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Photocatalytic initiation of thiol–ene reactions: synthesis of thiomorpholin-3-ones

Mitchell H. Keylor [a], James E. Park [b], Carl-Johan Wallentin [b], Corey R.J. Stephenson [a,*]

[a] Department of Chemistry, University of Michigan, 930 North University Avenue, Ann Arbor, MI 48109, USA
[b] Department of Chemistry, Boston University, 590 Commonwealth Avenue, Boston, MA 02215, USA

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ABSTRACT

A mild, redox neutral photocatalytic method for alkene hydrothiolation is reported. Utilizing visible-light activation, catalytic radical initiation is achieved with the transition metal complex $Ru(bpy)_3Cl_2$, enabling rapid access to a diverse set of thiol–ene coupled products in excellent yield. On the basis of a strong observed background reaction in some cases, we have developed a solvent-free, Lewis acid-promoted tandem amidation–hydrothiolation sequence, providing thiomorpholin-3-ones in a one-pot operation from commercially available materials.

1. Introduction

Described by Schlaad as the thiol–ene click (TEC) reaction,[1] the hydrothiolation of olefins is a century-old synthetic transformation[2] that has become a powerful tool in polymer and materials chemistry,[3] with applications ranging from surface patterning[4] and lithography[5] to dendrimer synthesis,[6] and biomolecule functionalization.[7,8] Traditionally, the TEC reaction is performed under base-catalysis with electron-deficient alkenes or with radical initiation when using unactivated olefins. While the radical process is largely driven by propagation,[9] initiation is typically achieved with UV irradiation or by thermolysis of a chemical additive, limiting the application of the TEC reaction to relatively simple systems.

Photoredox catalysis has been developed as an attractive alternative to traditional methods of generating synthetically useful radical intermediates in complex settings.[10] Visible-light driven catalysts enable reductive, oxidative, and redox neutral transformations to be performed chemoselectively via single electron transfers that are tunable by ligand modification and choice of additive.[10,11] Herein, we report a photocatalytic radical initiation system for thiol–ene reactions employing $Ru(bpy)_3Cl_2$. This work has also led to the development of an operationally simple method to access thiomorphilin-3-one heterocycles via a solvent-free Lewis acid-promoted tandem amidation–hydrothiolation sequence.

It is worth noting that during our work in this area, Yoon and coworkers reported novel applications of photoredox catalysis in radical thiol–ene additions using the ruthenium complex $Ru(bpz)_3(PF_6)_2$.[12] While the method here is similar in concept, the systems are mechanistically distinguished by the way in which thiyl radical generation is achieved.[13] Contrary to our method in which redox manipulations are not performed directly on either the thiol or olefin coupling partners, Yoon proposes that the photoexcited complex, $Ru(bpz)_3^{2+*}$, initiates coupling by either direct[12a] or aminium-mediated[12b] single electron oxidation of the mercaptan, with subsequent deprotonation to produce the requisite thiyl radical.

We envisioned a system for thiol–ene coupling in which photoredox catalytic initiation and reaction propagation operate concurrently in distinct but synergistic cycles (Scheme 1). Irradiation of $Ru(bpy)_3Cl_2$ with visible light promotes metal-to-ligand charge transfer (MLCT), thus generating a photoexcited state in which the metal center can perform a single electron oxidation of a sacrificial electron donor. This provides a $[Ru]^+$ species capable of single electron reduction of an acceptor such as bromotrichloromethane. We reasoned that the trichloromethyl radical thus produced could initiate thioether bond formation by hydrogen atom abstraction from the mercaptan. Subsequent capture of the electrophilic thiyl radical by an alkene would take place exclusively with anti-Markovnikov regioselectivity, generating a carbon-centered

* Corresponding author. Tel.: +1 734 763 8283; fax: +1 734 647 4865; e-mail address: crjsteph@umich.edu (C.R.J. Stephenson).

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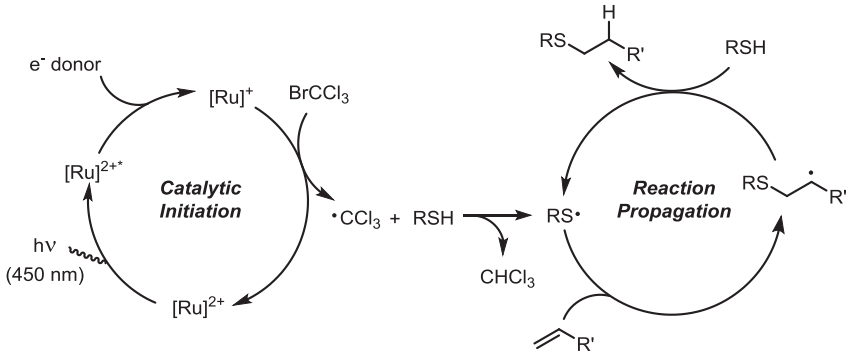


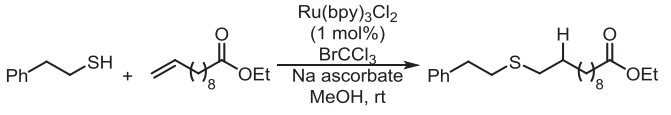
Scheme 1. Proposed system for implementation of mild photocatalytic radical initiation of the TEC reaction.

radical that, upon H-atom abstraction from another thiol molecule, propagates the radical chain process. Reaction propagation for TEC is known to be extremely efficient, with up to 100,000 thioether linkages formed per thiyl radical generated.[3a] Such levels of reaction amplification would allow for low catalyst loading and substoichiometric quantities of both bromochloroform and the sacrificial electron donor. Additionally, these conditions may be better suited to systems that are sensitive to oxidation ($E_{ox(2+*/+)}$ $Ru(bpz)_3(PF_6)_2$=+1.35 V) or Brønsted acid formation.

