Note

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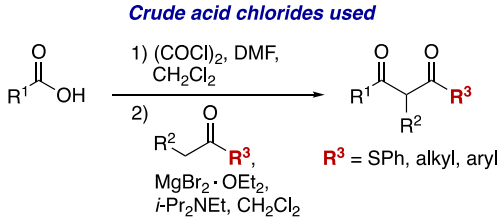

Abstract: Ketones and thioesters undergo soft enolization and acylation using crude acid chlorides on treatment with $MgBr_2 \cdot OEt_2$ and *i*-Pr_2NEt to give 1,3-diketones and β-keto thioesters, respectively. The use of crude acid chlorides adds efficiency and cost reduction by avoiding the need to purify and/or purchase them. The process is conducted in a direct fashion that does not require prior enolate formation, further enhancing its efficiency and making it very easy to carry out. The method is suitable for large scale applications.

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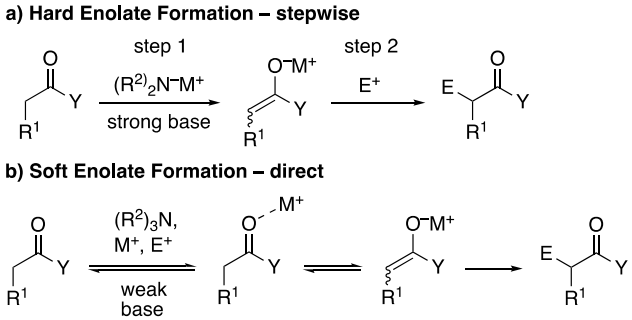
Introduction

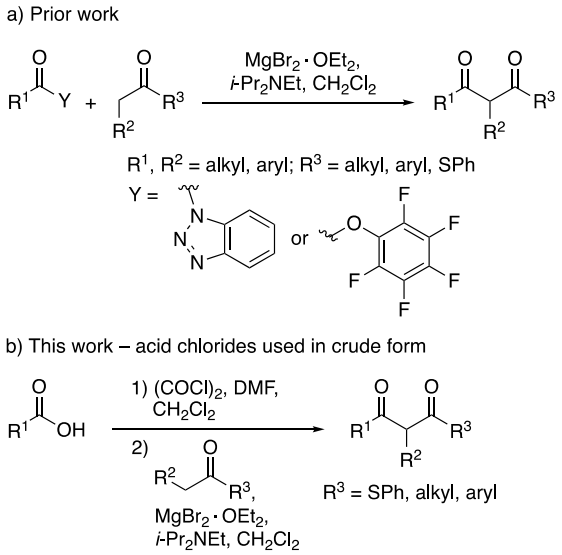
1,3-Diketones and β-keto esters are fundamentally important compounds in synthetic organic chemistry.[1,2] These structural motifs are widely represented in natural products, pharmaceuticals, and other biologically relevant compounds in either their native or derivatized form.[1] Included among such compounds are those having antioxidant, antitumor, antimicrobial, antiviral, and antifungal activity.[1] In addition to their biological significance, 1,3-diketones and β-keto esters are used to facilitate many other highly useful synthetic transformations, including alkylation reactions and the preparation of heterocycles.[2]

Scheme 1. Hard and Soft Enolate Formation.



Despite the prevalence of 1,3-diketones and β-keto esters, their synthesis using conventional hard enolization methods (Scheme 1a) can be problematic.[3] As part of a research program aimed at developing operationally-simple approaches to key carbon–carbon bond-forming reactions via soft enolization (Scheme 1b),[4] we previously reported methods for the synthesis of 1,3-diketones and β-keto thioesters.[3] These methods provide simple solutions to the long-standing challenges

Scheme 2. Established and proposed $MgBr_2 \cdot OEt_2$-Promoted Direct Acylation of Ketones and Thioesters.



associated with the preparation of such compounds, and use either *N*-acylbenzotriazoles[5] or *O*-Pfp esters as the acylating components, along with either ketones or thioesters as the enolate precursors. Despite their effectiveness, the acylating agents used in these transformations were not ideal from either a cost or atom economy perspective. Acid chlorides provide an obvious potential solution to this issue and were tried previously (Scheme 2b).[3a] Unfortunately, they did not prove to be as effective in our preliminary tests with regard to reaction yield as *N*-acylbenzotriazoles or *O*-Pfp esters and, therefore, were not pursued further. However, upon reflection we felt that since many acid chlorides are commercially available, even if they did not function quite as well as *N*-acylbenzotriazoles and *O*-Pfp esters in these transformations, their ease of accessibility and atom economy would justify their use in many synthetic applications. Indeed, a reaction based on

our preliminary work[3a] has been employed by process chemists at Abbott Laboratories on a large scale to produce material to support their efforts on the development of DGAT-1 inhibitors.[6] In that case cylcohexanone (23.6 mL) and 4-bromobenzoyl chloride (50.0 g) were used to prepare 2-(4-bromobenzoyl)cyclohexanone (61.2 g).

