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Fluoride ion-catalyzed conjugate addition for easy synthesis of 3-sulfanylpropionic acid from thiol and α,β-unsaturated carboxylic acid

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Abstract

3-Sulfanylpropionic acids are obtained in excellent yields by proceeding through a simple, mild, and efficient procedure utilizing tetrabutylammonium fluoride (TBAF) as catalyst.

1. Introduction

The conjugate addition is one of the efficient methods in organic synthesis for the formation of carbon–carbon, carbon–sulfur, and carbon–nitrogen bonds.[1] Among various nucleophilic additions, the conjugate addition of thiols to various unsaturated systems to form a carbon–sulfur bond is of much importance, as it comprises a key reaction in the biosynthesis and the synthesis of several biologically active compounds.[2] A number of methods have been reported in the literature, regarding the conjugate addition of thiols to unsaturated carbonyl compounds such as α,β-unsaturated aldehyde, ketone, ester, and nitrile.[3] Comparatively, the conjugate addition of thiols to α,β-unsaturated carboxylic acids is more difficult, due to low reactivity of carboxylic acid, and the functional group itself involves or even destroys such reaction. In the literature, the treatment of free α,β-unsaturated carboxylic acids with organometallic reagents such as magnesium, lithium, and copper afforded the desired products in lower yields or even afforded 1,2-addition products and other side products.[4] In 2000, Avery et al. reported that the same reaction with primary carbon radicals also suffers from lower yields.[5] To avoid the interference from carboxylic acid functional group, these reactions were carried out under conventional condition, which involves a three-step process such as protection, conjugate addition, and deprotection.[6] The alternative approach to prepare the β-substituted propionic acids is by hydrolyzing the corresponding β-substituted propionitriles, which are generated from α,β-unsaturated nitriles.[7] Our previous study found the use of molecular iodine (I_2) as a catalyst for conjugate addition of thiols to α,β-unsaturated ketones.[8] The catalytic system could been also successfully applied to a variety of α,β-unsaturated carboxylic acids as well as thiols to synthesize various 3-sulfanylpropionic acids, however, the reaction of acrylic acid with thiol afforded the desired products accompanied by a small amount of iodo adducts.[9] In this context, exploring efficient reagent as catalyst and the development of simple and mild procedures for the preparation of β-substituted propionic acids from free α,β-unsaturated carboxylic acids are still an interesting topic for organic chemists.

Over the past years, tetrabutylammonium fluoride (TBAF) in organic synthesis has been widely used for most fluoride-assisted reactions,[10] deprotection of silyl groups,[11] desilyation,[12] and fluorination.[13] TBAF has been widely recognized as a convenient, organic-soluble source of naked fluoride ion. It has also been widely used for a variety of base-catalyzed reactions such as alkylation, elimination, Michael addition, and

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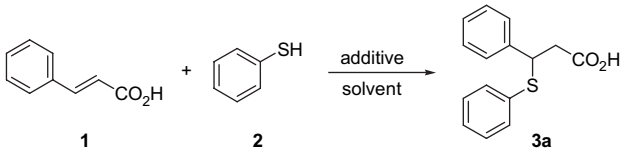
aldol condensation.[14] The potential ability of the fluoride ion to act as a base might be predicated by considering the strength of the H–F bond. Most ionic fluorides are easy to prepare and use, and are stable over long periods of time. The fluoride ions are hygroscopic, but they do not react with water and may therefore be recovered from aqueous solution by conventional techniques. The reactions are usually carried out below 100 °C due to the low thermal stability of TBAF. As part of our incessant research efforts with α,β-unsaturated system chemistry,[15] we now report a new, simple, and efficient catalyst, TBAF, for the synthesis of 3-sulfanylpropionic acid from thiols and α,β-unsaturated carboxylic acids.

