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An efficient transesterification of β-oxodithioesters catalyzed by stannous chloride under solvent-free conditions

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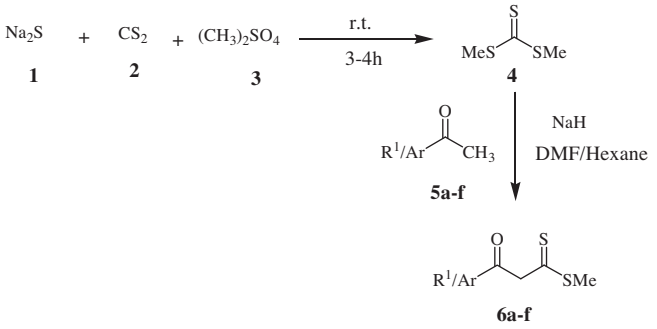
ABSTRACT

Transesterification of β-oxodithioesters catalyzed by stannous chloride under solvent-free condition has been reported for the first time. The short reaction time and good to excellent yields using inexpensive catalysts are attractive features of this synthetic protocol.

The toxicity and volatile nature of many organic solvents, particularly chlorinated hydrocarbons that are widely used in huge amounts for organic reactions have posed a serious threat to the environment. Designing of efficient chemical transformation in a single operation by a catalytic process avoiding stoichiometric toxic reagents, large amounts of solvents, and expensive purification techniques represents a fundamental target of the green chemistry.[1] Thus, the design of solvent-less catalytic reaction has received tremendous attention in recent times in the area of green synthesis.[2,3] This prompted us to initiate a systematic investigation to look into the feasibility of solvent-free reactions toward the development of green methodology for biologically useful molecules.

The transesterification is an important synthetic process used as an alternative method to synthesize various carboxylic esters. The transesterification of β-ketoesters has been found to be a very useful tool in organic synthesis having wide applications in academic as well as industrial research. β-Ketoesters are employed widely as chemical intermediates in the pharmaceutical, agrichemical, chemical, and polymer industries.[4] The electrophilic and nucleophilic sites of β-ketoesters make them a valuable tool for the synthesis of complex natural products,[5a] such as paclitaxel,[5b] podophyllotoxin,[5c] serricornine,[5d] trichodiene,[5e] karrikinolide (KAR1), and tetrahydrozerumbone.[5f] The chelate complex of β-ketoesters suppresses the activity of some pathogenic viruses through the formation of a coordinate bond to metal ions at the active site of the virus enzyme responsible for virus replication.[6] The transesterification is an important organic transformation and provides essential synthons for pheromones and additives for paints.[7] In addition, this reaction is an essential part of the manufacturing process of polyethylene terephthalate.[8]



Scheme 1. Synthesis of β-oxodithioesters.

A number of useful and reliable esterification methods catalyzed by a variety of reagents such as DMAP,[9a] DBU,[9b] titanium tetraalkoxide,[9c] tetrabutyl distannoxanes,[9d,e] *p*-TSA,[9f] indium triiodide,[9g] iodotrimethylsilane/I_2,[9h] iodine,[9i] $BiCl_3$,[9j] zeolite H-FER,[9k] and $Yb(OTf)_3$[9l] have been well documented for transesterification. Recent developments include variation and improvements of well established procedures and the discovery and application of new reagents.[9j–l]

A careful literature survey reveals that there have been no reports on the transesterification of β-oxodithioesters. The existing

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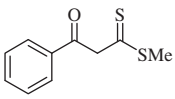
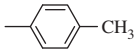
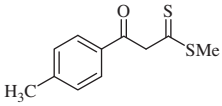
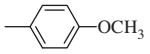
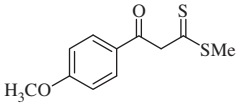
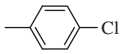
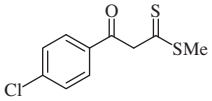
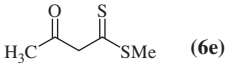
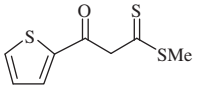
Table 1
Synthesis of β-oxodithioesters

Entry	Ar/R[1]	Dithioesters	Yield[a] (%)
1		 **(6a)**	72
2		 **(6b)**	75
3		 **(6c)**	73
4		 **(6d)**	71
5	CH_3	 **(6e)**	50
6		 **(6f)**	61

[a] Yield of isolated product.