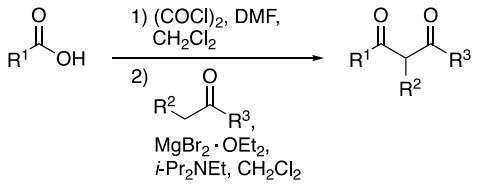
An even more appealing aspect of the use of acid chlorides as acylating agents in the synthesis of 1,3-diketones and β-keto thioesters is that, in principle, the acid chlorides could be prepared from carboxylic acids and used in crude form in the carbon–carbon bond-forming step (Scheme 2b). This would provide even greater efficiency and cost reduction by avoiding the task of purifying the acid chlorides under anhydrous conditions and/or the need to purchase them from a commercial source. It would also diminish problems related to the long-term storage of acid chlorides, such as their tendency to degrade hydrolytically over time. In what follows, we describe the development of a procedure for the synthesis of 1,3-diketones and β-keto esters using carboxylic acids as the acylating agent source. The products generated from these reactions are highly useful synthetic intermediates. Notably, the β-keto thioesters produced can be converted directly into a variety of useful compounds under mild conditions, in addition to those commonly obtained from β-keto esters.[3c]

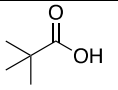
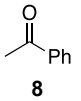
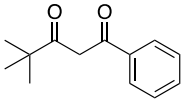
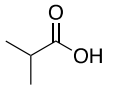
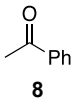
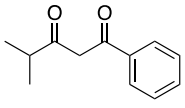
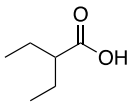
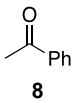
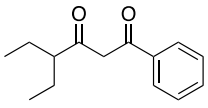
Results and Discussion

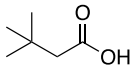
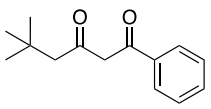
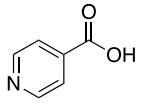
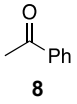
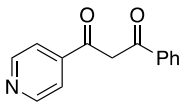
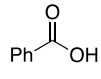
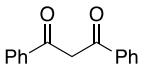
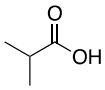
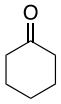
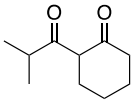
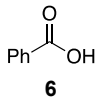
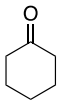
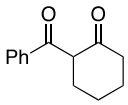
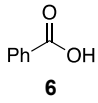
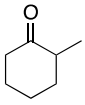
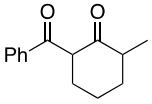
We began our study on the development of a procedure for the synthesis of 1,3-diketones and β-keto thioesters using crude acid chlorides as acylating agents by

treating a solution of 2-methylpropionic acid (**1**) in DMF and CH_2Cl_2 with oxalyl chloride. The solvent was removed after 12 hours and the resulting residue was dissolved in CH_2Cl_2, and combined with $MgBr_2 \cdot OEt_2$, *i*-Pr_2NEt, and acetophenone (**8**). Gratifying, this led to the formation of 1,3-diketone **11** in excellent yield (91%). The coupling reaction with acetophenone was tested further using a variety of carboxylic acids. In all cases the desired 1,3-diketone was generated in synthetically useful yields ranging from 63% to 94% (Table 1, entries 1-6). The ketone substrate was also varied to test the reaction with cyclic ketones, with the desired products being formed in a range of 63% to 70% yield (Table 1, entries 7-9). We note that the regioselective formation of **19** is likely due to its greater thermodynamic stability in comparison to the product derived from substitution at the 2-postion of 2-methylcyclohexanone.

Table 1. $MgBr_2 \cdot OEt_2$-Promoted Acylation of Ketones Using Crude Acid Chlorides.

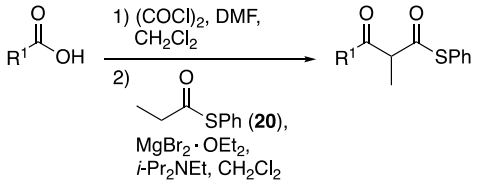


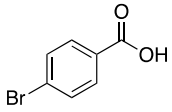
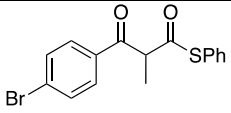
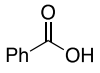
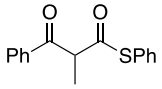
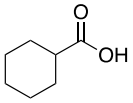
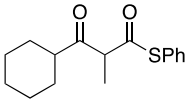
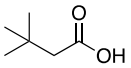
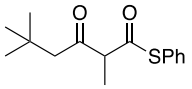
entry	carboxylic acid	ketone	1,3-diketone	yield (%)[a]
1	 **1**	 **8**	 **11**	94
2	 **2**	 **8**	 **12**	91
3	 **3**	 **8**	 **13**	76

4	 **4**	 **8**	 **14**	71
5	 **5**	 **8**	 **15**	67
6	 **6**	 **8**	 **16**	63
7	 **7**	 **9**	 **17**	70
8	 **6**	 **9**	 **18**	68
9	 **6**	 **10**	 **19**	63

As mentioned above, we have previously reported the acylation of thioesters using *N*-acylbenzotriazoles in the presence of $MgBr_2 \cdot OEt_2$ and Hunig's base to give β-keto thioesters.[3c] Given the positive results obtained for the synthesis of 1,3-diketones using crude acid chlorides (Table 1), we also tried this simplified approach for the synthesis of β-keto thioesters. This was done by direct analogy to the work shown in Table 1, and in all cases the desired β-keto thioester was obtained in good to excellent yield (Table 2).