2. Results and discussion

Preliminary efforts were mainly focused on the evaluation of different additives; the yields of 3-sulfanylpropionic acid obtained by reacting *trans*-cinnamic acid with thiophenol under various conditions are shown in Table 1. First, it was clearly suggested that TBAF certainly catalyzed the conjugate addition of thiophenol to *trans*-cinnamic acid (compare entries 1 and 2, Table 1). It is noteworthy to observe that corresponding product was obtained in excellent yield, but no decarboxylation[16] or desulfurization[17] product was observed. The reactions carried out by using different ammonium halides such as bromide, chloride, and iodide showed that the fluoride ion was more active than other halides (entries 3–5, Table 1). The result accords with the literature revealed that quaternary ammonium halides are known to give rise to an order of nucleophilicity for the halide ions, which parallels their electronegativities, i.e., fluoride>chloride>bromide>iodide. We tried to explore an effective system for the conjugate addition by screening other fluoride sources under the same conditions; it was found that the fluoride ion of TBAF is the most reactive than other fluoride sources (entries 6–11, Table 1). It is especially useful when other inorganic bases or fluoride sources face solubility problems in organic solvents. Although the desired products were obtained in good yield in the cases of the alkali metal, KF, and CsF, the reactions needed longer periods of time to be completed and the reactions could not be carried out in solventless condition. Moreover, the effect of solvents on the conjugate addition was also studied in the alkali metal fluorides. In the case of KF, the desired products were obtained in 85% in DMF, 12% in CH_3CN, 9% in MeOH, and 3% in THF, respectively. Similarly, the yields of the reaction in the presence of CsF were 91% in DMF, 64% in CH_3CN, 15% in MeOH, and 7% in THF, respectively. In the cases of the alkali metal fluorides, the product yields obtained in DMF are higher than in any other solvents due to the higher solvating ability of DMF, which makes the fluoride ions more naked. No reactions could occur in the presence of H_2SiF_6, NH_4F, and HF–pyridine either in solventless or even in solvent conditions, because these prefer to afford acidic HF molecular, not basic F^- ion (entries 9–11, Table 1). On the basis of the optimization of the reaction conditions, the scope of this TBAF-catalyzed conjugate addition of various thiols with various α,β-unsaturated carboxylic acids was explored. Not only aromatic α,β-unsaturated carboxylic acids, but also aliphatic α,β-unsaturated carboxylic acids in the reactions with thiophenol afforded 3-sulfanylpropionic acids in excellent yield (Table 2). The 3-sulfanylpropionic acids thus formed (92–99% yield) can be obtained in pure form by passing the crude through a short plug of silica. The β-bulky substituted acids took longer reaction times as compared to the other α,β-unsaturated acids. This may be due to steric hindrance of bulky substitution at β-position (compare entries 1–9, 11, 12 vs 10, 13, 14, Table 2). In order to extend the scope of the conjugate addition of thiols, thiophenol was replaced with various thiols (Table 3). For thiols, both aromatic thiols and aliphatic thiols could react with acrylic acid to give the corresponding products in 94–99% isolated yields. Similarly, the rate of the reaction of acrylic acid with aromatic thiol is faster than with aliphatic thiol, because the election-rich aromatic thiols are more active than aliphatic thiols (compare entries 1–9 vs 10–13, Table 3). The electronic effect of substituent group on aromatic thiol is not obvious as a result of the high activity of aromatic thiols. The reaction of aromatic thiols with electron-donating group or electron-withdrawing group can complete in the same period of time (entries 1, 3, 7, 8, and 9, Table 3). However, the reaction of aliphatic thiols with electron-withdrawing group is faster than that of the normal aliphatic thiols; this phenomena may attribute to the difference in acidity between the thiols (compare entries 11, 14 vs 10, 12, 13, Table 3). The steric effect of thiols also affects the rate of thiol conjugated to acrylic acid (compare entries 1 vs 2, 3 vs 4, 10 vs 12, 13, Table 3). The scope of the conjugate addition has been demonstrated by using a wide range of α,β-unsaturated carboxylic acids as well as thiols in which the phenyl group was substituted with different groups.