2. Results and discussion

To realize this idea, we began investigating the TEC reaction between phenylethyl mercaptan and ethyl undecylenate (Table 1). Conditions were optimized along the following parameters: stoichiometry, solvent, concentration, electron donor, electron acceptor/initiator, and reaction time. The highest levels of conversion were observed when employing at least a threefold excess of thiol relative to alkene. Presumably, excess thiol facilitates H-atom abstraction and radical chain propagation. The reaction performed best in highly polar solvents, both protic and aprotic, and was not sensitive to the presence of water. Sodium ascorbate performed best as a reductive quencher (electron donor) for the photocatalyst, with ammonium oxalate salts and tertiary amines being slightly inferior. Under the optimized conditions, reaction initiation was accomplished using $Ru(bpy)_3Cl_2$ (1 mol %) and bromotrichloromethane (5 mol %) in the presence of sodium ascorbate (3 mol %) as a reductive quencher of the catalyst photoexcited state (Table 1, entry 2).

Table 1
Reaction optimization[a]

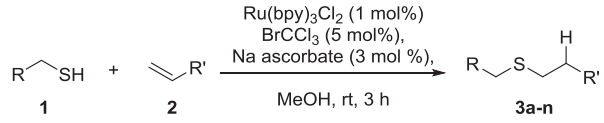


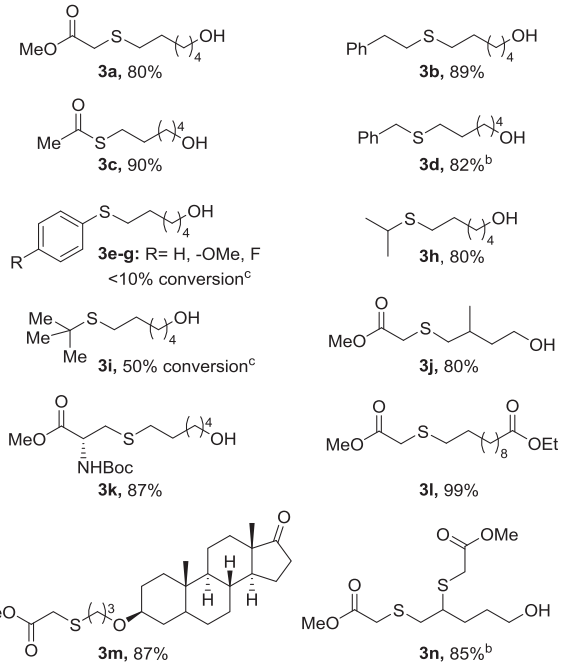
Entry	R-SH (equiv)	R' (equiv)	Concn (M)	Time (h)	Conversion[b] (%)
1	*5*	1	0.4	1.5	91
2	*3*	1	0.4	1.5	91[c,d]
3	1.5	1	0.4	*0.5*	69
4	1.5	1	0.4	*3*	75
5	1.5	1	*0.2*	0.5	48
6	1.5	1	*0.8*	0.5	68

[a] All reactions performed with 10 mol % $BrCCl_3$ and 6 mol % Na-ascorbate unless otherwise noted.
[b] Conversions determined by NMR analysis of crude reaction mixtures.
[c] Identical result obtained using 5 mol % $BrCCl_3$ and 3 mol % Na-ascorbate.
[d] The lipophilicity of the addition product in Table 1 precluded its clean isolation. Analogous trends observed for optimization model system using: RSH=phenylethylmercaptan, alkene=5-hexen-1-ol (see Table 2, entry **3b**).

With the optimized conditions in hand, we began to evaluate the scope of thiols and olefins that are suitable for this transformation. Alkyl, acyl, and benzyl thiols were tolerated, each giving clean conversion within 3 h to the coupled product (Table 1, **3a**–**d**). However, the reaction was unsuccessful with aryl thiols, giving almost no conversion for electron rich, electron neutral, and electron poor thiophenols (**3e**–**g**). Additionally, low conversions were observed for tertiary mercaptans **3i**. Substituted alkenes were incorporated successfully, giving products with the expected anti-Markovnikov regioselectivity **3j**. A more complex substrate was subjected to the optimized conditions and furnished the desired coupled product **3m** in high yield. Finally, the conditions proved to be suitable for thiol–yne coupling as well, giving the 1,2-dithioether **3n** in 85% yield. Notably, the photoredox conditions developed by Yoon and co-workers under the reductive quenching manifold convert alkynes to the corresponding vinyl sulfides.[12a]

Table 2
Representative substrate scope[a]





[a]Isolated yields unless otherwise noted. [b]Yield has been adjusted for trace impurity. [c]NMR-Based conversions.

