2.49 (m, 4H), 1.61–1.47 (m, 2H), 1.30–1.05 (m, 14H), 0.84–0.78 (m, 3H); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ: 118.4, 32.3, 31.9, 29.5, 29.5, 29.4, 29.3, 29.2, 28.8, 27.6, 22.7, 18.9, 14.1; IR (neat): ν (cm^{-1})=2249 (CN). Anal. Calcd for $C_{13}H_{25}NS$: C, 68.66; H, 11.08; N, 6.16; S, 14.10. Found: C, 68.60; H, 11.06; N, 6.19; S, 14.15.

*4.2.3. Butyl 3-(decylthio)propanoate (**3**)*

Colourless oil; ^{1}H NMR (250 MHz, $CDCl_3$) δ: 4.03 (t, J=6.7 Hz, 2H), 2.74–2.68 (m, 2H), 2.59–2.45 (m, 4H), 1.64–1.45 (m, 4H), 1.39–1.19 (m, 16H), 0.89–0.78 (m, 6H); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ: 172.1, 64.5, 34.9, 32.1, 31.9, 30.6, 29.5, 29.5, 29.3, 29.2, 28.9, 27.0, 22.7, 19.1, 14.1, 13.7; IR (neat): ν (cm^{-1})=1736 (C=O). Anal. Calcd for $C_{17}H_{34}O_2S$: C, 67.49; H, 11.33; S, 10.60. Found: C, 67.53; H, 11.27; S, 10.65.

*4.2.4. Ethyl 3-(decylthio)butanoate (**4**)*

Colourless oil; ^{1}H NMR (250 MHz, $CDCl_3$) δ: 4.09 (q, J=7.1 Hz, 2H), 3.19–3.06 (m, 1H), 2.59–2.31 (m, 4H), 1.56–1.45 (m, 2H), 1.32–1.17 (m, 20H), 0.83–0.78 (m, 3H); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ: 171.5, 60.5, 42.4, 36.2, 31.9, 30.6, 29.7, 29.5, 29.5, 29.3, 29.2, 29.0, 22.7, 21.4, 14.2, 14.1; IR (neat): ν (cm^{-1})=1736 (C=O); MS (m/e)=288 [M^+]. Anal. Calcd for $C_{16}H_{32}O_2S$: C, 66.61; H, 11.18; S, 11.11. Found: C, 66.65; H, 11.12; S, 11.13.

*4.2.5. Ethyl 3-(decylthio)-2-methylpropanoate (**5**)*

Colourless oil; ^{1}H NMR (250 MHz, $CDCl_3$) δ: 4.09 (q, J=7.1 Hz, 2H), 2.80–2.73 (m, 1H), 2.62–2.44 (m, 4H), 1.56–1.44 (m, 2H), 1.22–1.16 (m, 20H), 0.83–0.78 (m, 3H); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ: 175.2, 60.5, 40.2, 35.5, 32.6, 31.9, 29.6, 29.5, 29.5, 29.3, 29.2, 28.8, 22.7, 16.8, 14.2, 14.1; IR (neat): ν (cm^{-1})=1736 (C=O); MS (m/e)=288 [M^+]. Anal. Calcd for $C_{16}H_{32}O_2S$: C, 66.61; H, 11.18; S, 11.11. Found: C, 66.66; H, 11.16; S, 11.14.

*4.2.6. 3-(Octylthio)cyclohexanone[22] (**6**)*

Colourless oil; ^{1}H NMR (250 MHz, $CDCl_3$) δ: 2.99–2.94 (m, 1H), 2.65 (dd, J=14.2, 4.5 Hz, 1H), 2.47 (t, J=7.5 Hz, 2H), 2.35–2.24 (m, 3H), 2.10–2.03 (m, 2H), 1.68–1.59 (m, 2H), 1.53–1.44 (m, 2H), 1.32–1.20 (m, 10H), 0.83–0.78 (m, 3H); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ: 209.0, 48.3, 42.8, 41.0, 31.8, 31.7, 30.5, 29.7, 29.1, 28.9, 24.3, 22.6, 14.1; IR (neat): ν (cm^{-1})=1717 (C=O). Anal. Calcd for $C_{14}H_{26}OS$: C, 69.36; H, 10.81; S, 13.23. Found: C, 69.33; H, 10.75; S, 13.29.

*4.2.7. 3-(Octylthio)propanenitrile[23] (**7**)*

Colourless oil; ^{1}H NMR (250 MHz, $CDCl_3$) δ: 2.66–2.60 (m, 2H), 2.50–2.40 (m, 4H), 1.53–1.38 (m, 2H), 1.25–1.12 (m, 10H), 0.75–0.65 (m, 3H); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ: 118.4, 32.2, 31.8, 29.4, 29.1, 28.8, 27.6, 22.6, 18.9, 14.1; IR (neat): ν (cm^{-1})=2249 (CN). Anal. Calcd for ($C_{11}H_{21}NS$): C, 66.27; H, 10.62; N, 7.03, S, 16.08. Found: C, 66.33; H, 10.67; N, 6.99, S, 16.01.

