One-Step Tethering of ω-Mercaptoalkyl Function to Alcohols

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Abstract: A new method of attachment of ω-mercaptoalkyl function to primary, secondary, and tertiary hydroxy groups based on ω-mercaptoalkyl monomalonates is reported. The attachment process proceeds in one stage and does not require a deprotection step thus directly providing high yields of unsymmetric malonates possessing a terminal thiol functionality.

Key words: thiols, acylations, chemoselectivity, esters, self-assembly

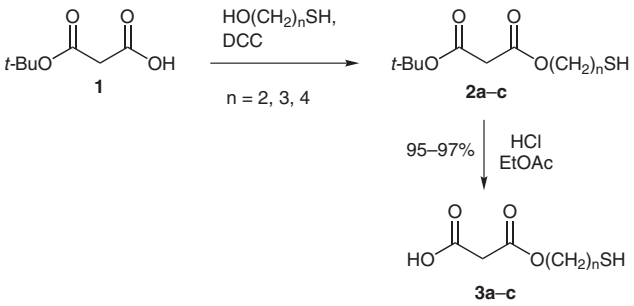
Fabrication of well-ordered Self-Assembled Monolayers (SAM) of thiols on a gold surface has emerged as the most commonly used method for the preparation of functionalized surfaces.[1] It has found numerous applications in nanofabrication,[2] molecular electronics,[3] bioanalytics,[4] and sensors.[5] Other important applications of SAM such as protective coatings,[6] lubricants,[7] and templates for crystal nucleation[8] have also been reported. Growing applications of SAM necessitated preparation of tailor made monolayers using functionalized thiols. Since terminal alkylthiols form very stable SAM, the derivatization of organic molecules with a ω-mercaptoalkyl functionality is a highly efficient approach toward functionalized monolayers.

ω-Mercaptoalkyl functions can be attached to organic molecules by alkylation,[9] acylation,[10] free-radical addition,[11] and other methods.[12] The high reactivity of thiol groups to electrophiles usually necessitates its protection as disulfides,[13] thioesters[14] and dithiocarbonates,[15] *tert*-butyl[16] or trityl[17] thioesters, and other protecting groups,[18] with final deprotection stage releasing the thiol function. The expansion of SAM to bioanalytical applications requires derivatization of polyfunctional biopolymers thus introducing a stricter requirement for chemoselectivity in reactions involving the introduction and deprotection of ω-mercaptoalkyl function.

Here we report a new method of attachment of a ω-mercaptoalkyl function to primary, secondary, and tertiary hydroxy groups. In contrast to existing approaches the attachment process involves one stage and does not require a deprotection step thus directly providing high yields of the corresponding thiols.

We have previously reported that carbodiimide couplings of most carboxylic acid with thiols proceed with much higher reaction rates than do those with alcohols.[19] However, the chemoselectivity of carbodiimide couplings is radically different for carboxylic acids possessing strong electron-withdrawing groups in the alpha position. These acids, upon treatment with carbodiimides as well as other coupling reagents, form ketene intermediates[20] that are capable of efficient acylation of even highly sterically hindered alcohols. Rates of acylation of alcohols with electron-withdrawing group substituted ketenes are extremely high,[21] thus enabling their selective acylation in the presence of other functionalities such as phenols.[19]

Our synthetic approach was based on ω-mercaptoalkyl monoesters of malonic acid as common precursors for the derivatization of model alcohols. ω-Mercaptoalkyl monoesters of type **2** were prepared (Scheme 1) by a reaction of mono *tert*-butyl malonate **1** with corresponding ω-mercapto alcohols and DCC. In contrast to previously reported S-acylation[19] this reaction proceeded with complete O-selectivity providing malonates of type **2** in essentially quantitative yields. No traces of S-acylation products were observed in the reaction mixture.



Scheme 1 Preparation of ω-mercaptoalkyl malonates.

Deprotection of ω-mercaptoalkyl *tert*-butyl malonates of type **2a–c** with TFA provided a very low yield of monomalonates **3**. This can be expected since the thiol function is very reactive toward carbocations[22] and lower thiols are commonly used for trapping *tert*-butyl cations.[23] However, replacement of TFA with 2 M HCl in ethyl acetate eliminated undesired reactions of the thiol group and provided monomalonates **3a–c** in quantitative yields.