2.1. Control studies

The impact of each reaction parameter was analyzed through a series of control experiments employing phenylethyl mercaptan and ethyl undecylenate. Crude reaction mixtures were analyzed by ^{1}H NMR. We were pleased to find that in the absence of a radical initiator, photocatalyst, or a light source, only low conversion was detected (<10%), supporting our proposed use of visible-light active $Ru(bpy)_3Cl_2$ as a radical initiator. Later in the course of these studies, however, a substantial background reaction was discovered while attempting to develop this reaction in a flow-reactor. Initially, we attributed this reactivity to the use of a more intense light source (5.9 W vs 2 W blue LED) given the low BDE of bromotrichloromethane (49 kcal/mol).[14] However, this finding prompted us to revisit control experiments in our batch reactions, as these reactions are prone to substrate-dependent anomalies. A non-zero background reaction was detected, with both the reaction rate and the yield highly dependent on the thiol and alkene coupling partners employed. In fact, methyl thioglycolate and 1-hexenol were found to react nearly quantitatively even in the absence of light. This thiol has seen recent use as a hydrogen atom transfer (HAT) agent for photocatalytic C–H activation.[15] The large background reaction was overlooked in the original control studies due to an apparent induction period for the reaction (Fig. 1).

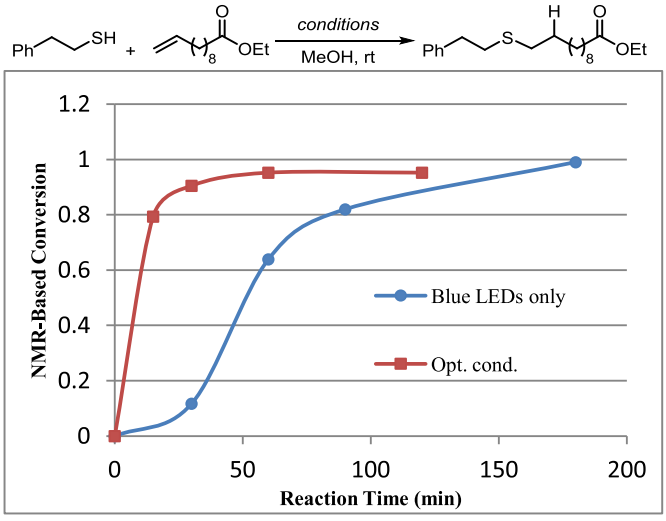
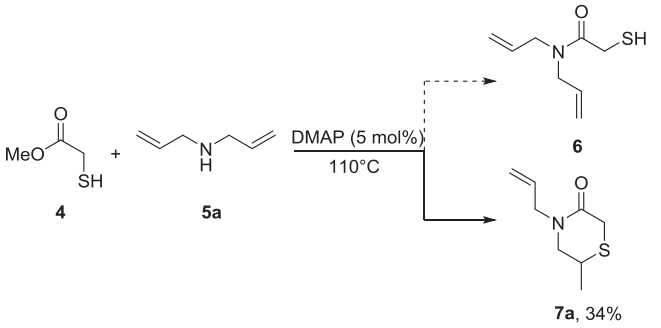


Fig. 1. Comparison of rates of photocatalytic and uncatalyzed reactions.

To account for this reactivity, we propose that molecular oxygen in the reaction mixtures (present in trace quantities despite thorough sparging with argon), can initiate the radical chain process via a thiol–olefin co-oxidation 'TOCO'-type process from a thiol–olefin charge-transfer complex.[16] Nonetheless, the observed kinetics for our optimized photocatalytic system clearly demonstrate that catalytic initiation is operative, enabling rapid access to a diverse set of thiol–ene coupled products under mild conditions.

2.2. Solvent-free synthesis of thiomorpholin-3-ones

In an attempt to construct a substrate to demonstrate an intramolecular thiol–ene cyclization, diallylamine (**5a**) was combined with methyl thioglycolate (**4**) in the presence of 4-dimethylaminopyridine (DMAP, Scheme 2). However, upon workup and purification, we discovered that the thiol–ene reaction had transpired in the absence of any source of initiation. The isolation of Markovnikov isomer **7a** in 34% yield suggests that amide bond formation takes place first, followed by a 6-*exo*-*trig* cyclization to form the thiomorpholin-3-one.



Scheme 2. Discovery of a solvent-free amidation/thiol–ene cyclization sequence to access thiomorpholinones.

Thiomorpholin-3-one and its derivatives are important structural motifs with a heavy presence in the patent literature as a result of their interesting pharmacological profiles. These heterocycles demonstrate a multitude of biological activities, including antihypertensive[17] and antimycobacterial[18] activities, enhancement of neurotransmitter turnover,[19] 5-HT1b[20] and EP4[21] receptor antagonism, and autophagy inhibition.[22] As a result, the development of efficient methods for their preparation is a worthwhile pursuit. Current approaches to the synthesis of thiomorpholinones include Ugi reactions,[23] microwave-assisted Smiles rearrangements,[24] copper-catalyzed cascade reactions,[25] and ring-opening/ring-closing rearrangements of 1,2-cyclic sulfamidates.[26] Herein, we report an alternative synthetic route to thiomorpholin-3-ones by a one-pot solvent-free tandem amidation/hydrothiolation.