*4.2.8. Butyl 3-(octylthio)propanoate (**8**)*

Colourless oil; ^{1}H NMR (250 MHz, $CDCl_3$) δ: 4.03 (t, J=6.6 Hz, 2H), 2.74–2.68 (m, 2H), 2.56–2.43 (m, 4H), 1.61–1.45 (m, 4H), 1.39–1.20 (m, 12H), 0.90–0.78 (m, 6H); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ: 172.1, 64.5, 35.0, 32.1, 31.8, 30.6, 29.6, 29.2, 28.9, 27.0, 22.6, 19.1, 14.1, 13.7; IR (neat): ν (cm^{-1})=1736 (C=O). Anal. Calcd for $C_{15}H_{30}O_2S$: C, 65.64; H, 11.02; S, 11.68. Found: C, 65.66; H, 11.06; S, 11.62.

*4.2.9. Ethyl 3-(octylthio)butanoate (**9**)*

Colourless oil; ^{1}H NMR (250 MHz, $CDCl_3$) δ: 4.09 (q, J=7.1 Hz, 2H), 3.19–3.06 (m, 1H), 2.59–2.31 (m, 4H), 1.56–1.45 (m, 2H), 1.29–1.17 (m, 16H), 0.83–0.78 (m, 3H); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ: 171.5, 60.5, 42.4, 36.1, 31.8, 30.6, 29.7, 29.2, 29.0, 22.6, 21.4, 14.2, 14.1; IR (neat): ν (cm^{-1})=1736 (C=O). Anal. Calcd for $C_{14}H_{28}O_2S$: C, 64.56; H, 10.84; S, 12.31. Found: C, 64.63; H, 10.80; S, 12.33.

*4.2.10. 4-(Phenethylthio)butan-2-one[24] (**10**)*

Colourless oil; ^{1}H NMR (250 MHz, $CDCl_3$) δ: 7.33–7.19 (m, 5H), 2.81–2.65 (m, 8H), 2.15 (s, 3H); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ: 206.9, 140.4, 128.5, 128.5 126.4, 43.7, 36.2, 34.0, 30.1, 25.9; IR (neat): ν (cm^{-1})=1717 (C=O), 1605, 1496 (aromatic C=C). Anal. Calcd for $C_{12}H_{16}OS$: C, 69.19; H, 7.74; S, 15.39. Found: C, 69.14; H, 7.80; S, 15.34.

*4.2.11. 3-(Phenethylthio)propanenitrile (**11**)*

Colourless oil; ^{1}H NMR (250 MHz, $CDCl_3$) δ: 7.34–7.22 (m, 5H), 2.91–2.84 (m, 4H), 2.76–2.70 (m, 2H), 2.58–2.53 (m, 2H); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ: 142.3, 128.6, 126.6, 118.6, 36.1, 33.8, 27.8, 18.9; IR (neat): ν (cm^{-1})=2249 (CN), 1601, 1497 (aromatic C=C). Anal. Calcd for $C_{11}H_{13}NS$: C, 69.07; H, 6.85; N, 7.32; S, 16.76. Found: C, 69.12; H, 6.80; N, 7.30; S, 16.78.

*4.2.12. Butyl 3-(phenethylthio)propanoate (**12**)*

Colourless oil; ^{1}H NMR (250 MHz, $CDCl_3$) δ: 7.17–7.06 (m, 5H), 3.99 (t, J=6.6, 2H), 2.77–2.63 (m, 6H), 2.47 (t, J=7.2 Hz, 2H), 1.58–1.42 (m, 2H), 1.32–1.15 (m, 2H), 0.83 (t, J=7.3 Hz, 3H); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ: 171.9, 140.4, 128.5, 126.4, 64.5, 36.3, 34.9, 33.7, 30.7, 27.2, 19.2, 13.7; IR (neat): ν (cm^{-1})=1736 (C=O), 1605, 1497 (aromatic C=C). Anal. Calcd for $C_{15}H_{22}O_2S$: C, 67.63; H, 8.32; S, 12.04. Found: C, 67.59; H, 8.33; S, 12.06.

*4.2.13. Ethyl 3-(phenethylthio)butanoate (**13**)*

Colourless oil; ^{1}H NMR (250 MHz, $CDCl_3$) δ: 7.13–7.06 (m, 5H), 4.04 (q, J=7.1 Hz, 2H), 3.22–3.13 (m, 1H), 2.83–2.64 (m, 4H), 2.51 (dd, J=15.4, 6.3 Hz, 1H), 2.33 (dd, J=15.4, 8.1 Hz, 1H), 1.23 (d, J=6.8 Hz, 3H), 1.15 (t, J=7.1 Hz, 3H); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ: 171.3, 138.8, 128.5, 128.5, 126.3, 60.4, 42.3, 36.3, 32.2, 21.5, 14.3; IR (neat): ν (cm^{-1})=1736 (C=O), 1605, 1497 (aromatic C=C). Anal. Calcd for $C_{14}H_{20}O_2S$: C, 66.63; H, 7.99; S, 12.71. Found: C, 66.67; H, 8.03; S, 12.67.