Carbodiimide couplings of monomalonates **3a–c** with model alcohols (Scheme 2) proceeded smoothly providing the corresponding malonates **4a–i**. Primary and secondary alcohols provided equally high yields. No traces of either inter- or intramolecular S-acylation products were

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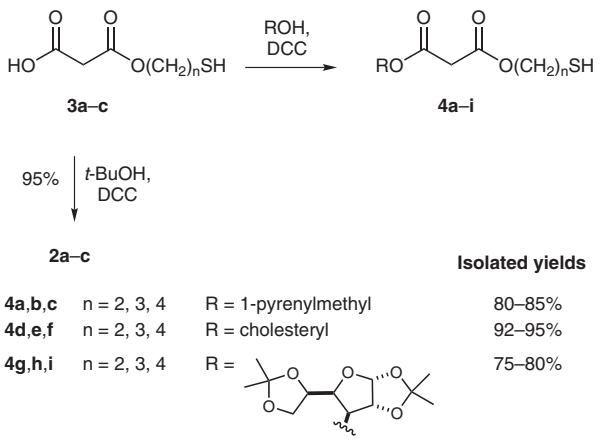

Scheme 2 Attachment of malonyl-tethered ω-mercaptoalkyl function to model alcohols.

observed. Similar reactions with *tert*-butanol provided compounds **2a–c**.

In conclusion, we report a one-step synthetic method that attaches a ω-mercaptoalkyl function to primary, secondary, and tertiary alcohols in high yields. Very high chemoselectivity of acylation through ketene intermediates allows the O-acylation of mercaptoalchols without protecting the thiol functionality.

Unless otherwise stated, all reagents used are commercially available. Solvents for reactions were purified by standard procedures. Reactions were conducted under a nitrogen atmosphere. The ^{1}H NMR spectra were acquired on Bruker AMX-300 and DRX-400 instruments in $CDCl_3$ using the residual solvent peaks for calibration. IR spectra were recorded on a Bruker Tensor 27 FT-IR spectrometer in thin films. Microanalyses were performed at the Microanalysis Laboratory of the Hebrew University of Jerusalem. Flash chromatography was performed on Merck Si 60 silica gel (230–400 mesh) using chloroform alone or a mixture with methanol as the eluent. Reactions were monitored by analytical TLC, which was performed on Merck silica gel 60 F254 covered aluminum sheets.

Preparation of *tert*-Butyl Mercaptoalkyl Malonates 2a–c; General Procedure

To a mixture of mono *tert*-butyl malonate (1 mL; 1 M solution in anhyd CH_2Cl_2) and ω-mercaptoalkanol (1.1 mmol) stirring at 25 °C was added DCC (1.1 mL, 1 M solution in anhyd CH_2Cl_2). The reaction mixture was stirred for 45 min, filtered, evaporated, and purified by flash chromatography using $CHCl_3$ as eluent.

***tert*-Butyl 2-Mercaptoethyl Malonate (2a)**

Colorless oil; yield: 95%.

IR ($CDCl_3$): 3019, 1732, 1507, 1215, 757, 669 cm^{-1}.

^{1}H NMR (300 MHz): δ = 1.47 (s, 9 H), 1.54 (t, *J* = 9 Hz, 1 H), 2.77 (q, *J* = 7 Hz, 2 H), 3.31 (s, 2 H), 4.26 (t, *J* = 6 Hz, 2 H).

^{13}C NMR (75 MHz): δ = 22.5, 27.3, 42.1, 65.9, 81.4, 164.9, 166.0.

Anal. Calcd for $C_9H_{16}O_4S$: C, 49.07; H, 7.32. Found: C, 49.28; H, 7.20.

***tert*-Butyl 3-Mercaptopropyl Malonate (2b)**

Colorless oil; yield: 97%.

IR ($CDCl_3$): 2980, 2550, 1728, 1332, 1144, 757, 667 cm^{-1}.

^{1}H NMR (300 MHz): δ = 1.28 (t, *J* = 9 Hz, 1 H), 1.29 (s, 9 H), 1.78 (quin, *J* = 6.7 Hz, 2 H), 2.44 (q, *J* = 7 Hz, 2 H), 3.11 (s, 2 H), 4.08 (t, *J* = 6 Hz, 2 H).