Initial screening using **4** and **5a** as the model substrates revealed that the highest yields were obtained when running the reaction neat. In fact, only trace amounts of the desired product could be isolated when employing various high boiling solvents. While the rate of reaction was affected by the presence or absence of DMAP, it was quite insensitive to the quantity employed. We isolated 48% of the desired thiomorpholin-3-one **7a** when performing the reaction in refluxing diallylamine (1.5 equiv) in the presence of DMAP (5 mol %).

Since DMAP provided only modest yields of the desired lactam, we began to explore Lewis acid additives in an effort to improve reaction yield and efficiency. Indeed, in nearly all cases the presence of a Lewis acid offered improved yields (Table 3). The best results were obtained using highly oxophilic Lewis acids such as gadolinium (III) chloride (entry 2) and scandium (III) triflate (entry 6).

Finally, we optimized reaction time using GC–MS. Using product ion count as a metric for reaction progress, we determined that product formation in the $Sc(OTf)_3$-promoted reaction reached completion at approximately 24 h.

With the optimized reaction conditions in hand, we probed whether the reaction would tolerate differentially substituted allylamines (Scheme 3). It was discovered that secondary amines bearing just one reactive olefin (**5b**–**c**) gave lower yields of the corresponding thiomorpholin-3-ones. This lends support to the proposed mechanism in which amide bond formation takes place prior to thiol–ene coupling, as restricted rotation about the amide bond would not allow ready access to the requisite conformer for hydrothiolation of the alkene. Importantly, this method allows for the synthesis of thiomorpholinones bearing *N*-benzyl groups, which can be deprotected in high yields by Birch-type reductive dealkylation.[27]

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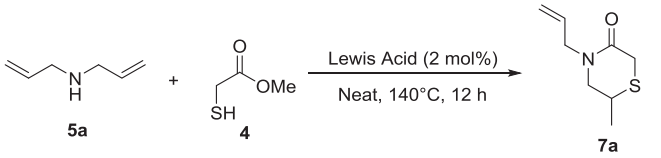
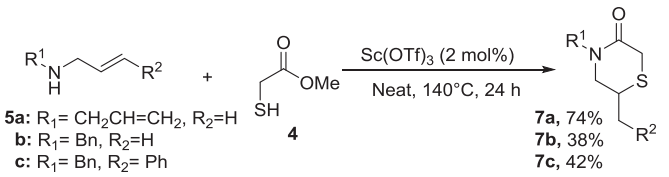
Table 3
Optimization studies for Lewis acid-promoted thiomorpholin-3-one formation[a]



Entry	Lewis acid	Yield[b] (%)
1	Bismuth(III) chloride	54
2	Gadolinium(III) chloride hexahydrate	67
3	Hafnium(IV) triflate	54
4	Lanthanum(III) chloride	54
5	Lithium perchlorate	62
6	*Scandium(III) triflate*	*70*
7	Titanium(IV) isopropoxide	48
8	Yttrium(III) chloride	51
9	Zirconium(IV) chloride	54

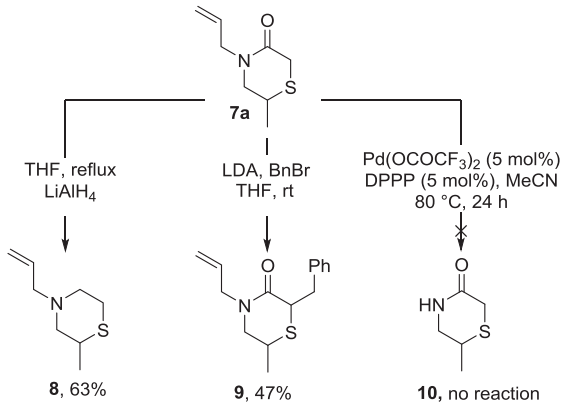
[a] All reactions performed using 1.5 equiv of diallylamine and 1 equiv of methyl thioglycolate.
[b] Isolated yields unless otherwise noted.



Scheme 3. Scope of allyl amine reaction partners.

While differentially substituted amines were tolerated, methyl thioglycolate (**4**) proved to be the only thiol amenable to this transformation; no product formation was observed when employing the corresponding carboxylic acid. It is known that mercaptopropionates exhibit similarly high thiol–ene reactivity to thioglycolates as compared to alkyl thiols. However, neither 2- nor 3-mercaptopropionate esters were tolerated in the reaction. We were particularly surprised to see that ethyl 2-mercaptopropionate did not react as it was expected to exhibit similar reactivity as methyl thioglycolate, and would provide direct access to thiomorpholin-3-one substrates that are methylated at the 2-position. However, it has been shown that alkyl groups can readily be introduced at this position of thiomorpholin-3-ones by enolization and alkylation (vide infra).[22]

Lastly, a handful of synthetic operations were performed on the *N*-allyl-6-methylthiomorpholin-3-one product (Scheme 4). We found that **7a** could serve as a convenient access point to functionalized thiomorpholines by simple reduction of the amide using



Scheme 4. Synthetic applications of thiomorpholin-3-one **7a**. DPPP=1,3-bis(diphenylphosphino)propane.