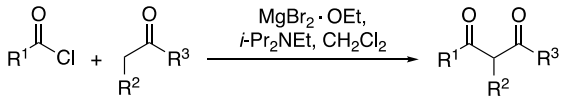
Table 2. $MgBr_2 \cdot OEt_2$-Promoted Acylation of Thioesters Using Crude Acid Chlorides.

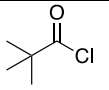
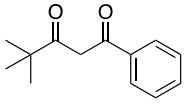
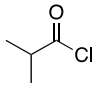
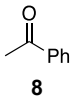
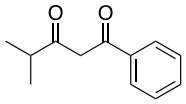
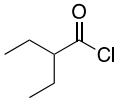
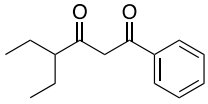
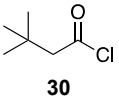
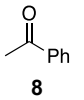
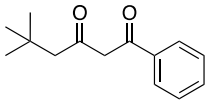
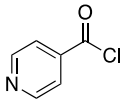
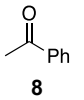
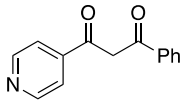
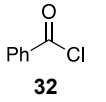
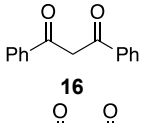
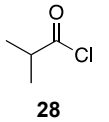
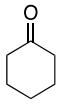
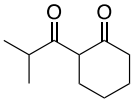
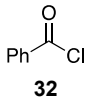
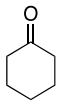
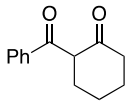
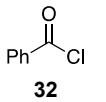
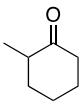
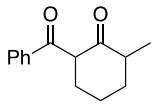


entry	carboxylic acid	β-keto thioester	yield (%)[a]
1	 **21**	 **23**	91
2	 **6**	 **24**	75
3	 **22**	 **25**	72
4	 **4**	 **26**	63

In order to validate the above methods, we carried out the synthesis of each of the 1,3-diketones and the β-keto thioesters prepared, but this time using acid chlorides that were either purchased from commercial sources or, when unavailable, prepared from the corresponding carboxylic acid and purified prior to use in the carbon-carbon bond–forming step. As shown in Table 3, in all cases the yield obtained was comparable to the approach using the acid chlorides in their crude form. Indeed, in some cases better yields were obtained using the crude acid chlorides.

Table 3. $MgBr_2 \cdot OEt_2$-Promoted Acylation of Ketones Using Purified or Commercially-Available Acid Chlorides.

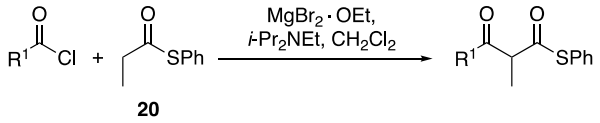


entry	carboxylic acid	ketone	1,3-diketone	yield (%)[a]
1	 **27**	 **8**	 **11**	64
2	 **28**	 **8**	 **12**	91
3	 **29**	 **8**	 **13**	89
4	 **30**	 **8**	 **14**	79
5	 **31**	 **8**	 **15**	67
6	 **32**	 **8**	 **16**	79
7	 **28**	 **9**	 **17**	81
8	 **32**	 **9**	 **18**	69
9	 **32**	 **10**	 **19**	68

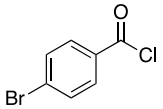
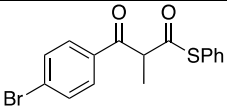
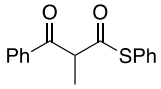
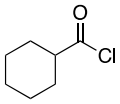
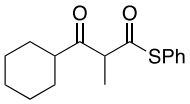
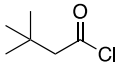
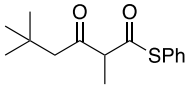
The results obtained for the synthesis of β-ketothioesters using commercially-available acid chlorides are shown in Table 4. Just as for the synthesis of 1,3-

diketones (Table 3), the yield obtained for each of these reactions was comparable to the approach using the acid chlorides in their crude form (Table 2).

Table 4. $MgBr_2 \cdot OEt_2$-Promoted Acylation of Thioesters Using Purified or Commercially-Available Acid Chlorides.



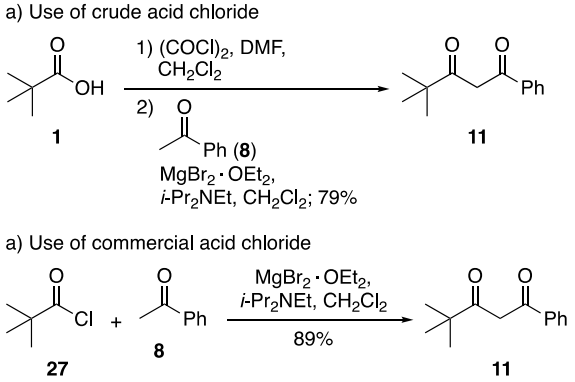
20

entry	carboxylic acid	β-keto thioester	yield (%)[a]
1	 **31**	 **23**	72
2	 **32**	 **24**	86
3	 **33**	 **25**	59
4	 **30**	 **26**	97