Table 1
Conjugate addition of thiophenol to cinnamic acid in the presence of various derivatives[a]

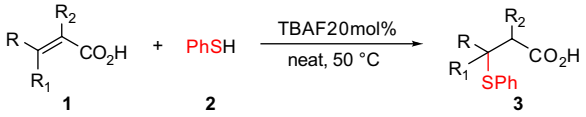


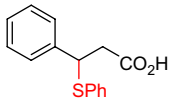
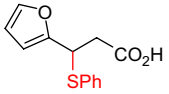
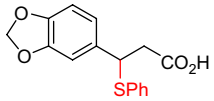
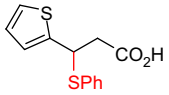
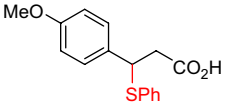
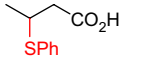
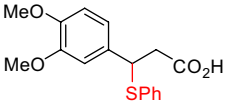
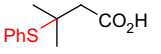
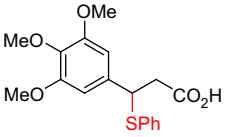
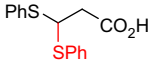
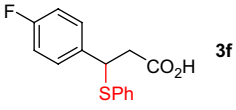
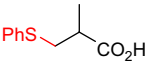
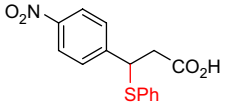
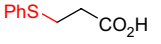
1 2 3a

Entry	Additive (equiv)	Solvent	Temp (°C)	Time (h)	**3a**[b] (%)	**1**[b] (%)
1	—	Neat	50	24	0	>99
2	TBAF (0.2)	Neat	50	24	>99	0
3	TBACl (0.2)	Neat	50	24	15	85
4	TBABr (0.2)	Neat	50	24	10	90
5	TBAI (0.2)	Neat	50	24	Tr	>99
6[c]	KF (0.2)	DMF	50	24	85	15
7[c]	CsF (0.2)	DMF	50	24	91	2
8[c]	CaF_2 (0.2)	DMF	50	24	39	61
9	H_2SiF_6 (0.2)	Neat	50	24	0	>99
10	NH_4F (0.2)	Neat	50	24	0	>99
11	HF–pyridine (0.2)	Neat	50	24	0	>99

[a] Condition: the reaction was performed by using 1 equiv (2 mmol) of cinnamic acid and 1.5 equiv (3 mmol) of thiophenol in the presence of 20 mol % of additive at 50 °C.
[b] NMR yield.
[c] Reaction was carried out in 1 mL of solvent.

Table 2
Fluoride ion-catalyzed conjugate addition of thiophenol to various unsaturated acids[a]



Entry	Product	Time (h)/yield[b] (%)	Entry	Product	Time (h)/yield[b] (%)
1	 **3a**	24/98	8	 **3h**	36/94
2[c]	 **3b**	44/95	9	 **3i**	36/92
3	 **3c**	24/98	10	 **3j**	2/97
4	 **3d**	15/98	11	 **3k**	24/96
5	 **3e**	12/97	12	 **3l**	18/98
6	 **3f**	22/99	13	 **3m**	1/94
7	 **3g**	22/96	14	 **3n**	1/99

[a] Condition: the reaction was performed by using 1 equiv (2 mmol) of unsaturated acid and 1.5 equiv (3 mmol) of thiophenol in the presence of 20 mol % of TBAF at 50 °C in solventless condition.
[b] Isolated yield.
[c] Reaction was carried out in 1 mL of THF.

3. Conclusion

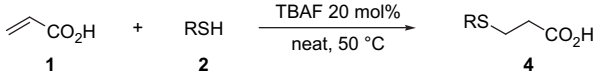
In conclusion, we have developed a novel procedure for the synthesis of 3-sulfanylpropionic acid, which is often encountered in molecules of biologically active compounds. The procedures described here are simple, mild, and efficient. The use of TBAF as a base has the advantages of being economically viable and more efficient for the conjugate addition. The reaction system can be successfully applied to a variety of α,β-unsaturated acids as well as thiols to synthesize a wide variety of sulfur containing carboxylic acids in excellent yields.