^{13}C NMR (75 MHz): δ = 20.69, 27.68, 32.45, 42.60, 62.91, 81.66, 165.37, 166.55.

Anal. Calcd for $C_{10}H_{18}O_4S$: C, 51.26; H, 7.74. Found: C, 51.46; H, 7.70.

***tert*-Butyl 4-Mercaptobutyl Malonate (2c)**

Colorless oil; yield: 95%.

IR ($CDCl_3$): 2978, 2550, 1728, 1333, 1144, 757, 666 cm^{-1}.

^{1}H NMR (300 MHz): δ = 1.28 (t, *J* = 9 Hz, 1 H), 1.38 (s, 9 H), 1.57–1.73 (m, 4 H), 2.48 (q, *J* = 7 Hz, 2 H), 3.20 (s, 2 H), 4.07 (t, *J* = 6 Hz, 2 H).

^{13}C NMR (75 MHz): δ = 23.88, 26.97, 27.68, 30.01, 42.65, 64.41, 81.72, 165.44, 166.70.

Anal. Calcd for $C_{11}H_{20}O_4S$: C, 53.20; H, 8.12. Found: C, 53.24; H, 8.06.

Preparation of ω-Mercaptoalkyl Monomalonates 3a–c; General Procedure

To a 1 M solution of a *tert*-butyl ω-mercaptoalkyl malonates **3a–c** (1 mL) in CH_2Cl_2 was added under stirring at 25 °C a 2 M solution of HCl in EtOAc (5.0 mL). The reaction mixture was stirred for 2 h, evaporated, and purified by flash chromatography ($CHCl_3$–MeOH, 0–50%) to afford the title compounds in quantitative yields.

2-Mercaptoethyl Monomalonate (3a)

Colorless oil.

IR ($CDCl_3$): 3019, 2399, 1748, 1508, 1215, 928, 757, 669 cm^{-1}.

^{1}H NMR (300 MHz): δ = 1.53 (t, *J* = 9 Hz, 1 H), 2.76 (q, *J* = 7 Hz, 2 H), 3.45 (s, 2 H), 4.28 (t, *J* = 6 Hz, 2 H), 8.49 (br s, 1 H, OH).

^{13}C NMR (75 MHz): δ = 22.89, 40.79, 66.85, 166.25, 171.27.

Anal. Calcd for $C_5H_8O_4S$: C, 36.58; H, 4.91. Found: C, 36.36; H, 4.78.

3-Mercaptopropyl Monomalonate (3b)

Colorless oil.

IR ($CDCl_3$): 3019, 1717, 1508, 1418, 1215, 757, 669 cm^{-1}.

^{1}H NMR (300 MHz): δ = 1.39 (t, *J* = 9 Hz, 1 H), 1.93 (quin *J* = 6.7 Hz, 2 H), 2.57 (q, *J* = 7 Hz, 2 H), 3.41 (s, 2 H), 4.26 (t, *J* = 6 Hz, 2 H), 9.24 (br s, 1 H, OH).

^{13}C NMR (75 MHz): δ = 20.73, 32.30, 40.83, 63.68, 166.53, 171.34.

Anal. Calcd for $C_6H_{10}O_4S$: C, 40.44; H, 5.66. Found: C, 40.36; H, 5.64.

4-Mercaptobutyl Monomalonate (3c)

Colorless oil.

IR ($CDCl_3$): 3020, 1718, 1508, 1418, 1215, 757, 668 cm^{-1}.

^{1}H NMR (300 MHz): δ = 1.33 (t, *J* = 9 Hz, 1 H), 1.61–1.79 (m, 4 H), 2.53 (q, *J* = 7 Hz, 2 H), 3.41 (s, 2 H), 4.15 (t, *J* = 6 Hz, 2 H), 9.89 (br s, 1 H, OH).

^{13}C NMR (75 MHz): δ = 23.97, 26.95, 30.02, 40.84, 65.17, 166.56, 171.52.

Anal. Calcd for $C_7H_{12}O_4S$: C, 43.74; H, 6.29. Found: C, 43.86; H, 6.24.