To test the scalability of the reactions using crude acid chlorides the synthesis of 1,3-diketone **11** was carried out staring from carboxylic acid **1** and ketone **8**. Thus, a solution of **1** in DMF and CH_2Cl_2 was treated with oxalyl chloride. The solvent was removed after 12 hours and the resulting residue was dissolved in CH_2Cl_2, and $MgBr_2 \cdot OEt_2$, *i*-Pr_2NEt, and **8** (3.8 mL) were then added. This led to the formation of the desired 1,3-diketone in 79% yield. For comparison purposes the corresponding reaction using commercially-available acid chloride **27** was carried out, also using 3.8

mL of **8**. Compound **11** was generated from this reaction in a similar yield (89%) to the transformation using the crude acid chloride, thereby supporting the synthetic utility of the latter approach even in larger reaction scale context .

Scheme 3. Larger Scale $MgBr_2 \cdot OEt_2$-Promoted Acylation Reaction.



Conclusion

In conclusion, when conducted under soft enolization conditions, the acylation of ketones and thioesters using acid chlorides in their crude form is a useful approach to the synthesis of 1,3-diketones and β-keto thioesters, respectively. The reactions are conducted with the crude acid chloride, which is prepared from the corresponding carboxylic acid and oxalyl chloride. Given the general importance of 1,3-dicarbonyl compounds, along with the efficiency and operational simplicity of this method, we expect that it will meet with wide application in synthetic chemistry.

Experimental Section

General Considerations. Unless stated to the contrary, where applicable, the following considerations apply. Reactions were carried out using dried solvents (see below) under a slight static pressure of Ar (pre-purified quality) that had been passed through a column (5 x 20 cm) of Drierite. Glassware was dried in an oven at 120 °C for at least 12 hours prior to use and then either cooled in a desiccator cabinet over Drierite or assembled quickly while hot, sealed with rubber septa, and allowed to cool under a stream of Ar. Reaction mixtures were stirred magnetically using Teflon-coated magnetic stirring bars. Teflon-coated magnetic stirring bars and syringe needles were dried in an oven at 120 °C for at least 12 h prior to use then cooled in a desiccator cabinet over Drierite. Hamilton microsyringes were dried in an oven at 60 °C for at least 24 h prior to used and cooled in the same manner. Commercially available Norm-Jet disposable syringes were used. Dry solvents were obtained using an Innovative Technologies solvent purification system. Commercial grade solvents were used for routine purposes without further purification. Amines were distilled from CaH_2 under a N_2 atmosphere prior to use. Flash column chromatography was performed using silica gel 60 (230-400 mesh). ^{1}H and ^{13}C NMR spectra were recorded on a JEOL ECA-500 or ECX-400P spectrometer at ambient temperature. High-resolution Mass Spectrometry was acquired using an Agilent Technologies 6530 Accurate Mass Q-Tof LC/MS for electrospray ionization (ESI), or a Micromass Autospec Ultima for chemical ionization (CI).

General procedure for the synthesis of 1,3 diketones 11-19 starting from carboxylic acids

4-methyl-1-phenyl-pentane-1,3-dione (12).

DMF (0.23 ml, 2.88 mmol) was added to a stirred solution of 2-methylpropionic acid (2.0 ml, 22.2 mmol), oxalyl chloride (5.7 ml, 66.5 mmol), and CH_2Cl_2 (50 mL) (Ar atmosphere). The solution was stirred for 12 h and then evaporated under reduced pressure to give a mixture consisting of a yellow oil and a dark-brown residue.

In a separate flask $MgBr_2{\cdot}OEt_2$ (0.71 g, 2.80 mmol) was added to a stirred solution of acetophenone (0.13 mL, 0.915 mmol) and the above-generated yellow oil [0.2 mL; ~1.9 mmol (based on the density of 2-methylpropanoyl chloride)] in CH_2Cl_2 (3 mL) (Ar atmosphere), and the resulting mixture was stirred for 15 min. *i*-Pr_2NEt (0.636 mL, 3.66 mmol) was then added drop-wise over ~1 min, the reaction flask was capped with a plastic stopper, sealed with Parafilm, and the mixture was stirred for 12 h. The reaction was quenched with 10% $HCl_{(aq)}$ (4 mL), and the resulting mixture was partitioned between CH_2Cl_2 (15 mL) and water (8 mL). The aqueous phase was washed with CH_2Cl_2 (3 x 20 mL) and the combined organic extracts were washed with brine (2 x 15 mL), dried ($MgSO_4$), filtered, and evaporated under reduced pressure to give a red oil. Flash chromatography over silica gel using 5:95 EtOAc-hexanes (v/v) gave **12** as a pure, red oil (0.164 g, 91%). **^{1}H NMR** ($CDCl_3$, 400 MHz): δ 7.99 (m, 2H), 7.34 (m, 1H), 7.30 (m, 2H), 6.10 (s, 1H), 4.10 (s, 1H), 2.70 (m, 1H), 1.20 (d, J = 9.2 Hz, 6H); **^{13}C{^{1}H} NMR** ($CDCl_3$, 100 MHz): δ 201.3, 183.9, 135.3, 132.3, 128.7, 127.1, 94.3, 37.6, 19.5. Spectroscopic data was identical to that reported previously.[7]