$LiAlH_4$. Additionally, **7a** was benzylated at the α-position to provide **9** as a 3:2 mixture of diastereomers. Finally, deallylation of the amide was attempted using the conditions reported by Tokunaga and co-workers.[28] However, this reaction was unsuccessful with our substrate, likely due to catalyst poisoning by the sulfide.

3. Conclusions

In conclusion, we have demonstrated the utility of photoredox catalysis as a mild and selective method for radical initiation in the thiol–ene click (TEC) reaction. This method is characterized by low catalyst loadings and substoichiometric quantities of redox additives, enabling net redox neutral hydrothiolation reactions between a wide scope of olefins and thiols. During the method development, we fortuitously discovered a very efficient solvent-free tandem amidation/hydrothiolation methodology that we then utilized to prepare *N*-substituted-6-methylthiomorpholin-3-ones. This operationally simple protocol provides efficient access to a pharmacologically relevant structural motif and allows for the rapid synthesis of structurally diversified thiomorpholinone derivatives.

4. Experimental section

4.1. General

Commercially available starting materials were used as received without further purification unless otherwise noted. Bromotrichloromethane was purified immediately prior to use by passage through a short plug of neutral alumina. Glassware was dried in a 170 °C oven or flame-dried before use. All reaction mixtures were degassed by sparging for 15 min with argon. Reactions were monitored by TLC and visualized by either dual short-wave/long-wave UV lamp or staining with an ethanolic solution of potassium permanganate or with subliming iodine. Column flash chromatography was performed using 43–60 μm (230–400 mesh) silica gel. ^1H and ^{13}C NMR spectra were recorded at ambient temperature at 93.94 kG and 117.3 kG (^1H 400 MHz and 500 MHz, ^{13}C 100 MHz and 125 MHz) using an internal deuterium lock on a Varian Unity Plus 400 or a Varian 500 spectrometer. Hydrogen chemical shifts are expressed in parts per million (ppm) relative to the residual protio solvent resonance in $CDCl_3$ using δ 7.26 as standard for residual $CHCl_3$. Multiplicity is reported as follows: (br=broad, s=singlet, d=doublet, t=triplet, q=quartet, spt=septet, dd=doublet of doublets, dt=doublet of triplets, m=multiplet), and the corresponding coupling constants are indicated as *J* values in units of hertz (Hz). For ^{13}C spectra, the center line of the solvent signal was used as internal reference: $CDCl_3$ δ 77.23. Infrared spectra were recorded on a Nicolet Nexus 670 FT-IR spectrophotometer using an ATR mount. Absorption bands are expressed in wavenumbers (cm^{-1}). High-resolution mass spectra (HRMS) were obtained on a Waters quadrupolar time-of-flight (Q-TOF) API-US mass spectrometer using electrospray ionization (ESI), positive ion mode. Chemical names were generated using ChemDraw Ultra 13.0 (CambridgeSoft).

4.2. General procedure for photoredox-initiated thiol–ene click (TEC) reactions

A 5 mL round-bottom flask equipped with a magnetic stir bar and rubber septum was charged with the starting olefin (1 mmol, 1.0 equiv) and thiol (3.0 mmol, 3 equiv) coupling partners, and sodium ascorbate (0.03 mmol, 3 mol %). The reaction components were dissolved in MeOH (0.4 M). The metal complex $Ru(bpy)_3Cl_2$ (0.01 mmol, 1 mol %) was finally added, and the resultant mixture was degassed by sparging with argon for 15 min in the dark. Finally, while stirring at room temperature under an argon atmosphere,

$BrCCl_3$ (0.05 mmol, 5 mol %) was added and the reaction vessel was surrounded by blue LEDs (2 W). Powering on of this light source signified reaction commencement. Reactions were typically run for 3 h, at, which point the LEDs were powered off and the MeOH removed by rotary evaporation. The reaction mixture was then dissolved in a 7:3 hexanes/ethyl acetate mixture and filtered through a plug of Celite. The crude filtrate was concentrated in vacuo and purified by flash chromatography over SiO_2.

*4.2.1. Methyl 2-((6-hydroxyhexyl)thio)acetate (**3a**).* IR (neat) 3374, 2929, 2857, 1730, 1462, 1436, 1411, 1276, 1131, 1029 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 3.69 (s, 3H), 3.59 (t, J=6.7 Hz, 2H), 3.18 (s, 2H), 2.59 (t, J=7.3 Hz, 2H), 1.60–1.50 (m, overlap, 4H), 1.41–1.31 (m, overlap, 4H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.0, 62.7, 52.3, 33.4, 32.6, 32.50, 28.8, 28.4, 25.3; HRMS (ESI) m/z calculated for $C_9H_{18}O_3S^+$ ($[M+1]^+$) 207.1055, found 189.0952 ($-H_2O$).

*4.2.2. 3-(Phenethylthio)hexan-1-ol (**3b**).* IR (neat) 3351, 3062, 3027, 2930, 2857, 1604, 1497, 1453, 1053, 1030 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.31–7.28 (m, 2H), 7.23–7.20 (m, 3H), 3.64 (t, J=6.6 Hz, 2H), 2.89 (tt, J=8.6, 7.0 Hz, 2H), 2.77 (tt, J=8.6, 8.2 Hz, 2H), 2.54 (t, J=7.0 Hz, 2H), 1.64–1.54 (m, overlap, 4H), 1.45–1.34 (m, overlap, 4H), 1.36 (br s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 140.7, 128.5 (2C), 126.3, 62.9, 36.4, 33.7, 32.6, 32.2, 29.5, 28.6, 25.4; HRMS (ESI) m/z calculated for $C_{14}H_{22}OS^+$ ($[M+1]^+$) 239.1470, found 239.1460.