*4.2.14. 3-(Methylthio)cyclohexanone[16] (**14**)*

Colourless oil; ^{1}H NMR (250 MHz, $CDCl_3$) δ: 2.93–2.85 (m, 1H), 2.65 (dd, J=14.1, 4.2 Hz, 1H), 2.36–2.19 (m, 3H), 2.08–2.05 (m, 5H), 1.73–1.57 (m, 2H); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ: 208.9, 47.6, 44.2, 40.9, 31.0, 24.1, 13.5; IR (neat): ν (cm^{-1})=1713 (C=O). Anal. Calcd for $C_7H_{12}OS$: C, 58.29; H, 8.39; S, 22.23. Found: C, 58.22; H, 8.42; S, 22.20.

*4.2.15. 3-(Methylthio)propanenitrile[16] (**15**)*

Colourless oil; ^{1}H NMR (250 MHz, $CDCl_3$) δ: 2.74–2.68 (m, 2H), 2.62–2.54 (m, 2H), 2.15 (s, 3H); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ: 118.4, 29.7, 18.4, 15.6; IR (neat): ν (cm^{-1})=2249 (CN). Anal. Calcd for C_4H_7NS: C, 47.49; H, 6.97; N, 13.84; S, 31.69. Found: C, 47.57; H, 6.95; N, 13.80; S, 31.68.

*4.2.16. Butyl 3-(methylthio)propanoate[25] (**16**)*

Colourless oil; ^{1}H NMR (250 MHz, $CDCl_3$) δ: 4.03 (t, J=6.6 Hz, 2H), 2.72–2.67 (m, 2H), 2.57–2.51 (m, 2H), 2.05 (s, 3H), 1.61–1.50 (m, 2H), 1.39–1.24 (m, 2H), 0.87 (t, J=7.3 Hz, 3H); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ: 171.9, 64.4, 34.4, 30.6, 29.0, 19.0, 15.3, 13.6; IR (neat): ν (cm^{-1})=1736 (C=O). Anal. Calcd for $C_8H_{16}O_2S$: C, 54.51; H, 9.15; S, 18.19. Found: C, 54.57; H, 9.10; S, 18.12.

*4.2.17. Ethyl 3-(methylthio)butanoate (**17**)*

Colourless oil; ^{1}H NMR (250 MHz, $CDCl_3$) δ: 3.91 (q, J=7.1 Hz, 2H), 2.93–2.81 (m, 1H), 2.39 (dd, J=15.3, 6.4 Hz, 1H), 2.19 (dd, J=15.3, 8.2 Hz, 1H), 1.86 (s, 3H), 1.08 (d, J=6.8 Hz, 3H), 1.03 (t, J=7.1 Hz, 3H); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ: 171.4, 60.4, 41.7, 37.2, 20.6, 14.1, 13.2; IR (neat): ν (cm^{-1})=1736 (C=O). Anal. Calcd for $C_7H_{14}O_2S$: C, 51.82; H, 8.70; S, 19.76. Found: C, 51.80; H, 8.73; S, 19.72.

*4.2.18. 3-(Allylthio)cyclohexanone[16] (**18**)*

Colourless oil; ^{1}H NMR (250 MHz, $CDCl_3$) δ: 5.69–5.53 (m, 1H), 5.00–4.88 (m, 2H), 3.00 (d, J=7.0 Hz, 2H), 2.87–2.81 (m, 1H), 2.50 (dd, J=14.3, 4.5 Hz, 1H), 2.24–2.12 (m, 3H), 1.98–1.90 (m, 2H), 1.57–1.43 (m, 2H); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ: 208.8, 134.2, 117.2, 47.9, 41.4, 40.9, 33.5, 31.3, 24.2; IR (neat): ν (cm^{-1})=1716 (C=O), 1634 (C=C). Anal. Calcd for $C_9H_{14}OS$: C, 63.48; H, 8.29; S, 18.83. Found: C, 63.55; H, 8.35; S, 18.76.

*4.2.19. 3-(Allylthio)propanenitrile[16] (**19**)*

Colourless oil; ^{1}H NMR (250 MHz, $CDCl_3$) δ: 5.82–5.64 (m, 1H), 5.15–5.08 (m, 2H), 3.17 (d, J=7.2 Hz, 2H), 2.71–2.66 (m, 2H), 2.60–2.54 (m, 2H); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ: 133.6, 118.4, 118.0, 34.7, 25.8, 18.6; IR (neat): ν (cm^{-1})=2249 (CN), 1634 (C=C). Anal. Calcd for C_6H_9NS: C, 56.65; H, 7.13; N, 11.01; S, 25.21. Found: C, 56.59; H, 7.09; N, 11.07; S, 25.25.