1-phenyl-5,5-dimethylhexane-1,3-dione (14)

Flash chromatography over silica gel using 5:95 CH_2Cl_2-hexanes (v/v) gave **14** as a pure, red oil (0.355 g, 71%). **^{1}H NMR** ($CDCl_3$, 400 MHz): δ 7.90 (d, *J* = 6.8 Hz, 2H), 7.55-7.42 (m, 3H), 6.13 (s, 1H), 2.28 (s, 2H) 1.06 (s, 9H); **^{13}C{^{1}H } NMR** ($CDCl_3$, 100 MHz): δ 193.9, 185.4, 135.6, 132.4, 128.7, 127.2, 98.3, 52.4, 32.1, 30.1. Spectroscopic data was identical to that reported previously.[8]

4,4-Dimethyl-1-phenyl-pentane-1,3-dione (11)

Flash chromatography over silica gel using 10:90 CH_2Cl_2-hexanes (v/v) gave **11** as a pure, a red oil (0.165 g, 94%). **^{1}H NMR** ($CDCl_3$, 500 MHz): δ 7.99 (d, *J* = 7.6 Hz, 2H), 7.53-7.49 (m, 1H), 7.47-7.43 (m, 2H), 6.31 (s, 1H), 1.25 (s, 9H); **^{13}C{^{1}H } NMR** ($CDCl_3$,100 MHz): δ 202.9, 184.7, 135.6, 132.3, 128.7, 127.1, 92.2, 39.9, 27.5.Spectroscopic data was identical to that reported previously.[8]

4-ethyl-1-phenylhexane-1,3-dione (13)

Flash chromatography over silica gel using 5:95 EtOAc-hexanes (v/v) gave **13** as a pure, red oil (0.142 g, 76%). **^{1}H NMR** ($CDCl_3$, 400 MHz): δ 7.99 (m, 2H), 7.4 (m, 1H), 7.5 (m, 2H), 6.1 (s, 1H), 4.1 (s, 8H), 2.1 (m, 1H), 1.7 (m, 2H), 1.5 (m, 2H), 0.9 (t, *J* = 7.4 Hz, 6H); **^{13}C{^{1}H } NMR** ($CDCl_3$, 100 MHz): δ 199.4, 184.4, 135.4, 132.3, 128.7, 127.2, 96.5, 52.7, 25.7, 12.1. Spectroscopic data was identical to that reported previously.[9]

1,3-diphenyl-1,3-propanedione (16)

Flash chromatography over silica gel using 5:95 EtOAc-hexanes (v/v) gave **16** as a pure, yellow solid (0.116 g, 64%). **^{1}H NMR** ($CDCl_3$, 400 MHz): δ 7.99 (d, *J* = 8.0 Hz, 2H), 7.59-7.48 (m, 4H), 6.87 (s, 1H), 3.46 (s, 1H); **^{13}C{^{1}H } NMR** ($CDCl_3$, 100 MHz): 187.3, 185.9, 132.8, 130.1, 129.1, 128.8, 127.3. Spectroscopic data was identical to that reported previously.[9]

1-phenyl-3-(4-pyridyl)-1,3-propanedione (15)

Flash chromatography over silica gel using 5:95 EtOAc-hexanes (v/v) gave **15** as a pure, yellow solid (0.219 g, 75%). **^{1}H NMR** ($CDCl_3$, 400 MHz): δ 8.78 (d, *J* = 3.6 Hz, 1H), 8.39-8.37 (m, 1H), 7.99 (m, 2H), 7.6-7.48 (m, 5H), 6.89 (s, 1H); **^{13}C{^{1}H } NMR** ($CDCl_3$, 100 MHz): δ 186.4, 183.4, 152.9, 148.6, 134.7, 133.0, 128.9, 127.4, 123.7, 93.6. Spectroscopic data was identical to that reported previously.[10]

2-(2-Methylpropanoyl)cyclohexanone (17)

Flash chromatography over silica gel using 5:95 EtOAc-hexanes (v/v) gave **17** as a pure, yellow solid (0.227 g, 70%). **^{1}H NMR** ($CDCl_3$, 400 MHz): δ 2.86 (m, 1H), 2.33 (m, 4H), 1.67 (m, 4H), 1.07 (d, *J* = 6.8 Hz, 6H); **^{13}C{^{1}H } NMR** ($CDCl_3$, 100 MHz): δ 205.5, 183.1, 105.7, 33.3, 31.4, 23.7, 23.1, 21.7, 18.8. Spectroscopic data was identical to that reported previously.[11]

2-benzoylcyclohexanone (18)