*4.2.3. S-(6-Hydroxyhexyl) ethanethioate (**3c**).* IR (neat) 3360, 2932, 2858, 1690, 1462, 1431, 1354, 1134, 1054, 954 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 3.54 (t, J=6.6 Hz, 2H), 2.80 (t, J=7.3 Hz, 2H), 2.30 (s, 1H), 2.25 (s, 3H), 1.54–1.46 (m, overlap, 4H), 1.35–1.27 (m, overlap, 4H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 196.3, 62.6, 32.6, 30.7, 29.5, 20.1, 28.6, 25.3. HRMS (ESI) m/z calculated for $C_8H_{16}O_2S^+$ ($[M+1]^+$) 177.0949, found 159.0844 ($-H_2O$).

*4.2.4. 6-(Benzylthio)hexan-1-ol (**3d**).* IR (neat) 3343, 3061, 3028, 2930, 2857, 1602, 1494, 1453, 1238, 1071, 1053, 1028 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.33–7.29 (m, overlap, 4H), 7.26–7.21 (m, 1H), 3.70 (s, 2H), 3.63 (t, J=6.6 Hz, 2H), 2.42 (t, J=7.3 Hz, 2H), 1.60–1.52 (m, overlap, 4H), 1.41–1.32 (m, overlap, 4H), 1.34 (br s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 138.8, 129.0, 128.7, 127.1, 63.1, 36.5, 32.8, 31.5, 29.3, 28.8, 25.5; HRMS (ESI) m/z calculated for $C_{13}H_{20}OS^+$ ($[M+1]^+$) 225.1313, found 207.1239 ($-H_2O$).

*4.2.5. 6-(Isopropylthio)hexan-1-ol (**3h**).* IR (neat) 3346, 2929, 2860, 1461, 1382, 1365, 1241, 1155, 1052 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 3.64 (t, J=6.6 Hz, 2H), 2.91 (spt, J=6.7 Hz, 1H), 2.53 (t, J=7.3 Hz, 2H), 1.62–1.55 (m, overlap, 2H), 1.45–1.35 (m, overlap, 5H), 1.26 (d, J=6.7 Hz, 3H), 1.25 (d, J=6.7 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 63.1, 35.0, 32.8, 30.7, 30.0, 29.0, 25.6, 23.7; HRMS (ESI) m/z calculated for $C_9H_{20}OS^+$ ($[M+1]^+$) 177.1313, found 159.1208 ($-H_2O$).

*4.2.6. Methyl 2-((4-hydroxy-2 methylbutyl)thio)acetate (**3j**).* IR (neat) 3410, 2955, 2926, 2867, 2845, 1733, 1458, 1436, 1378, 1278, 1133, 1051, 1008 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 3.74 (dddd, J=10.7, 6.7, 6.4,1.5 Hz, 1H), 3.68 (dddd, J=10.7, 6.7, 6.5, 1.5 Hz, 1H), 3.73 (s, 3H), 3.21 (s, 2H), 2.67 (dd, J=12.7, 5.8 Hz, 1H), 2.51 (dd, J=12.7, 7.3 Hz, 1H), 1.89 (ddqdd, J=7.8, 7.3, 7.0, 6.7, 5.8 Hz, 1H), 1.72 (dddd, J=13.6, 7.0, 6.5, 1.2 Hz, 1H), 1.55 (br s, 1H), 1.49 (dddd, J=13.6, 7.8, 6.4, 1.5 Hz, 1H), 1.02 (d, J=6.7 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.3, 60.7, 52.6, 40.2, 38.9, 33.9, 29.7, 19.6; HRMS (ESI) m/z calculated for $C_8H_{16}O_3S^+$ ($[M+1]^+$) 193.089, found 175.0787 ($-H_2O$).

*4.2.7. Methyl N-(tert-butoxycarbonyl)-S-(6-hydroxyhexyl)-L-cysteinate (**3k**).* IR (neat) 3372, 2976, 2931, 2857, 1746, 1701, 1503, 1437, 1392, 1367, 1249, 1215, 1163, 1052, 1024 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 5.35 (br d, J=6.7 Hz, 1H), 4.51 (m, 1H), 3.74 (s, 3H), 3.61 (t, J=6.6 Hz, 2H), 2.93 (br dd, J=13.9, 5.0 Hz, 2H), 2.51 (t, J=7.3 Hz, 2H), 1.61 (br s, 1H), 1.59–1.52 (m, overlap, 4H), 1.43 (s, 9H), 1.40–1.33 (m, overlap, 4H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.8, 155.4, 80.3, 62.9, 53.5, 52.7, 34.7, 32.8, 32.7, 29.6, 28.6, 28.5, 25.5; HRMS (ESI) m/z calculated for $C_{15}H_{29}NO_5S^+$ ($[M+1]^+$) 336.1845, found 358.1665 ($[M+Na]^+$).