Table 2
Optimization of catalyst on model reaction[a]

Entry	Catalyst	Mol %[b]	Time (min)	Yield[c] (%)
1	$SnCl_2$	5	60	80
2	$SnCl_2$	10	40	75
3	$SnCl_2$	15	35	73
4	$FeCl_3$	15	30	55
5	$ZnCl_2$	25	40	61
6	$CuCl_2$	20	50	57
7	$AlCl_3$	15	30	62
8	None	—	30	Nil

[a] Reaction conditions: acetophenone dithioester (1 mmol), benzyl alcohol (1 mmol) under neat condition at 110 °C.
[b] Amount of catalyst used based on **7a**.
[c] Isolated yield based on **7a**.

methods involve the esterification of only β-ketoesters such as methyl acetoacetate and ethyl acetoacetate and variations designed in the structures of alcohol yielding an esterification product either in improved yield or by the application of new methodologies are always reported. During the course of our studies on the synthetic application of β-oxodithioesters in various organic transformations,[10a–d] we report herein a novel and efficient method for facile transesterification of β-oxodithioesters using stannous chloride under solvent-free conditions.

The desired β-oxodithioesters **6a–f** are obtained by treating active methylene compounds **5** with (*S*,*S*)-dimethyl trithiocarbonate **4**[11] in the presence of NaH (Scheme 1, Table 1).

The transesterification reaction of easily accessible β-oxodithioesters **6a** (1 mmol) with benzyl alcohol **7a** (1 mmol) was studied in the presence of 5 mol % $SnCl_2$ as a model reaction (Table 2, entry 1). After completion of the reaction (monitored by TLC), the catalysts were filtered, and the filtrate was concentrated to get a crude product which was purified by column chromatography using ethyl acetate and petroleum ether to give the desired transesterified product **8a** as a viscous pale yellow liquid (Scheme 2). The reaction smoothly proceeded in the solvent-free condition to give transesterified product **8a** in 80% yield in 1 h. The formation of compound **8a** was confirmed by the spectral and analytical data.

The model reaction was also tried with different catalysts such as $CuCl_2$, $ZnCl_2$, $AlCl_3$, and $FeCl_3$ (Table 2). However, the use of these catalysts cannot improve the yield of the reaction. An increase in the catalyst showed no substantial improvement in the yield, though a slight improvement in the reaction time was observed. Thus, the reaction was optimized with the use of 5 mol % of $SnCl_2{\cdot}2H_2O$.

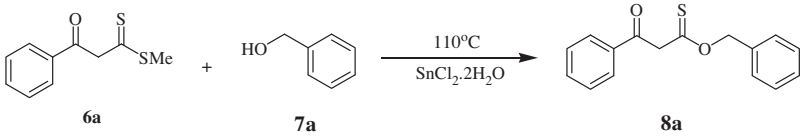
Under these optimized conditions, various β-oxodithioesters **6b–f** underwent a smooth transesterification with various alcohols like benzyl alcohol, *n*-butanol, isopropanol, and tertiary butyl alcohol giving good yields of transesterification products (Table 3).

A noteworthy merit of the present protocol is that a variety of structurally different alkyl/aryl/heteroaryl β-oxodithioesters underwent the smooth transesterification with various alcohols. In all the cases, 5 mol % of the catalyst can effectively catalyze the reaction to completion. The role of the catalyst is probably to increase the electrophilicity of thiocarbonyl carbon to facilitate the nucleophilic attack of the alcoholic OH group.