Acylation of Alcohols with ω-Mercaptoalkyl Monomalonates 4a–i; General Procedure

To a mixture of a 1 M solution of ω-mercaptoalkyl monomalonates **3a–c** (1 mL) in anhyd CH_2Cl_2, molecular sieves (4 Å), and the appropriate alcohol (1.15 mmol) stirring at 25 °C was added a 1 M solution of DCC in CH_2Cl_2 (1.1 mL). The reaction mixture was stirred for 45 min, filtered, evaporated, and purified by flash chromatography (100% $CHCl_3$) to afford the title compounds.

Pyren-1-ylmethyl 2-Mercaptoethyl Malonate (4a)

Prepared from **3a** and 1-pyrene methanol; greenish amorphous mass; yield: 85%.

IR ($CDCl_3$): 2926, 2253, 1733, 1147, 908, 847, 733 cm^{-1}.

^1H NMR (300 MHz): δ = 1.34 (t, *J* = 9 Hz, 1 H), 2.56 (q, *J* = 7 Hz, 2 H), 3.47 (s, 2 H), 4.15 (t, *J* = 6 Hz, 2 H), 5.90 (s, 2 H), 8.03–8.24 (m, 9 H).

^{13}C NMR (75 MHz): δ = 22.74, 41.40, 65.74, 66.53, 122.64, 124.45, 124.49, 124.71, 125.45, 125.54, 126.05, 127.20, 127.85, 127.86, 127.89, 128.25, 129.48, 130.51, 131.06, 131.82, 165.95, 166.25.

Anal. Calcd for $C_{22}H_{18}O_4S$: C, 69.82; H, 4.79. Found: C, 69.43; H, 4.98.

Pyren-1-ylmethyl 3-Mercaptopropyl Malonate (4b)

Prepared from **3b** and 1-pyrene methanol, greenish amorphous mass; yield: 83%.

IR ($CDCl_3$): 3019, 2927, 2359, 2341, 1732, 1215, 848, 756 cm^{-1}.

^1H NMR (300 MHz): δ = 1.20 (t, *J* = 8 Hz, 1 H), 1.73 (quin, *J* = 6.7 Hz, 2 H), 2.36 (q, *J* = 7 Hz, 2 H), 3.45 (s, 2 H), 4.15 (t, *J* = 6 Hz, 2 H), 5.90 (s, 2 H), 8.00–8.28 (m, 9 H).

^{13}C NMR (75 MHz): δ = 20.70, 32.32, 41.57, 63.43, 65.75, 122.74, 124.54, 124.58, 124.60, 124.81, 125.51, 125.60, 126.12, 127.29, 127.96, 127.98, 128.32, 129.59, 130.59, 131.13, 131.91, 166.27, 166.39.

Anal. Calcd for $C_{23}H_{20}O_4S$: C, 70.39; H, 5.14. Found: C, 70.54; H, 5.70.

Pyren-1-ylmethyl 4-Mercaptobutyl Malonate (4c)

Prepared from **3c** and 1-pyrene methanol; greenish amorphous mass; yield: 80%.

IR ($CDCl_3$): 3019, 2927, 2855, 2360, 2342, 1731, 1215, 756 cm^{-1}.

^1H NMR (300 MHz): δ = 1.17 (t, *J* = 8 Hz, 1 H), 1.38–1.53 (m, 4 H), 2.29 (q, *J* = 7 Hz, 2 H), 3.44 (s, 2 H), 4.02 (t, *J* = 6 Hz, 2 H), 5.91 (s, 2 H), 8.01–8.29 (m, 9 H).

^{13}C NMR (75 MHz): δ = 23.94, 26.91, 29.66, 29.99, 41.65, 64.91, 65.75, 122.83, 124.58, 124.83, 125.52, 125.62, 126.15, 127.31, 127.93, 127.98, 128.03, 128.06, 128.30, 129.63, 130.62, 131.15, 131.91, 166.34, 166.44.

Cholesteryl 2-Mercaptoethyl Malonate (4d)

Prepared from **3a** and cholesterol; pale yellow oil; yield: 92%.

IR ($CDCl_3$): 2949, 2254, 1730, 1466, 1380, 1331, 1151, 1006, 908, 733, 649 cm^{-1}.