*4.2.8. Ethyl 11-((2-methoxy-2-oxoethyl)thio)undecanoate (**3l**).* IR (neat) 2927, 2854, 1734, 1436, 1373, 1276, 1178, 1133, 1012 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 4.10 (q, J=7.0 Hz, 2H), 3.71 (s, 3H), 3.20 (s, 2H), 2.60 (t, J=7.3 Hz, 2H), 2.26 (t, J=7.5 Hz, 2H), 1.62–1.53 (m, overlap, 4H), 1.34 (m, 2H), 1.29–1.24 (m, overlap, 10H), 1.23 (t, J=1.23 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 174.0, 171.2, 60.3, 52.5, 34.5, 33.6, 32.9, 29.6, 29.5, 29.4, 29.3, 29.3, 29.1, 28.9, 25.1, 14.4; HRMS (ESI) m/z calculated for $C_{16}H_{30}O_4S^+$ ($[M+1]^+$) 319.1943, found 341.1769 ($[M+Na]^+$).

*4.2.9. Methyl 2-((3-(((3S,8R,9S,10S,13S,14S)-10,13-dimethyl-17-oxohexadecahydro-1H-cyclopenta[a]phenanthren-3-yl)oxy)propyl)thio)acetate(**3m**).* IR (neat) 2926, 2852, 1737, 1437, 1407, 1373, 1276, 1132, 1105, 1012, 916, 731 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 3.69 (s, 3H), 3.49 (t, J=6.1 Hz, 2H), 3.19 (s, 2H), 3.16 (dddd, J=10.9, 9.5, 4.6, 4.6 Hz, 1H), 2.67 (t, J=7.3 Hz, 2H), 2.38 (ddd, J=19.2, 8.9, 0.9 Hz, 1H), 2.01 (dt, J=19.2, 8.9 Hz, 1H), 1.88 (dddd, J=12.4, 8.2, 6.1, 0.9 Hz, 1H), 1.82 (m, overlap, 1H), 1.79 (t, J=7.3 Hz, 2H), 1.77–1.72 (m, 2H), 1.68 (dt, J=13.4, 3.5 Hz, 1H), 1.60 (m, 2H), 1.53–1.41 (m, overlap, 2H), 1.35–1.15 (m, overlap, 8H), 1.04 (dddd, J=12.4, 11.6, 4.0, 3.1 Hz, 1H), 0.96–0.87 (m, overlap, 2H), 0.81 (s, 3H), 0.78 (s, 3H), 0.64 (ddd, 11.9, 10.9, 4.0 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 221.3, 171.0, 78.6, 66.2, 54.6, 52.4, 51.6, 47.9, 45.0, 37.1, 36.1, 35.9, 35.2, 34.9, 33.6, 31.7, 31.0, 29.7, 29.7 (2C), 28.6, 28.3, 21.9, 20.6, 13.9, 12.4; HRMS (ESI) m/z calculated for $C_{25}H_{40}O_4S^+$ ($[M+1]^+$) 437.2726, found 437.2724.

*4.2.10. Dimethyl 2,2′-((5-hydroxypentane-1,2-diyl)bis-(sulfanediyl)) diacetate (**3n**).* IR (neat) 3445, 2951, 2926, 2853, 1730, 1436, 1409, 1279, 1195, 1152, 1130, 1058, 1007 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 3.74 (s, 3H), 3.74 (s, 3H), 3.67 (t, J=6.2 Hz, 2H), 3.35 (d, J=14.8 Hz, 1H), 3.29 (d, J=14.7 Hz, 1H), 3.26 (d, J=14.7 Hz, 1H), 3.25 (d, J=14.8 Hz, 1H), 3.06–3.00 (m, overlap, 2H), 2.80 (dd, J=14.8, 9.8 Hz, 1H), 1.95 (dddd, J=9.8, 9.8, 5.8, 4.4 Hz, 1H), 1.79 (dddd, J=13.6, 9.8, 6.2, 5.2 Hz, 1H), 1.69 (dddd, J=13.6, 9.8, 6.2, 6.1 Hz, 1H), 1.58 (dddd, J=13.4, 9.5, 8.2, 5.2 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.2, 171.1, 62.5, 52.7 (2C), 45.6, 38.4, 34.0, 32.6, 29.8, 29.7; HRMS (ESI) m/z calculated for $C_{11}H_{20}O_5S_2^+$ ($[M+1]^+$) 297.0831, found 279.0903 ($-H_2O$).

4.3. General procedure for Lewis acid-promoted synthesis of thiomorpholin-3-ones

A 5 mL round-bottom flask equipped with a magnetic stir bar, reflux condenser, and rubber septum was charged with ScOTf (2 mol %) followed by the allyl amine (10 mmol, 1.5 equiv) and methyl thioglycolate (6.67 mmol, 1 equiv). The glass joint was sealed with Teflon tape and the reaction mixture heated to 140 °C for 24 h, stirring under a nitrogen atmosphere. The reaction mixture was cooled to room temperature, diluted with dichloromethane, and transferred to a separatory funnel containing cold 1 N aqueous HCl. The layers were separated and the aqueous phase was extracted with additional dichloromethane. The organic layers were then combined, washed with brine, and dried over Na_2SO_4. The crude material was concentrated in vacuo and purified by flash chromatography over SiO_2.