Flash chromatography over silica gel using 5:95 EtOAc-hexanes (v/v) gave **18** as a pure, yellow solid (0.133 g, 68%). **^{1}H NMR** ($CDCl_3$, 400 MHz): δ 7.89 (d, *J* = 7.2 Hz, 1H), 7.6-7.5 (m, 2H), 7.54-7.45 (m, 3H), 4.4 (dd, *J* = 3.5 Hz, 1H), 2.56 (m, 1H), 2.51(t, *J* = 6.1 Hz, 2H), 2.41 (t, *J* = 6.2 Hz, 2H), 2.3-2.2 (m, 1H), 2.109 (m, 1H), 1.9-1.8 (m, 1H), 1.77 (m, 2H), 1.59 (m, 2H); **^{13}C{^{1}H } NMR** ($CDCl_3$, 100 MHz): 191.2, 189.6, 130.5, 128.7, 128.6, 128.2, 127.7, 59.3, 42.5, 26.6, 23.5, 21.9. Spectroscopic data was identical to that reported previously.[12]

2-benzoyl-6-methyl-cyclohexanone (19)

Flash chromatography over silica gel using 5:95, EtOAc-hexanes (v/v) gave **19** as a pure, colorless solid (0.150 g, 84%). **^{1}H NMR** ($CDCl_3$, 400 MHz): δ 7.57-7.50 (m, 2H), 7.46-7.39 (m, 3H), 4,45 (dd, *J*= 3.2 Hz, 1H), 2.56 (m, 1H), 2.41-2.36 (m, 1H), 2.11-1.89 (m, 2H), 1.75-1.67 (m, 1H), 1.54-1.39 (m, 2H), 1.26 (d, *J* = 7.2 Hz, 3H); **^{13}C{^{1}H } NMR** ($CDCl_3$, 100 MHz): δ 210.31, 210.14, 198.1, 197.2, 193.4, 191.1, 128.90, 128.78, 128.65, 128.20, 128.15, 127.7, 106.6, 59.2, 58.6, 46.4, 44.9, 37.2, 36.9, 35.9, 30.6, 24.5, 21.8, 21.6, 18.2, 14.5. Spectroscopic data was identical to that reported previously.[12]

General procedure for the synthesis of β-keto thioesters 23-26 starting from carboxylic acids

S-phenyl 1-(4-bromophenyl)-3-propane- 1, 3-dione (23).

DMF (0.11ml, 1.43 mmol) was added to a stirred solution of 4-bromobenzoic acid (2.50 g, 11.4 mmol), oxalyl chloride (3.0 ml, 34.9 mmol), and CH_2Cl_2 (80 mL) (Ar atmosphere). The solution was stirred for 12 h and then evaporated under reduced pressure to give light-yellow solid.

In a separate flask $MgBr_2{\cdot}OEt_2$ (1.0 g, 3.90 mmol) was added to a stirred solution of S-phenyl propanethioate (0.20 mL, 1.30 mmol) and the above-generated yellow solid (0.36 g; ~2.6 mmol) in CH_2Cl_2 (4 mL) (Ar atmosphere), and the resulting mixture was stirred for 15 min. *i*-Pr_2NEt (0.90 mL, 5.20 mmol) was added drop-wise over ~1 min, the reaction flask was capped with a plastic stopper, sealed with Parafilm, and the mixture was stirred for 12 h. The reaction was quenched with 10% $HCl_{(aq)}$ (4 mL), and the resulting mixture was partitioned between CH_2Cl_2 (15 mL) and water (8 mL). The aqueous phase was washed with CH_2Cl_2 (3 x 20 mL) and the combined organic extracts were washed with brine (2 x 15 mL), dried ($MgSO_4$), filtered, and evaporated under reduced pressure to give a red oil. Flash chromatography over silica gel using 5:95 EtOAc-hexanes (v/v) gave **23** as a pure, white solid (0.414 g, 91%). **^{1}H NMR** ($CDCl_3$, 400 MHz): δ 7.85-7.83 (m, 2H), 7.68-7.6 (m, 2H), 7.39-7.25 (m, 5H), 4.66 (q, *J*= 6.8 Hz, 1H) , 2.16 (s, 1H), 1.60 (d, *J* = 6.8 Hz, 3H); **^{13}C{^{1}H } NMR** ($CDCl_3$, 100 MHz): δ 194.9, 193.8, 134.6, 130.4, 129.9, 129.5, 129.2, 126.6, 123.3, 56.4, 14.8. **HRMS ESI-MS** m / z $[M + H]^+$ calcd for $C_{16}H_{13}BrO_2S$ 348.9892, found 348.9900 and 350.9882.

S-phenyl 2,5,5-trimethyl-3-oxohexanethioate (26)

Flash chromatography over silica gel using 30:70 CH_2Cl_2-hexanes (v/v) gave **26** as a pure, yellow oil (0.207 g, 63%). **^{1}H NMR** ($CDCl_3$, 400 MHz): δ 7.48 (m, 5H), 3.81 (q, *J* = 6.8 Hz, 1H), 2.49 (s, 2H), 1.40 (d, *J* = 6.8 Hz, 3H), 1.03 (s, 9H); **^{13}C{^{1}H } NMR** ($CDCl_3$, 100 MHz): δ 203.8, 196.1, 194.9, 134.5, 134.5, 129.8,129.7, 129.5, 129.4, 129.3, 128.5, 127.5, 126.9, 62.7, 56.4, 53.6, 31.9, 31.1, 29.9, 29.7, 13.6. Spectroscopic data was identical to that reported previously.[3a]

S-phenyl 2-methyl-3-oxo-3-phenylpropanethioate (24)