^1H NMR (300 MHz): δ = 0.67 (s, 3 H), 0.85 (s, 3 H), 0.87 (s, 3 H), 0.91 (s, 3 H), 1.00 (s, 3 H), 1.10–2.10 (m, 27 H, cholesterol, SH), 2.34 (d, *J* = 7.7 Hz, 2 H), 2.77 (q, *J* = 7 Hz, 2 H), 3.38 (s, 2 H), 4.27 (t, *J* = 6 Hz, 2 H), 4.60–4.72 (m, 1 H), 5.38 (d, *J* = 4.8 Hz, 1 H).

^{13}C NMR (75 MHz): δ = 11.78, 18.65, 19.22, 20.95, 22.49, 22,75, 23.01, 23.76, 24.20, 27.93, 28.15, 31.76, 31.81, 35.71, 36.11, 36.48, 36.82, 39.44, 39.63, 41.70, 42.17, 42.23, 49.92, 56.06, 56.59, 66.51, 75.37, 122.90, 139.19, 165.70, 166.28.

Anal. Calcd for $C_{32}H_{52}O_4S$: C, 72.13; H, 9.84. Found: C, 72.34; H, 10.10.

Cholesteryl 3-Mercaptopropyl Malonate (4e)

Prepared from **3b** and cholesterol; pale yellow oil; yield: 94%.

IR ($CDCl_3$): 3019, 2951, 2400, 2253, 1732, 1473, 1215, 908, 759, 735, 669 cm^{-1}.

^1H NMR (300 MHz): δ = 0.66 (s, 3 H), 0.84 (s, 3 H), 0.87 (s, 3 H), 0.91 (s, 3 H), 1.00 (s, 3 H), 1.10–2.10 (m, 27 H, SH, cholesterol), 1.95 (quin, *J* = 6.7 Hz, 2 H), 2.34 (d, *J* = 7.7 Hz, 2 H), 2.61 (q, *J* = 7 Hz, 2 H), 3.35 (s, 2 H), 4.27 (t, *J* = 6 Hz, 2 H), 4.60–4.72 (m, 1 H), 5.38 (d, *J* = 4.8 Hz, 1 H).

^{13}C NMR (75 MHz): δ = 11.81, 18.67, 19.26, 20.23, 20.92, 22.52, 22.77, 23.78, 24.23, 27.56, 27.96, 28.17, 31.79, 32.59, 35.74, 36.14, 36.52, 37.85, 39.47, 39.67, 41.86, 42.26, 43.79, 49.95, 56.08, 56.62, 63.29, 75.34, 122.94, 139.24, 165.84, 166.58.

Cholesteryl 4-Mercaptobutyl Malonate (4f)

Prepared from **3c** and cholesterol; pale yellow oil; yield: 95%.

IR ($CDCl_3$): 3019, 2950, 2868, 2360, 2341, 1727, 1467, 1215, 926, 757, 668 cm^{-1}.

^1H NMR (300 MHz): δ = 0.67 (s, 3 H), 0.85 (s, 3 H), 0.86 (s, 3 H), 0.90 (s, 3 H), 1.00 (s, 3 H), 1.10–2.04 (m, 31 H, cholesterol, SH, $HSCH_2CH_2CH_2$), 2.34 (d, *J* = 7 Hz, 2 H), 2.56 (q, *J* = 7 Hz, 2 H), 3.34 (s, 2 H), 4.16 (t, *J* = 6 Hz, 2 H), 4.63–4.71 (m, 1 H), 5.38 (d, *J* = 5 Hz, 1 H).

^{13}C NMR (75 MHz): δ = 11.81, 18.67, 19.27, 20.98, 22.52, 22.78, 23.78, 24.13, 24.24, 27.18, 27.57, 28.18, 30.22, 31.80, 31.85, 35.75, 36.14, 36.53, 37.86, 39.47, 39.67, 41.90, 42.27, 43.70, 49.95, 56.08, 56.63, 64.80, 75.30, 122.92, 139.28, 165.91, 166.68.

Anal. Calcd for $C_{34}H_{56}O_4S$: C, 72.81; H, 10.06. Found: C, 72.45; H, 10.23.