As seen from Table 3, the esterification reaction proceeds smoothly with primary, secondary, and tertiary alcohols with the reactivity of the alcohols decreasing in the order primary > secondary > tertiary. The yields of the products also showed a trend in the same order as that of the reactivity. Esters of tertiary alcohols which are difficult to prepare are obtained in moderate yields due to steric hindrance. It is noteworthy to mention that phenol, *p*-cresol, and *m*-chlorophenol failed to undergo transesterification due to low reactivity.

The structure of all the products was characterized by IR, ^1H NMR, ^{13}C NMR, CHN analysis, and mass spectrometry.[12]

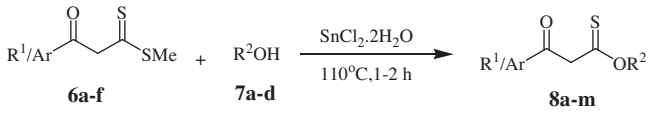
In conclusion, we have successfully demonstrated the transesterification of β-oxodithioesters in the presence of a catalytic amount of stannous chloride under solvent-free condition. The short reaction time, mild reaction condition, and good to excellent yields using inexpensive catalysts are attractive features of this protocol. We believe that transesterification products of β-oxodithioesters will provide an essential synthons for asymmetric Mannich reactions with acyl imines. Further, the products from the Mannich reaction will be of use in the synthesis of highly biologically active enantioenriched dihydropyrimidones and β-amino alcohols. Besides this, they may be employed for the production of chiral alcohols by reduction.

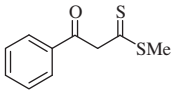
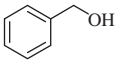
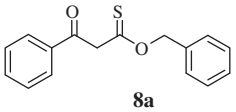
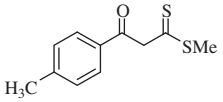
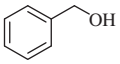
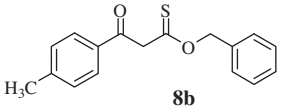
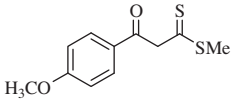
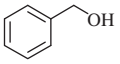
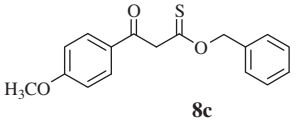
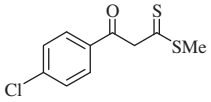
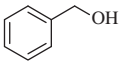
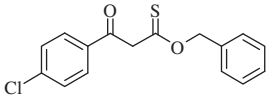
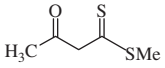
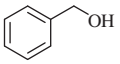
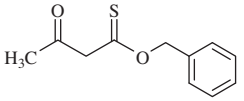
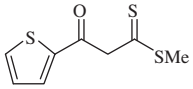
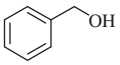
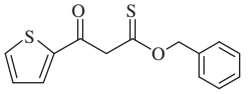
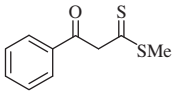
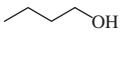
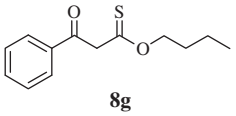
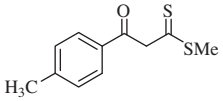
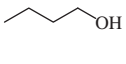
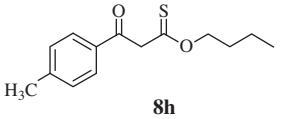
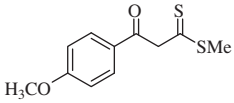
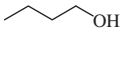
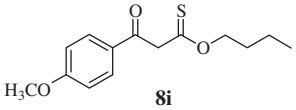
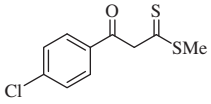
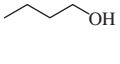
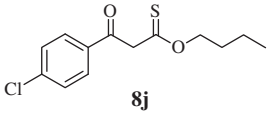
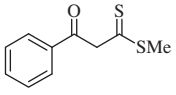
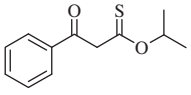
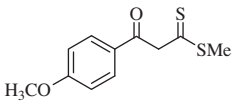
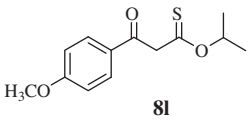
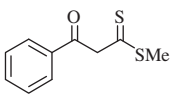
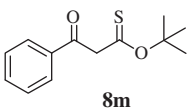


6a **7a** **8a**

Scheme 2. Esterification of acetophenone dithioester with benzyl alcohol as model reaction.