*4.2.20. Ethyl 3-(allylthio)propanoate[26] (**20**)*

Colourless oil; ^{1}H NMR (250 MHz, $CDCl_3$) δ: 5.86–5.69 (m, 1H), 5.14–5.07 (m, 2H), 4.14 (q, J=7.1 Hz, 2H), 3.14 (d, J=7.1 Hz, 2H), 2.75–2.69 (m, 2H), 2.59–2.53 (m, 2H), 1.25 (t, J=7.1 Hz, 3H); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ: 171.9, 134.1, 117.2, 60.6, 34.7, 34.6, 25.5, 14.2; IR (neat): ν (cm^{-1})=1732 (C=O), 1634 (C=C). Anal. Calcd for $C_8H_{14}O_2S$: C, 55.14; H, 8.10; S, 18.40. Found: C, 55.20; H, 8.02; S, 18.42.

*4.2.21. Ethyl 3-(allylthio)butanoate (**21**)*

Colourless oil; ^{1}H NMR (250 MHz, $CDCl_3$) δ: 5.83–5.67 (m, 1H), 5.11–5.00 (m, 2H), 4.08 (q, J=7.1 Hz, 2H), 3.17–3.03 (m, 3H), 2.55 (dd, J=15.4, 6.1 Hz, 1H), 2.35 (dd, J=15.4, 8.3 Hz, 1H), 1.25–1.16 (m, 6H); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ: 171.3, 134.4, 116.9, 60.4, 42.0, 35.1, 33.9, 21.1, 14.2; IR (neat): ν (cm^{-1})=1736 (C=O), 1636 (C=C). Anal. Calcd for $C_9H_{16}O_2S$: C, 57.41; H, 8.57; S, 17.03. Found: C, 57.44; H, 8.50; S, 17.06.

*4.2.22. 4-(2-Methylallylthio)butan-2-one (**22**)*

Colourless oil; ^{1}H NMR (250 MHz, $CDCl_3$) δ: 4.69 (s, 2H), 2.96 (s, 2H), 2.59–2.41 (m, 4H), 2.01 (s, 3H), 1.58 (s, 3H); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ: 207.0, 141.1, 113.6, 43.3, 39.7, 30.0, 24.7, 20.6; IR (neat): ν (cm^{-1})=1717 (C=O), 1647 (C=C). Anal. Calcd for $C_8H_{14}OS$: C, 60.71; H, 8.92; S, 20.26. Found: C, 60.66; H, 8.99; S, 20.25.

*4.2.23. 3-(2-Methylallylthio)propanenitrile[27] (**23**)*

Colourless oil; ^{1}H NMR (250 MHz, $CDCl_3$) δ: 4.75–4.72 (m, 2H), 3.04 (s, 2H), 2.61–2.44 (m, 4H), 1.67 (s, 3H); ^{13}C NMR (62.5 MHz,

$CDCl_3$) δ: 140.6, 118.5, 114.4, 39.2, 26.1, 20.3, 18.4; IR (neat): ν (cm^{-1})=2249 (CN), 1647 (C=C). Anal. Calcd for $C_7H_{11}NS$: C, 59.53; H, 7.85; N, 9.92; S, 22.70. Found: C, 59.55; H, 7.81; N, 9.86; S, 22.78.

*4.2.24. Butyl 3-(2-methylallylthio)propanoate (**24**)*

Colourless oil; ^1H NMR (250 MHz, $CDCl_3$) δ: 4.78–4.77 (m, 2H), 4.03 (t, J=6.6 Hz, 2H), 3.06 (s, 2H), 2.65–2.59 (m, 2H), 2.53–2.46 (m, 2H), 1.75 (s, 3H), 1.60–1.49 (m, 2H), 1.39–1.27 (m, 2H), 0.86 (t, J=7.3 Hz, 3H); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ: 172.0, 141.0, 113.6, 64.5, 39.3, 34.4, 30.6, 25.8, 20.5, 19.1, 13.7; IR (neat): ν (cm^{-1})=1736 (C=O), 1647 (C=C). Anal. Calcd for $C_{11}H_{20}O_2S$: C, 61.07; H, 9.32; S, 14.82. Found: C, 61.01; H, 9.35; S, 14.87.

*4.2.25. Ethyl 3-(2-methylallylthio)butanoate (**25**)*

Colourless oil; ^1H NMR (250 MHz, $CDCl_3$) δ: 4.59–4.55 (m, 2H), 3.88 (q, J=7.0 Hz, 2H), 2.88 (s, 2H), 2.83–2.74 (m, 1H), 2.32 (dd, J=15.3, 6.3 Hz, 1H), 2.13 (dd, J=15.3, 8.2 Hz, 1H), 1.53 (s, 3H), 1.03–0.94 (m, 6H); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ: 171.2, 141.3, 113.3, 60.3, 41.9, 38.4, 21.0, 20.8, 20.6, 14.1; IR (neat): ν (cm^{-1})=1736 (C=O), 1647 (C=C). Anal. Calcd for $C_{10}H_{18}O_2S$: C, 59.37; H, 8.97; S, 15.85. Found: C, 59.41; H, 8.90; S, 15.89.