Tetrahydro-2,2-dimethyl-5-(2,2-dimethyl-1,3-dioxolan-4-yl)furo[2,3-*d*][1,3]dioxol-6-yl 2-Mercaptoethyl Malonate (4g)

Prepared from **3a** and diisopropylidene glucose; white amorphous mass; yield: 75%.

IR ($CDCl_3$): 2988, 2554, 1380, 1260, 1216, 1148, 1077, 1024, 733, 649 cm^{-1}.

^1H NMR (300 MHz): δ = 1.30 (s, 3 H), 1.31 (s, 3 H), 1.40 (s, 3 H), 1.51 (s, 3 H), 1.53 (t, *J* = 9 Hz, 1 H), 2.77 (q, *J* = 7 Hz, 2 H), 3.45 (s, 2 H), 3.98–4.10 (m, 5 H), 4.26 (t, *J* = 6 Hz, 2 H), 4.56 (d, *J* = 3.6 Hz, 1 H), 5.87 (d, *J* = 3.6 Hz, 1 H).

^{13}C NMR (75 MHz): δ = 22.91, 25.15, 26.10, 26.58, 26.80, 41.11, 66.71, 67.71, 72.13, 76.66, 79.45, 82.96, 104.93, 109.36, 112.29, 164.95, 165.69.

Tetrahydro-2,2-dimethyl-5-(2,2-dimethyl-1,3-dioxolan-4-yl)furo[2,3-*d*][1,3]dioxol-6-yl 3-Mercaptopropyl Malonate (4h)

Prepared from **3b** and diisopropylidene glucose; white amorphous mass; yield: 75%.

IR ($CDCl_3$): 3019, 1215, 908, 757, 668 cm^{-1}.

^1H NMR (300 MHz): δ = 1.30 (s, 3 H), 1.32 (s, 3 H), 1.41 (s, 3 H), 1.51 (t, 1 H and s, 3 H), 1.96 (quin, *J* = 6.7 Hz, 2 H), 2.60 (q, *J* = 7 Hz, 2 H), 3.43 (s, 2 H), 3.98–4.20 (m, 5 H), 4.27 (t, *J* = 6 Hz, 2 H), 4.55 (d, *J* = 3.6 Hz, 1 H), 5.87 (d, *J* = 3.6 Hz, 1 H).

^{13}C NMR (75 MHz): δ = 20.85, 25.23, 26.17, 26.65, 26.87, 30.89, 41.25, 63.63, 67.24, 68.40, 72.21, 79.54, 83.04, 105.00, 109.44, 112.39, 165.13, 166.05.

Tetrahydro-2,2-dimethyl-5-(2,2-dimethyl-1,3-dioxolan-4-yl)furo[2,3-*d*][1,3]dioxol-6-yl 4-Mercaptobutyl Malonate (4i)

Prepared from **3c** and diisopropylidene glucose; white amorphous mass; yield: 80%.

IR ($CDCl_3$): 3019, 2360, 1261, 908, 756, 669 cm^{-1}.

^{1}H NMR (300 MHz): δ = 1.21 (s, 3 H), 1.25 (s, 3 H), 1.27 (t, *J* = 8 Hz, 1 H), 1.33 (s, 3 H), 1.39 (s, 3 H), 1.57–1.67 (m, 4 H), 2.45 (q, *J* = 7 Hz, 2 H), 3.18 (s, 2 H), 3.89–4.18 (m, 5 H), 4.23 (t, *J* = 6 Hz, 2 H), 4.41 (d, *J* = 3.6 Hz, 1 H), 5.81 (d, *J* = 3.6 Hz, 1 H).

^{13}C NMR (75 MHz): δ = 23.90, 25.32, 26.19, 26.65, 26.75, 27.00, 29.98, 41.65, 64.30, 65.60, 73.30, 74.90, 76.70, 81.50, 104.93, 109.13, 111.43, 165.48, 166.73.

***tert*-Butyl ω-Mercaptoethyl Malonates 2a–c from ω-Mercaptoethyl Malonates 3a–c**

Prepared from **3a**–c and *tert*-BuOH according to the general procedure for compounds of type **4**, all as colorless oils, all with yield 95%, all data as above.

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