4. Experimental

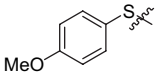
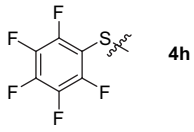
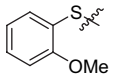
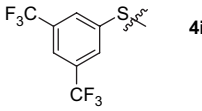
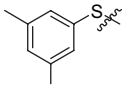
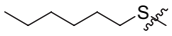
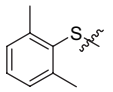
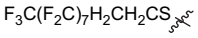
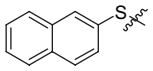
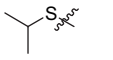
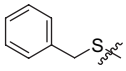
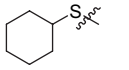
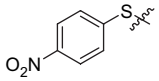
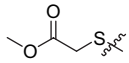
4.1. General

All analytical thin layer chromatographies were performed with E. Merck silica gel $60F_{254}$ aluminum sheets and were visualized with UV light. Flash column chromatography, following the method of still, was carried out with E. Merck silica gel 60 (Kieselgel 60, 230–400 mesh) using the indicated eluents. ^{1}H nuclear magnetic resonance (NMR) spectra were recorded routinely with a Bruker Avance 400 (400 MHz) spectrometer. The ^{1}H NMR data are described as following: chemical shifts (δ, given in parts per million with tetramethylsilane (0.00 ppm) as internal reference), multiplicity (s=singlet, d=doublet, t=triplet, q=quartet, br=broad, m=multiplet), coupling constants (J, given in Hertz), with integration. ^{13}C NMR spectra were obtained with a Bruker Avance 400 (100 MHz) spectrometer using $CDCl_3$ (77.23 ppm) as internal reference. Mass spectra were obtained on a JOEL SX-102A spectrometer at an ionization potential of 70 eV and reported as mass/charge (m/z) with percent relative abundance. High-resolution mass spectra (HRMS) were acquired with a FINNIGAN MAT-95XL spectrometer. Solvents for extraction and chromatography were of reagent grade. All reagents such as a series of

Table 3
Fluoride ion-catalyzed conjugate addition of acrylic acids with various thiols[a]



1 2 4

Entry	Product	Time (h)/yield[b] (%)	Entry	Product	Time (h)/yield[b] (%)
1	 **4a**	0.5/98	8	 **4h**	0.5/99
2	 **4b**	1/96	9	 **4i**	0.5/97
3	 **4c**	0.5/96	10	 **4j**	18/95
4	 **4d**	2.5/94	11	 **4k**	10/96
5[c]	 **4e**	0.5/98	12[d]	 **4l**	45/97
6	 **4f**	4/94	13[d]	 **4m**	45/98
7[c]	 **4g**	0.5/95	14	 **4n**	1/99

[a] Condition: the reaction was performed by using 1 equiv (2 mmol) of acrylic acid and 1.5 equiv (3 mmol) of thiols in the presence of 20 mol % of TBAF at 50 °C in solventless condition.
[b] Isolated yield.
[c] Reaction was carried out in 1 mL of THF.
[d] The reaction was performed by using 1 equiv (2 mmol) of unsaturated acid and 2 equiv (4 mmol) of thiol in the presence of 50 mol % of TBAF at 50 °C in solventless condition.

substituted α,β-unsaturated carboxylic acids and thiols were commercially available from Acros and Aldrich Chemical Co. and were used directly without further purification.

4.2. Procedures and analytical data

To a mixture of *trans*-cinnamic acid (301 mg, 2 mmol) and thiophenol (341 mg, 3 mmol), TBAF·$3H_2O$ (127 mg, 0.4 mmol) was added and the mixture was stirred at 50 °C in solventless condition for 24 h. After completion of reaction (monitored by NMR), the crude product was purified by flash column chromatography using silica gel (eluent: ethyl acetate–hexane; 1:5) to obtain 3-sulfanylpropionic acid (**3a**) (506 mg, 98% yield).

4.2.1. 3-Phenyl-3-phenylsulfanyl-propionic acid (*3a*)

White solid with the melting point of 85–86 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.30–7.18 (m, 10H), 4.59 (t, J=7.4 Hz, 1H), 3.00–2.89 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.1, 140.3, 133.7, 133.5, 129.1, 128.7, 128.1, 127.84, 127.80, 48.8, 40.8; HRMS (EI) *m/z* calcd for $C_{15}H_{14}O_2S$ (M^+) 258.0715, found 258.0707.