*4.2.26. 4-((4-Methylphenyl)methylsulfanyl)butan-2-one[28] (**26**)*

Colourless oil; ^1H NMR (250 MHz, $CDCl_3$) δ: 7.07 (d, J=8.0 Hz, 2H), 6.98 (d, J=8.0 Hz, 2H), 3.53 (s, 2H), 2.48 (s, 4H), 2.17 (s, 3H), 1.95 (s, 3H); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ: 206.6, 136.5, 135.2, 129.2, 128.9, 43.5, 36.2, 29.9, 25.1, 21.1; IR (neat): ν (cm^{-1})=1717 (C=O), 1582 (aromatic C=C); MS (m/e)=208 [M^+]. Anal. Calcd for $C_{12}H_{16}OS$: C, 69.19; H, 7.74; S, 15.39. Found: C, 69.25; H, 7.80; S, 15.32.

*4.2.27. 3-((4-Methylphenyl)methylsulfanyl)propionitrile (**27**)*

Colourless oil; ^1H NMR (250 MHz, $CDCl_3$) δ: 7.07 (d, J=8.0 Hz, 2H), 6.99 (d, J=8.0 Hz, 2H), 3.61 (s, 2H), 2.52–2.46 (m, 2H), 2.38–2.31 (m, 2H), 2.19 (s, 3H); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ: 137.0, 134.3, 129.3, 128.7, 118.4, 35.9, 26.5, 21.0, 18.5; IR (neat): ν (cm^{-1})=2249 (CN), 1512 (aromatic C=C); MS (m/e)=191 [M^+]. Anal. Calcd for $C_{11}H_{13}NS$: C, 69.07; H, 6.85; N, 7.32; S, 16.76. Found: C, 69.01; H, 6.80; N, 7.37; S, 16.82.

*4.2.28. Butyl 3-((4-methylphenyl)methylsulfanyl)propanoate (**28**)*

Colourless oil; ^1H NMR (250 MHz, $CDCl_3$) δ: 7.11 (d, J=8.0 Hz, 2H), 7.03 (d, J=8.0 Hz, 2H), 4.00 (t, J=6.6 Hz, 2H), 3.61 (s, 2H), 2.62–2.56 (m, 2H), 2.48–2.42 (m, 2H), 2.24 (s, 3H), 1.55–1.46 (m, 2H), 1.33–1.24 (m, 2H), 0.85 (t, J=7.3 Hz, 3H); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ: 172.0, 136.7, 135.0, 129.2, 128.7, 64.5, 35.9, 34.5, 30.6, 26.2, 21.1, 19.1, 13.7; IR (neat): ν (cm^{-1})=1736 (C=O), 1589 (aromatic C=C); MS (m/e)=266 [M^+]. Anal. Calcd for $C_{15}H_{22}O_2S$: C, 67.63; H, 8.32; S, 12.04. Found: C, 67.70; H, 8.25; S, 12.07.

*4.2.29. Ethyl 3-((4-methylphenyl)methylsulfanyl)butanoate (**29**)*

Colourless oil; ^1H NMR (250 MHz, $CDCl_3$) δ: 7.13 (d, J=7.9 Hz, 2H), 7.03 (d, J=7.9 Hz, 2H), 4.05 (q, J=7.2 Hz, 2H), 3.65 (s, 2H), 3.10–2.97 (m, 1H), 2.53 (dd, J=15.3, 6.0 Hz, 1H), 2.34 (dd, J=15.3, 8.4 Hz, 1H), 2.24 (s, 3H), 1.23–1.14 (m, 6H); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ: 171.4, 136.6, 135.1, 129.2, 128.7, 60.5, 42.1, 35.9, 35.0, 21.2, 21.1, 14.2; IR (neat): ν (cm^{-1})=1736 (C=O), 1512 (aromatic C=C); MS (m/e)=252 [M^+]. Anal. Calcd for $C_{14}H_{20}O_2S$: C, 66.63; H, 7.99; S, 12.71. Found: C, 66.66; H, 7.92; S, 12.79.

*4.2.30. Ethyl 2-methyl-3-((4-methylphenyl)methylsulfanyl)-propanoate (**30**)*

Colourless oil; ^1H NMR (250 MHz, $CDCl_3$) δ: 7.12 (d, J=8.0 Hz, 2H), 7.04 (d, J=8.0 Hz, 2H), 4.07 (q, J=7.1 Hz, 2H), 3.61 (s, 2H), 2.71–2.63 (m, 1H), 2.59–2.45 (m, 1H), 2.41–2.33 (m, 1H), 2.25 (s, 3H), 1.19 (t, J=7.1 Hz, 3H), 1.13 (d, J=6.8 Hz, 3H); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ: 175.2, 136.7, 135.0, 129.2, 128.8, 60.5, 39.9, 36.2, 34.5, 21.1, 16.8, 14.2; IR (neat): ν (cm^{-1})=1732 (C=O). Anal. Calcd for $C_{14}H_{20}O_2S$: C, 66.63; H, 7.99; S, 12.71. Found: C, 66.67; H, 7.95; S, 12.77.