Flash chromatography over silica gel using 20:80 CH_2Cl_2-hexanes (v/v) gave **24** as a pure, yellow oil (0.115 g, 75%). **^{1}H NMR** ($CDCl_3$, 400 MHz): δ 8.04 (s, 1H), 8.02 (d, *J* = 1.2 Hz, 1H), 7.62-7.56 (m, 1H), 7.52-7.48 (m, 2H), 7.39-7.34 (m, 5H), 4.71 (q, *J* = 7.2 Hz, 1H), 1.61 (d, *J* = 6.8 Hz, 3H); **^{13}C{^{1}H } NMR** ($CDCl_3$, 100 MHz): δ 195.01, 194.8, 135.9, 134.6, 133.8, 129.8, 129.4,128.96, 128.91, 126.9, 56.3, 14.9. Spectroscopic data was identical to that reported previously.[3a]

S-phenyl 3-cyclohexyl-2-methyl-3-oxopropanethioate (25)

Flash chromatography over silica gel using 20:80 CH_2Cl_2-hexanes (v/v) gave **25** as a pure, red oil (0.261 g, 72%). **^{1}H NMR** ($CDCl_3$, 400 MHz): δ 13.6 (s, OH), 7.46-7.38 (m, 5H), 4.01 (q, *J* = 6.8Hz, 1H), 2.68-2.58 (m, 1H), 1.91-1.66 (m, 6H), 1.42 (d, *J* = 6.8 Hz, 3H), 1.34-1.19 (m, 4H); **^{13}C{^{1}H } NMR** ($CDCl_3$, 100 MHz): δ 207.7, 194.8, 134.5, 129.8, 129.4, 127.03, 59.3, 50.3, 29.1, 28.4, 26.1, 25.8, 25.4, 14.0. Spectroscopic data was identical to that reported previously.[3a]

General procedure for the synthesis of 1,3 diketones 11-19 starting from pure acid chlorides

4-methyl-1-phenyl-pentane-1,3-dione (12).

$MgBr_2 \cdot OEt_2$ (1.38 g, 5.35 mmol) was added to a stirred solution of acetophenone (0.20 mL, 1.95 mmol), 2,2 dimethyl butyl chloride (0.20 mL, 2.19 mmol) and CH_2Cl_2 (7 mL) (Ar atmosphere), and the resulting mixture was stirred for 15 min. *i*-Pr_2NEt (1.16 mL, 7.13 mmol) was added to the solution, the reaction flask was capped with a plastic stopper, sealed with Parafilm, and reaction mixture was stirred for 12 h. The reaction mixture was then quenched with 10% $HCl_{(aq)}$ (4 mL), and the resulting mixture was partitioned between CH_2Cl_2 (15 mL) and water (8 mL). The aqueous phase was washed with CH_2Cl_2 (3 x 20 mL) and the combined organic extracts were washed with brine (2 x 15 mL), dried ($MgSO_4$), filtered, and evaporated under reduced pressure to give a red oil. Flash chromatography over silica gel using 5:95 EtOAc-hexanes (v/v) gave **12** as a pure, red oil (0.299 g, 91%). Spectroscopic data was identical to that given above.

1-phenyl-5,5-dimethylhexane-1,3-dione (14)

Flash chromatography over silica gel using 5:95 CH_2Cl_2-hexanes (v/v) gave **14** as a pure, red oil (0.125 g, 64%). Spectroscopic data was identical to that given above.

4,4-Dimethyl-1-phenyl-pentane-1,3-dione (11)

Flash chromatography over silica gel using 10:90 CH_2Cl_2-hexanes (v/v) gave **11** as a pure, a red oil (0.326 g, 94%). Spectroscopic data was identical to that given above.

4-ethyl-1-phenylhexane-1,3-dione (13)

Flash chromatography over silica gel using 5:95 EtOAc-hexanes (v/v) gave **13** as a pure, red oil (0.301 g, 89%). Spectroscopic data was identical to that given above.

1,3-diphenyl-1,3-propanedione (16)

Flash chromatography over silica gel using 5:95 EtOAc-hexanes (v/v) gave **16** as a pure, yellow solid (0.30 g, 79%). Spectroscopic data was identical to that given above.

1-phenyl-3-(4-pyridyl)-1,3-propanedione (15)

Flash chromatography over silica gel using 5:95 EtOAc-hexanes (v/v) gave **15** as a pure, yellow solid (0.089 g, 67%). Spectroscopic data was identical to that given above.

2-(2-Methylpropanoyl)cyclohexanone (17)

Flash chromatography over silica gel using 5:95 EtOAc-hexanes (v/v) gave **17** as a pure, yellow solid (0.169 g, 81%). Spectroscopic data was identical to that given above.

2-benzoylcyclohexanone (18)

Flash chromatography over silica gel using 5:95 EtOAc-hexanes (v/v) gave **18** as a pure, yellow solid (0.270 g, 69%). Spectroscopic data was identical to that given above.

2-benzoyl-6-methyl-cyclohexanone (19)

Flash chromatography over silica gel using 5:95, EtOAc-hexanes (v/v) gave **19** as a pure, colorless solid (0.356 g, 80%). Spectroscopic data was identical to that given above.