4.2.2. 3-Benzo[1,3]dioxol-5-yl-3-phenylsulfanyl-propionic acid (*3b*)

White solid with the melting point of 122–123 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.31 (d, J=2.6 Hz, 2H), 7.27–7.22 (m, 3H), 6.80 (s, 1H), 6.66 (s, 2H), 5.93 (s, 2H), 4.54 (t, J=7.7 Hz, 1H), 2.97–2.83 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.17, 148.00, 147.25, 134.17, 133.72, 133.53, 129.14, 128.14, 121.30, 108.27, 108.18, 101.33, 48.87, 41.04; HRMS (EI) *m/z* calcd for $C_{16}H_{14}O_4S$ (M^+) 302.0613, found 302.0618.

4.2.3. 3-(4-Methoxy-phenyl)-3-phenylsulfanyl-propionic acid (*3c*)

White solid with the melting point of 105–107 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.30 (d, J=3.3 Hz, 2H), 7.26–7.20 (m, 3H), 7.16 (d, J=8.8 Hz, 2H), 6.79 (d, J=8.8 Hz, 2H), 4.58 (t, J=7.7 Hz, 1H), 3.76 (s, 3H), 2.99–2.86 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.68, 159.18, 133.78, 133.60, 132.31, 129.09, 128.94, 128.06, 114.11, 55.44, 48.29, 40.94; HRMS (EI) *m/z* calcd for $C_{16}H_{16}O_3S$ (M^+) 288.0820, found 288.0819.

*4.2.4. 3-(3,4-Dimethoxyphenyl)-3-phenylsulfanyl-propanoic acid (**3d**)*

White solid with the melting point of 117–118 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32–7.27 (m, 2H), 7.27–7.20 (m, 3H), 4.57 (t, J=7.6 Hz, 1H), 3.83 (s, 3H), 3.79 (s, 3H), 3.00–2.85 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.82, 148.94, 148.59, 133.76, 133.58, 132.75, 129.05, 128.11, 119.87, 111.13, 111.02, 55.97, 48.66, 40.86; HRMS (EI) *m/z* calcd for $C_{17}H_{18}O_4S$ (M^+) 318.0926, found 318.0925.

*4.2.5. 3-(Phenylthio)-3-(3,4,5-trimethoxyphenyl)-propanoic acid (**3e**)*

White solid with the melting point of 120–121 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34–7.29 (m, 2H), 7.28–7.23 (m, 3H), 6.41 (s, 2H), 4.54 (t, J=7.7 Hz, 1H), 3.81 (s, 3H), 3.69 (s, 6H), 3.02–2.88 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.44, 153.25, 137.58, 135.92, 134.01, 13.41, 129.11, 128.30, 104.86, 61.01, 56.26, 49.27, 40.77; HRMS (EI) *m/z* calcd for $C_{18}H_{20}O_5S$ (M^+) 348.1031, found 348.1033.

*4.2.6. 3-(4-Fluorophenyl)-3-phenylsulfanyl-propanoic acid (**3f**)*

Colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.31–7.21 (m, 5H), 7.21–7.15 (m, 2H), 6.94 (t, J=8.6 Hz, 2H), 4.57 (t, J=7.6 Hz, 1H), 3.01–2.85 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.42, 162.29 (d, J=245.0 Hz), 136.18 (d, J=3.0 Hz), 133.88, 133.20, 129.46 (d, J=8 Hz), 129.17, 128.36, 115.61 (d, J=21 Hz), 48.23, 40.80; HRMS (EI) *m/z* calcd for $C_{15}H_{13}FO_2S$ (M^+) 276.0620, found 276.0627.

*4.2.7. 3-(4-Nitrophenyl)-3-phenylsulfanyl-propanoic acid (**3g**)*

White solid with the melting point of 148–150 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.10 (d, J=8.6 Hz, 2H), 7.34 (d, J=8.5 Hz, 2H), 7.25 (s, 5H), 4.63 (t, J=7.7 Hz, 1H), 3.10–2.90 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.75, 148.08, 147.42, 134.4, 132.04, 129.39, 128.97, 128.73, 123.94, 48.47, 39.99; HRMS (EI) *m/z* calcd for $C_{15}H_{13}NO_4S$ (M^+) 303.0565, found 303.0570.