*4.2.31. 4-((4-Nitrophenyl)methylsulfanyl)butan-2-one[29] (**31**)*

Colourless oil; ^1H NMR (250 MHz, $CDCl_3$) δ: 8.09 (d, J=8.5 Hz, 2H), 7.42 (d, J=8.5 Hz, 2H), 3.72 (s, 2H), 2.86–2.53 (m, 4H), 2.07 (s, 3H); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ: 206.4, 146.9, 146.2, 129.8, 123.8, 43.1, 36.2, 30.0, 25.2; IR (neat): ν (cm^{-1})=1713 (C=O), 1601 (aromatic C=C), 1520, 1346 (NO_2); MS (m/e)=239 [M^+]. Anal. Calcd for $C_{11}H_{13}NO_3S$: C, 55.21; H, 5.48; N, 5.85; S, 13.40. Found: C, 55.25; H, 5.56; N, 5.78; S, 13.43.

*4.2.32. 3-((4-Nitrophenyl)methylsulfanyl)propionitrile (**32**)*

Colourless oil; ^1H NMR (250 MHz, $CDCl_3$) δ: 8.06 (d, J=8.4 Hz, 2H), 7.46 (d, J=8.4 Hz, 2H), 3.83 (s, 2H), 2.66–2.52 (m, 4H); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ: 147.1, 145.3, 129.3, 123.9, 118.4, 35.7, 26.8, 18.7; IR (neat): ν (cm^{-1})=2249 (CN), 1601 (aromatic C=C), 1520, 1346 (NO_2); MS (m/e)=222 [M^+]. Anal. Calcd for $C_{10}H_{10}N_2O_2S$: C, 54.04; H, 4.53; N, 12.60; S, 14.43. Found: C, 53.98; H, 4.50; N, 12.65; S, 14.41.

*4.2.33. Butyl 3-((4-nitrophenyl)methylsulfanyl)propanoate (**33**)*

Colourless oil; ^1H NMR (250 MHz, $CDCl_3$) δ: 7.96 (d, J=8.4 Hz, 2H), 7.32 (d, J=8.4 Hz, 2H), 3.89 (t, J=6.7 Hz, 2H), 3.71 (s, 2H), 2.54–2.48 (m, 2H), 2.40–2.34 (m, 2H), 1.46–1.35 (m, 2H), 1.24–1.12 (m, 2H), 0.75–0.69 (m, 3H); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ: 171.6, 146.9, 146.1, 129.6, 124.1, 64.6, 35.7, 34.4, 30.5, 26.9, 19.0, 13.6; IR (neat): ν (cm^{-1})=1732 (C=O), 1601 (aromatic C=C), 1520, 1346 (NO_2); MS (m/e)=297 [M^+]. Anal. Calcd for $C_{14}H_{19}NO_4S$: C, 56.55; H, 6.44; N, 4.71; S, 10.78. Found: C, 56.60; H, 6.40; N, 4.73; S, 10.72.

*4.2.34. Ethyl 3-((4-nitrophenyl)methylsulfanyl)butanoate (**34**)*

Colourless oil; ^1H NMR (250 MHz, $CDCl_3$) δ: 8.09 (d, J=8.7 Hz, 2H), 7.44 (d, J=8.7 Hz, 2H), 4.03 (q, J=7.1 Hz, 2H), 3.77 (s, 2H), 3.10–2.96 (m, 1H), 2.53 (dd, J=15.5, 6.5 Hz, 1H), 2.36 (dd, J=15.5, 7.8 Hz, 1H), 1.24–1.13 (m, 6H); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ: 171.1, 147.9, 146.2, 129.7, 123.8, 60.7, 42.0, 36.2, 34.8, 21.3, 14.2; IR (neat): ν (cm^{-1})=1732 (C=O), 1601 (aromatic C=C), 1520, 1346 (NO_2); MS (m/e)=283 [M^+]. Anal. Calcd for $C_{13}H_{17}NO_4S$: C, 55.11; H, 6.05; N, 4.94; S, 11.32. Found: C, 55.17; H, 6.02; N, 5.00; S, 11.37.

*4.2.35. 4-(Isopropylthio)butan-2-one[30] (**35**)*

Colourless oil; ^1H NMR (250 MHz, $CDCl_3$) δ: 2.91–2.80 (m, 1H), 2.68–2.65 (m, 4H), 2.11 (s, 3H), 1.19 (d, J=6.7 Hz, 6H); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ: 207.0, 43.7, 35.2, 30.1, 24.2, 23.3; IR (neat): ν (cm^{-1})=1717 (C=O). Anal. Calcd for $C_7H_{14}OS$: C, 57.49; H, 9.65; S, 21.92. Found: C, 57.44; H, 9.64; S, 21.95.