General procedure for the synthesis of β-keto thioesters 23-26 starting from pure acid chlorides

***S*-phenyl 1-(4-bromophenyl)-3-propane- 1, 3-dione (23)**

$MgBr_2 \cdot OEt_2$ (1.38 g, 5.35 mmol) was added to a stirred solution of S-phenyl propanethioate (0.27 ml, 1.76 mmol), 4- bromo- benzoyl chloride (0.47 g, 2.16 mmol) and CH_2Cl_2 (6 ml) (Ar atmosphere), and the resulting mixture was stirred for 15 min. *i*-Pr_2NEt (1.24 ml, 7.13 mmol) was added to the solution, the reaction flask was capped with a plastic stopper, sealed with Parafilm, and reaction mixture was stirred for 12 h. The reaction mixture was then quenched with 10% HCl (4 mL), and the resulting mixture was partitioned between CH_2Cl_2 (15 mL) and water (8 mL). The aqueous phase was washed with CH_2Cl_2 (3 x 20 mL) and the combined organic extracts were washed with brine (2 x 15 mL), dried ($MgSO_4$), filtered, and evaporated under reduced pressure to give an brown solid. Flash chromatography over silica gel using 5:95 EtOAC-hexanes (v/v) gave **23** as a pure, white solid (0.597 g, 97%). Spectroscopic data was identical to that given above.

***S*-phenyl 2-methyl-3-oxo-3-phenylpropanethioate (26)**

Flash chromatography over silica gel using 20:80 CH_2Cl_2-hexanes (v/v) gave **26** as a pure, yellow oil (0.404 g, 97%). Spectroscopic data was identical to that given above.

S-phenyl 2,5,5-trimethyl-3-oxohexanethioate (24)

Flash chromatography over silica gel using 30:70 CH_2Cl_2-hexanes (v/v) gave **24** as a pure, yellow oil (0.405 g, 86%). Spectroscopic data was identical to that given above.

S-phenyl 3-cyclohexyl-2-methyl-3-oxopropanethioate (25)

Flash chromatography over silica gel using 20:80 CH_2Cl_2-hexanes (v/v) gave **25** as a pure, red oil (0.288 g, 59%). Spectroscopic data was identical to that given above.

Large scale synthesis of 4,4-Dimethyl-1-phenyl-pentane-1,3-dione (11) starting from carboxylic acid 1.

DMF (0.6 ml, 7.63 mmol) was added to a stirred solution of pivalic acid (6.0 g, 58.7 mmol), oxalyl chloride (15 ml, 174.0 mmol), and CH_2Cl_2 (73 mL) (Ar atmosphere). The solution was stirred for 12 h and then evaporated under reduced pressure to give a mixture consisting of a yellow oil and a dark-brown residue.

In a separate flask $MgBr_2{\cdot}OEt_2$ (22.5 g, 87.2 mmol) was added to a stirred solution of acetophenone (3.8 mL, 32.6 mmol) and the above-generated yellow oil [5.0 mL; ~40.6 mmol (based on the density of trimethylacetyl chloride)] in CH_2Cl_2 (50 mL) (Ar atmosphere), and the resulting mixture was stirred for 15 min. *i*-Pr_2NEt (21.3 mL, 130.8 mmol) was then added drop-wise over ~15 min, the reaction flask was capped with a plastic stopper, sealed with Parafilm, and the mixture was stirred for 12 h.The reaction was quenched with 10% $HCl_{(aq)}$ (35 mL), and the resulting mixture was partitioned between EtOAc (80 mL) and water (40 mL). The aqueous phase was washed with EtOAc (3 x 100

mL) and the combined organic extracts were washed with brine (2 x 100 mL), dried ($MgSO_4$), filtered, and evaporated under reduced pressure to give a red oil. Flash chromatography over silica gel using 10:90 EtOAc-hexanes (v/v) gave **11** as pure, red oil (5.14 g, 79%). Spectroscopic data was identical to that given above.

Large scale synthesis of 4,4-Dimethyl-1-phenyl-pentane-1,3-dione (11) starting from acid chloride 27.

$MgBr_2 \cdot OEt_2$ (2.3 g, 98.2 mmol) was added to a stirred solution of acetophenone (3.8 mL, 32.6 mmol), trimethylacetyl chloride (5.0 mL, 40.6 mmol), and CH_2Cl_2 (59 mL) (Ar atomosphere), and the resulting reaction mixture was stirred for 30 min. The mixture was cooled (ice-H_2O bath) and *i*-Pr_2NEt (21.0 mL, 130.0 mmol) was added dropwise over ~15 min. The reaction mixture was allowed to warm to rt and stirred for an additional 4 h. The reaction mixture was then quenched with water (30 mL) and 10% $HCl_{(aq)}$ (35 mL). The resulting mixture was filtered and partitioned between EtOAc (80 mL) and water (40 mL). The aqueous phase was washed with EtOAc (3 x 100 mL) and the combined organic extracts were washed with brine (2 x 100 mL), dried ($MgSO_4$), filtered, and evaporated under reduced pressure to give a red oil. Flash chromatography over silica gel using 10:90 EtOAc-hexanes (v/v) gave **11** as pure, red oil (5.89 g, 89%). Spectroscopic data was identical to that given above.

Supporting Information

NMR spectra for all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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