*4.2.8. 3-(Furan-2-yl)-3-phenylsulfanyl-propanoic acid (**3h**)*

White solid with the melting point of 88–89 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36 (d, J=0.7 Hz, 1H), 7.33–7.23 (m, 6H), 6.24 (dd, J=2.9, 1.8 Hz, 1H), 5.99 (d, J=3.3 Hz, 1H), 4.65 (t, J=7.7 Hz, 1H), 3.05–2.87 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.12, 152.74, 142.39, 134.65, 132.43, 129.08, 128.62, 110.52, 107.67, 42.24; HRMS (EI) *m/z* calcd for $C_{13}H_{12}O_3S$ (M^+) 248.0507, found 248.0501.

*4.2.9. 3-(Phenylsulfanyl)-3-(thiophen-2-yl)-propanoic acid (**3i**)*

White solid with the melting point of 68–69 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36–7.32 (m, 2H), 7.28–7.24 (m, 4H), 7.19 (dd, J=4.9, 0.9 Hz, 1H), 6.84 (dd, J=5.1, 3.7 Hz, 1H), 6.78 (d, J=3.3 Hz, 1H), 4.89 (t, J=7.5 Hz, 1H), 3.00 (d, J=7.7 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.88, 144.36, 134.01, 133.13, 129.17, 128.50, 126.73, 125.65, 125.15, 44.39, 41.78; HRMS (EI) *m/z* calcd for $C_{13}H_{12}O_2S_2$ (M^+) 264.0279, found 264.0273.

*4.2.10. 3-Phenylsulfanyl-butanoic acid (**3j**)*

Brown oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.45–7.42 (m, 2H), 7.38–7.24 (m, 3H), 3.64–3.55 (m, 1H), 2.68 (dd, J=16.0, 5.9 Hz, 1H), 5.47 (dd, J=16.0, 8.4 Hz, 1H), 1.35 (d, J=6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 178.0, 133.7, 133.2, 129.2, 127.8, 41.8, 39.3, 21.0; HRMS (EI) *m/z* calcd for $C_{10}H_{12}O_2S$ (M^+) 196.0558, found 196.0562.

*4.2.11. 3-Methyl-3-phenysulfanyl-butanoic acid (**3k**)*

Colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.58–7.55 (m, 2H), 7.39–7.34 (m, 3H), 2.56 (s, 2H), 1.41 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.3, 137.8, 131.3, 129.3, 128.8, 46.8, 46.5, 28.6; HRMS (EI) *m/z* calcd for $C_{11}H_{14}O_2S$ (M^+) 210.0715, found 210.0716.

*4.2.12. 3,3-Bis(phenylsulfanyl)-propanoic acid (**3l**)*

White solid with the melting point of 53–54 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.52–7.47 (m, 4H), 7.36–7.29 (m, 6H), 4.77 (t, J=7.3 Hz, 1H), 2.85 (d, J=7.3 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.40, 133.77, 133.05, 129.31, 128.64, 53.21, 41.05; HRMS (EI) *m/z* calcd for $C_{15}H_{14}O_2S_2$ (M^+) 290.0435, found 290.0439.

*4.2.13. 2-Methyl-3-phenylsulfanyl-propanoic acid (**3m**)*

Colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39–7.37 (m, 2H), 7.31–7.29 (m, 2H), 7.22–7.18 (m, 1H), 3.29 (dd, J=13.4, 7.0 Hz, 1H), 2.93 (dd, J=13.4, 7.0 Hz, 1H), 2.75–2.67 (m, 1H), 1.31 (d, J=7.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 181.1, 135.7, 130.5, 129.3, 126.9, 39.8, 37.4, 16.8; HRMS (EI) *m/z* calcd for $C_{10}H_{12}O_2S$ (M^+) 196.0558, found 196.0568.

*4.2.14. 3-Phenylsulfanyl-propanoic acid (**3n**)*

White solid with the melting point of 58–60 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40–7.36 (m, 2H), 7.32–7.28 (m, 2H), 7.24–7.20 (m, 1H), 3.16 (t, J=7.2 Hz, 2H), 2.67 (t, J=7.2 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.3, 135.1, 130.6, 129.3, 126.9, 34.3, 29.0; HRMS (EI) *m/z* calcd for $C_9H_{10}O_2S$ (M^+) 182.0402, found 182.0406.