*4.2.36. 3-(Isopropylthio)propanenitrile[31] (**36**)*

Colourless oil; ^1H NMR (250 MHz, $CDCl_3$) δ: 3.04–2.88 (m, 1H), 2.77–2.71 (m, 2H), 2.59–2.53 (m, 2H), 1.22 (d, J=6.7 Hz, 6H); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ: 118.4, 35.2, 26.0, 23.2, 19.0; IR (neat): ν (cm^{-1})=2249 (CN). Anal. Calcd for $C_6H_{11}NS$: C, 55.77; H, 8.58; N, 10.84; S, 24.81. Found: C, 55.81; H, 8.55; N, 10.80; S, 24.84.

*4.2.37. Butyl 3-(isopropylthio)propanoate (**37**)*

Colourless oil; ^1H NMR (250 MHz, $CDCl_3$) δ: 4.03 (t, J=6.6 Hz, 2H), 2.93–2.83 (m, 1H), 2.76–2.72 (m, 2H), 2.55–2.49 (m, 2H), 1.63–1.49 (m, 2H), 1.36–1.27 (m, 2H), 1.20 (d, J=6.7 Hz, 6H), 0.87 (t, J=7.3 Hz, 3H); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ: 172.1, 64.5, 35.0, 34.9, 30.6, 25.5, 23.3, 19.1, 13.7; IR (neat): ν (cm^{-1})=1736 (C=O). Anal. Calcd for $C_{10}H_{20}O_2S$: C, 58.78; H, 9.87; S, 15.69. Found: C, 58.81; H, 9.82; S, 15.66.

*4.2.38. Ethyl 3-(isopropylthio)butanoate (**38**)*

Colourless oil; ^1H NMR (250 MHz, $CDCl_3$) δ: 4.09 (q, J=7.1 Hz, 2H), 3.25–3.12 (m, 1H), 3.01–2.85 (m, 1H), 2.54 (dd, J=15.4, 6.1, Hz, 1H),

2.36 (dd, J=15.4, 8.3 Hz, 1H), 1.25 (d, J=6.8 Hz, 3H), 1.23–1.17 (m, 9H); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ: 171.5, 60.5, 42.6, 35.0, 34.1, 23.5, 21.9, 14.2; IR (neat): ν (cm^{-1})=1736 (C=O). Anal. Calcd for $C_9H_{18}O_2S$: C, 56.80; H, 9.53; S, 16.85. Found: C, 56.81; H, 9.55; S, 16.80.

4.2.39. 4-(Cyclopentylthio)butan-2-one[16] (***39***)

Colourless oil; ^{1}H NMR (250 MHz, $CDCl_3$) δ: 3.08–2.97 (m, 1H), 2.68 (s, 4H), 2.10 (s, 3H), 1.96–1.86 (m, 2H), 1.70–1.36 (m, 6H); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ: 207.0, 44.0, 43.8, 33.7, 30.0, 25.5, 24.7; IR (neat): ν (cm^{-1})=1717 (C=O). Anal. Calcd for $C_9H_{16}OS$: C, 62.74; H, 9.36; S, 18.61. Found: C, 62.77; H, 9.32; S, 18.64.

4.2.40. 3-(Cyclopentylthio)propanenitrile[16] (***40***)

Colourless oil; ^{1}H NMR (250 MHz, $CDCl_3$) δ: 3.17–3.06 (m, 1H), 2.78–2.72 (m, 2H), 2.62–2.56 (m, 2H), 2.03–1.90 (m, 2H), 1.73–1.37 (m, 6H); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ: 118.5, 43.9, 33.7, 27.4, 24.7, 19.0; IR (neat): ν (cm^{-1})=2249 (CN). Anal. Calcd for $C_8H_{13}NS$: C, 61.89; H, 8.44; N, 9.02; S, 20.65. Found: C, 61.85; H, 8.48; N, 9.00; S, 20.67.

4.2.41. Butyl 3-(cyclopentylthio)propanoate (***41***)

Colourless oil; ^{1}H NMR (250 MHz, $CDCl_3$) δ: 4.03 (t, J=6.6 Hz, 2H), 3.10–2.99 (m, 1H), 2.74 (t, J=7.3 Hz, 2H), 2.53 (t, J=7.3 Hz, 2H), 1.96–1.87 (m, 2H), 1.67–1.27 (m, 10H), 0.86 (t, J=7.3 Hz, 3H); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ: 172.1, 64.5, 43.8, 35.0, 33.7, 30.6, 26.8, 24.7, 19.1, 13.7; IR (neat): ν (cm^{-1})=1736 (C=O). Anal. Calcd for $C_{12}H_{22}O_2S$: C, 62.56; H, 9.63; S, 13.92. Found: C, 62.60; H, 9.65; S, 13.87.