*4.3.1. 4-Allyl-6-methylthiomorpholin-3-one (**7a**).* IR (neat): 2965, 2922, 1656, 1634, 1485, 1441, 1416, 1378, 1351, 1269, 1188, 1116, 994, 931, 817 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz, ~2:1 mixture of rotamers): δ 5.79–5.72 (m, 1H), 5.21–5.16 (m, 2H), 4.11 (m, 1H),

3.92 (m, 1H), 3.47 (dd, J=13, 3.8 Hz, 1H), 3.37 (dd, J=16.0, 1.5 Hz, 1H), 3.31 (dd, J=16.0, 1.5 Hz, 1H), 3.28–3.26 (m, 1H), 3.24–3.19 (m, 1H), 1.30 (d, J=6.6 Hz, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 166.3, 132.5, 117.9, 55.4, 50.2, 35.21, 30.20, 19.24; HRMS (ESI) m/z calculated for $C_8H_{13}NOS^+$ ($[M+1]^+$) 172.0791, found 172.0796.

*4.3.2. 4-Benzyl-6-methylthiomorpholin-3-one (**7b**).*[29] ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.35–7.27 (m, 5H), 4.77 (d, J=15 Hz, 1H), 4.50 (d, J=15 Hz, 1H), 3.47–3.38 (overlap, 3H), 3.27 (dd, J=13.5, 9.5 Hz, 1H), 3.20–3.13 (m, 1H), 1.22 (d, J=7.0 Hz, 3H).

*4.3.3. 4,6-Dibenzylthiomorpholin-3-one (**7c**).*[27] ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.34–7.03 (m, 10H), 4.74 (d, J=14.5 Hz, 1H), 4.46 (d, J=14.5 Hz, 1H), 3.47–3.25 (overlap, 5H), 2.79 (dddd, J=15.5, 7.5, 7.5, 7.5 Hz, 2H).

*4.3.4. 4-Allyl-2-methylthiomorpholine (**8**).* IR (neat): 3076, 2959, 2923, 2868, 2796, 1642, 1454, 1414, 1334, 1272, 1116, 1078, 991, 919 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.82 (dddd, J=16.7, 10.1, 6.5, 6.5 Hz, 1H), 5.19–5.12 (m, 2H), 3.05 (ddd, J=11.7, 3.4, 3.4 Hz, 1H), 3.01–2.93 (m, overlap, 4H), 2.88 (ddd, J=13.6, 11.2, 2.8 Hz, 1H), 2.51 (ddd, J=13.4, 3.2, 3.2 Hz, 1H), 2.21 (ddd, 11.6, 11.6, 2.3 Hz, 1H), 1.97 (dd, J=11.4, 9.9 Hz, 1H), 1.15 (d, J=6.8 Hz, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 135.1, 118.3, 62.8, 62.4, 54.3, 35.9, 28.5, 19.2; HRMS (ESI) m/z calculated for $C_8H_{15}NS^+$ ($[M+1]^+$) 158.0998, found 158.0992.

*4.3.5. 4-Allyl-2-benzyl-6-methylthiomorpholin-3-one (**9**).* IR (neat): 3082, 3025, 2906, 2865, 1654, 1494, 1476, 1413, 1377, 1351, 1306, 1274, 1211, 1182, 1115, 1075, 1030, 991, 926, 698 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$, ~3:2 mixture of diastereomers) δ 7.32–7.21 (m, 5H), 5.83–5.75 (m, 1H), 5.22–5.16 (m, 2H), 4.31 (dddd, J=15.1, 5.8, 1.5, 1.5 Hz, 1H), 4.15 (dddd, J=15.1, 5.8, 1.5, 1.5 Hz, 1H), 3.99 (dddd, J=15.1, 6.4, 1.5, 1.5 Hz, 1H), 3.85 (dddd, 15.1, 6.4, 1.5, 1.5 Hz, 1H), 3.79 (ddd, J=8.9, 8.9, 4.7 Hz, 1H), 3.61 (dd, J=14.3, 4.5 Hz, 1H), 3.53–3.49 (m, 1H), 3.47 (dd, J=14.3, 4.5 Hz, 1H), 3.38 (dd, J=13.5, 4.2 Hz, 1H), 3.31–3.22 (m, overlap, 3H), 3.21–3.14 (m, 1H), 2.89 (dd, J=14.2, 8.6 Hz, 1H), 2.83 (dd, J=14.4, 9.5 Hz, 1H), 1.22 (d, J=6.6 Hz, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 169.6, 169.0, 138.8, 133.2, 133.1, 129.6, 129.5, 128.52, 128.50, 126.9, 126.8, 118.14, 118.09, 54.71, 54.66, 51.3, 50.4, 44.8, 42.9, 37.4, 37.3, 35.88, 35.86, 20.5, 19.8; HRMS (ESI) m/z calculated for $C_{15}H_{19}NOS^+$ ($[M+1]^+$) 262.1260, found 262.1250.

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Supplementary data

Copies of ^{1}H and ^{13}C NMR spectra for all products. Supplementary data associated with this article can be found in the online version, at http://dx.doi.org/10.1016/j.tet.2014.03.041.

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