*4.2.15. 3-(4-Methoxyphenylsulfanyl)-propanoic acid (**4a**)*

White solid with the melting point of 82–83 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38 (d, J=8.6 Hz, 2H), 6.85 (d, J=8.6 Hz, 2H), 3.79 (s, 3H), 3.03 (t, J=7.2 Hz, 2H), 2.60 (t, J=7.3 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 178.32, 159.64, 134.55, 125.03, 114.90, 55.51, 34.55, 30.97; HRMS (EI) *m/z* calcd for $C_{10}H_{12}O_3S$ (M^+) 212.0507, found 212.0501.

*4.2.16. 3-(2-Methoxyphenylsulfanyl)-propanoic acid (**4b**)*

White solid with the melting point of 92–93 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34 (dd, J=7.6, 0.6 Hz, 1H), 7.25 (t, J=8.0 Hz, 1H), 6.94 (t, J=8.1 Hz, 1H), 6.88 (d, J=8.2 Hz, 1H), 3.90 (s, 3H), 3.14 (t, J=7.4 Hz, 2H), 2.67 (t, J=7.4 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 178.21, 158.32, 131.64,

128.50, 122.83, 121.26, 110.98, 55.96, 34.36, 27.37; HRMS (EI) *m/z* calcd for $C_{10}H_{12}O_3S$ (M^+) 212.0507, found 212.0505.

*4.2.17. 3-(3,5-Dimethylphenylsulfanyl)-propanoic acid (**4c**)*

White solid with the melting point of 93–94 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.99 (m, 2H), 6.85 (s, 1H), 3.13 (t, J=7.3 Hz, 2H), 2.67 (t, J=7.3 Hz, 2H), 2.28 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 178.13, 138.92, 134.56, 128.85, 128.16, 34.48, 28.92, 21.40; HRMS (CI) *m/z* calcd for $C_{11}H_{14}O_2S$ (M^+) 210.0715, found 210.0709.

*4.2.18. 3-(2,6-Dimethylphenylsulfanyl)-propanoic acid (**4d**)*

White solid with the melting point of 66–67 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.12 (s, 3H), 2.93 (t, J=7.3 Hz, 2H), 2.57 (t, J=7.5 Hz, 2H), 2.56 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 178.21, 143.45, 132.51, 128.73, 128.43, 34.71, 29.80, 22.21; HRMS (EI) *m/z* calcd for $C_{11}H_{14}O_2S$ (M^+) 210.0715, found 210.0714.

*4.2.19. 3-(Naphthalen-2-ylsulfanyl)-propanoic acid (**4e**)*

Pale yellow crystal with the melting point of 103–104 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.79–7.72 (m, 4H), 7.47–7.40 (m, 3H), 3.22 (t, J=7.3 Hz, 2H), 2.68 (t, J=7.3 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 178.3, 133.9, 132.5, 132.3, 128.9, 128.7, 128.2, 127.9, 127.4, 126.8, 126.2, 34.4, 28.8; HRMS (EI) *m/z* calcd for $C_{13}H_{12}O_2S$ (M^+) 232.0558, found 232.0562.

*4.2.20. 3-(Benzylsulfanyl)-propanoic acid (**4f**)*

White solid with the melting point of 82–83 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.31–7.23 (m, 5H), 3.73 (s, 2H), 2.69–2.65 (m, 2H), 2.59–2.56 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.1, 129.0, 128.8, 127.4, 36.5, 34.5, 26.1; HRMS (EI) *m/z* calcd for $C_{10}H_{12}O_2S$ (M^+) 196.0558, found 196.0555.

*4.2.21. 3-(4-Nitrophenylsulfanyl)-propanoic acid (**4g**)*

White solid with the melting point of 132–133 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.15 (d, J=8.6 Hz, 2H), 7.37 (d, J=8.6 Hz, 2H), 3.30 (t, J=7.2 Hz, 2H), 2.78 (t, J=7.2 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.48, 146.08, 145.78, 127.16, 124.35, 33.58, 27.07; HRMS (EI) *m/z* calcd for $C_9H_9NO_4S$ (M^+) 227.0252, found 227.0246.