4.2.42. Ethyl 3-(cyclopentylthio)butanoate (***42***)

Colourless oil; ^{1}H NMR (250 MHz, $CDCl_3$) δ: 4.08 (q, J=7.1 Hz, 2H), 3.24–3.02 (m, 2H), 2.56 (dd, J=15.4, 6.1 Hz, 1H), 2.36 (dd, J=15.4, 8.4 Hz, 1H), 1.96–1.87 (m, 2H), 1.73–1.37 (m, 6H), 2.26 (d, J=6.8 Hz, 3H), 1.20 (t, J=7.1 Hz, 3H); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ: 171.5, 60.4, 42.7, 42.6, 36.2, 33.7, 24.7, 21.7, 14.2; IR (neat): ν (cm^{-1})=1736 (C=O). Anal. Calcd for $C_{11}H_{20}O_2S$: C, 61.07; H, 9.32; S, 14.82. Found: C, 61.03; H, 9.32; S, 14.85.

4.2.43. 4-(tert-Butylthio)butan-2-one[32] (***43***)

Colourless oil; ^{1}H NMR (250 MHz, $CDCl_3$) δ: 2.72–2.58 (m, 4H), 2.10 (s, 3H), 1.26 (s, 9H); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ: 207.0, 43.6, 42.3, 30.8, 30.1, 22.0; IR (neat): ν (cm^{-1})=1717 (C=O). Anal. Calcd for $C_8H_{16}OS$: C, 59.95; H, 10.06; S, 20.01. Found: C, 59.90; H, 10.10; S, 19.96.

4.2.44. 3-(tert-Butylthio)propanenitrile[33] (***44***)

Colourless oil; ^{1}H NMR (250 MHz, $CDCl_3$) δ: 2.77–2.71 (m, 2H), 2.57–2.50 (m, 2H), 1.28 (s, 9H); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ: 118.4, 43.2, 30.9, 24.1, 19.0; IR (neat): ν (cm^{-1})=2249 (CN). Anal. Calcd for $C_7H_{13}NS$: C, 58.69; H, 9.15; N, 9.78; S, 22.38. Found: C, 58.73; H, 9.13; N, 9.75; S, 22.39.

4.2.45. Butyl 3-(tert-butylthio)propanoate (***45***)

Colourless oil; ^{1}H NMR (250 MHz, $CDCl_3$) δ: 4.03 (t, J=6.6 Hz, 2H), 2.76–2.70 (m, 2H), 2.53–2.47 (m, 2H), 1.61–1.49 (m, 2H), 1.39–1.26 (m, 11H), 0.86 (t, J=7.3 Hz, 3H); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ: 172.2, 64.5, 42.3, 34.9, 30.9, 30.6, 23.4, 19.1, 13.7; IR (neat): ν (cm^{-1})=1736 (C=O). Anal. Calcd for $C_{11}H_{22}O_2S$: C, 60.51; H, 10.16; S, 14.68. Found: C, 60.45; H, 10.13; S, 14.70.

4.2.46. Ethyl 3-(tert-butylthio)butanoate[34] (***46***)

Colourless oil; ^{1}H NMR (250 MHz, $CDCl_3$) δ: 4.08 (q, J=7.1 Hz, 2H), 3.19–3.06 (m, 1H), 2.55 (dd, J=15.5, 6.6 Hz, 1H), 2.39 (dd, J=15.5, 8.1 Hz, 1H), 1.30–1.25 (m, 12H), 1.20 (t, J=7.1 Hz, 3H); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ: 171.5, 60.4, 44.2, 43.5, 33.9, 31.4, 24.3, 14.2; IR (neat): ν (cm^{-1})=1736 (C=O). Anal. Calcd for $C_{10}H_{20}O_2S$: C, 58.78; H, 9.87; S, 15.69. Found: C, 58.81; H, 9.83; S, 15.72.

4.3. Typical large-scale procedure for one-pot preparation of butyl 3-(octylthio)propanoate (8) using 1-bromooctane, thiourea, *n*-butyl acrylate and sodium carbonate in wet PEG 200 at 30–35 °C

To a solution of thiourea (30 mmol, 2.28 g), *n*-butyl acrylate (20 mmol, 2.56 g), 1-bromooctane (24 mmol, 4.64 g) and H_2O (1.5 mL) in PEG 200 (30 mL), Na_2CO_3 (30 mmol, 3.80 g) was added. The mixture was stirred magnetically at room temperature (30–35 °C) and the progress of the reaction was monitored by GC until *n*-butyl acrylate was consumed (11 h). The mixture was then diluted with water (30 mL) and extracted with ethyl acetate (5×20 mL), dried over Na_2SO_4 and concentrated. Purification by silica gel chromatography afforded the desired product in (4.62 g) 84% yield.

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Supplementary data

^{1}H and ^{13}C NMR spectra of all thia-Michael adducts are provided. Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.tet.2009.04.079.

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