*4.2.22. 3-(Perfluorophenylsulfanyl)-propanoic acid (**4h**)*

White solid with the melting point of 111–112 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.12 (t, J=7.0 Hz, 2H), 2.67 (t, J=7.0 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.61, 149.20–149.06 (m), 146.80–146.50 (m), 143.60–142.90 (m), 140.90–139.90 (m), 139.50–139.00 (m), 136.90–136.50 (m), 108.80–108.20 (m), 34.99, 29.73; HRMS (EI) *m/z* calcd for $C_9H_5F_5O_2S$ (M^+) 271.9930, found 271.9929.

*4.2.23. 3-(3,5-Bis(trifluoromethyl)phenylsulfanyl)-propanoic acid (**4i**)*

White solid with the melting point of 59–60 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.74 (s, 2H), 7.69 (s, 1H), 3.28 (t, J=7.1 Hz, 2H), 2.75 (t, J=7.0 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.26, 139.58 (q, J=33.0 Hz), 128.72 (d, J=3.0 Hz), 127.27, 123.20 (d, J=271.2 Hz), 120.24–120.17 (m), 119.13, 33.88, 28.27; HRMS (EI) *m/z* calcd for $C_{11}H_8F_6O_2S$ (M^+) 318.0149, found 318.0148.

*4.2.24. 3-(Hexylsulfanyl)-propanoic acid (**4j**)*

Colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.78 (t, J=7.1 Hz, 2H), 2.66 (t, J=7.2 Hz, 2H), 2.54 (t, J=7.3 Hz, 2H), 1.62–1.52 (m, 2H), 1.42–1.22 (m, 6H), 0.93–0.85 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 178.15, 34.92, 32.44, 31.62, 29.71, 28.74, 26.83, 22.74, 14.22; HRMS (EI) *m/z* calcd for $C_9H_{18}O_2S$ (M^+) 190.1028, found 190.1025.

*4.2.25. 3-(3,3,4,4,5,5,6,6,7,7,8,8,9,9,10,10,10-Heptadecafluorodecylsulfanyl)-propanoic acid (**4k**)*

White solid with the melting point of 85–87 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.84 (t, J=7.1 Hz, 2H), 2.81–2.75 (m, 2H), 2.69 (t, J=7.1 Hz, 2H), 2.48–2.32 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.64, 118.81, 118.00, 117.70, 117.37, 116.27, 115.94, 113.76, 111.53, 111.19, 110.79, 108.84, 108.52, 34.62, 32.27 (t, J=22.0 Hz), 26.95, 23.09 (t, J=4.2 Hz); HRMS (EI) *m/z* calcd for $C_{13}H_9F_{17}O_2S$ (M^+) 552.0052, found 552.0051.

*4.2.26. 3-(Isopropylsulfanyl)-propanoic acid (**4l**)*

Colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.00–2.90 (m, 1H), 2.81 (t, J=7.4 Hz, 2H), 2.66 (t, J=6.7 Hz, 2H), 1.28 (d, J=6.7 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.48, 35.30, 34.92, 25.32, 23.52; HRMS (EI) *m/z* calcd for $C_6H_{12}O_2S$ (M^+) 148.0558, found 148.0525.

*4.2.27. 3-(Cyclohexylsulfanyl)-propanoic acid (**4m**)*

Colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.80 (t, J=7.4 Hz, 2H), 2.70–2.63 (m, 1H), 2.64 (t, J=7.3 Hz, 2H), 2.00–1.92 (m, 2H), 1.81–1.75 (m, 2H), 1.63–1.59 (m, 1H), 1.37–1.21 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 178.5, 43.8, 35.3, 33.7, 26.2, 25.9, 24.8; HRMS (EI) *m/z* calcd for $C_9H_{16}O_2S$ (M^+) 188.0871, found 188.0869.

*4.2.28. 3-(2-Methoxy-2-oxoethylsulfanyl)-propanoic acid (**4n**)*

Colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.75 (s, 3H), 3.27 (s, 2H), 2.92 (t, J=7.3 Hz, 2H), 2.71 (t, J=7.3 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.58, 171.00, 52.70, 34.27, 33.70, 27.42; HRMS (EI) *m/z* calcd for $C_6H_{10}O_4S$ (M^+) 178.0300, found 178.0301.

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Supplementary data

Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.tet.2007.11.064.

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