Table 3
Transesterification of β-oxodithioesters with various alcohols



Entry	Dithioesters	Alcohols	Product	Yield[a] (%)
1			 **8a**	80
2			 **8b**	83
3			 **8c**	85
4			 **8d**	77
5			 **8e**	75
6			 **8f**	79
7			 **8g**	75
8			 **8h**	79
9			 **8i**	80
10			 **8j**	77
11			 **8k**	73
12			 **8l**	69
13			 **8m**	51

[a] Yield of isolated product.

Acknowledgments

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12. *General procedure for the synthesis of propanethioate (**5a–m**):* a mixture of β-oxodithioesters (1 mmol), alcohol (1 mmol), and 5 mol% $SnCl_2{\cdot}2H_2O$ was heated at 110 °C in a round bottom flask provided with a distillation condenser to remove thiomethanol. After completion of the reaction (TLC), the catalyst was filtered, and the filtrate was concentrated to get a crude product which was purified by column chromatography on silica gel (5% EtOAc/Hex) as eluent to give pure products.
*O-Benzyl 3-oxo-3-phenylpropanethioate (**8a**):* viscous pale yellow liquid, ^{1}H NMR ($CDCl_3$, 400 MHz): δ 4.09 (s, 2H), 5.25 (s, 2H), 7.29–7.31 (m, 5H), 7.85 (m, 3H), 7.31 (d, J = 8 Hz, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 46.2, 69.7, 128.1, 128.3, 128.5, 129.7, 129.9, 135.6, 136.5, 145.5, 167.9, 192.3; IR (KBr) (ν max, cm^{-1}): 1715, 1687; EI MS (m/z): 270 (M^+). Anal. Calcd for $C_{16}H_{14}O_2S$: C, 71.08; H, 5.22; S, 11.86. Found: C, 71.15; H, 5.17; S, 11.83.
*O-Benzyl 3-oxo-3-p-tolylpropanethioate (**8b**):* viscous pale yellow liquid, ^{1}H NMR ($CDCl_3$, 400 MHz): δ 2.41 (s, 3H), 4.05 (s, 2H), 5.20 (s, 2H), 7.25 (d, J = 8 Hz, 2H), 7.33–7.35 (m, 5H), 7.82 (d, J = 8 Hz, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 25.3, 46.1, 69.9, 128.2, 128.5, 128.7, 129.5, 129.9, 135.5, 136.9, 145.7, 167.7, 192.7; IR (KBr) (ν max, cm^{-1}): 1717, 1690; EI MS (m/z): 284 (M^+). Anal. Calcd for $C_{17}H_{16}O_2S$: C, 71.80; H, 5.67; S, 11.28. Found: C, 71.87; H, 5.63; S, 11.25.
*O-Butyl 3-oxo-3-phenylpropanethioate (**8g**):* viscous pale yellow liquid, ^{1}H NMR ($CDCl_3$, 400 MHz): δ 0.88 (t, J = 7.4 Hz, 3H), 1.28–1.34 (m, 2H), 1.55–1.60 (m, 2H), 3.99 (s, 2H), 4.14 (t, J = 6.6 Hz, 2H), 7.39–7.94 (m, 5H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 13.5, 19.1, 30.7, 46.3, 69.1, 128.2, 128.5, 128.8, 133.6, 167.6, 192.5.; EI MS (m/z): 236 (M^+). Anal. Calcd for $C_{13}H_{16}O_2S$: C, 66.07; H, 6.82; S, 13.57. Found: C, 66.25; H, 6.73; S, 13.53.
*O-Isopropyl 3-oxo-3-phenylpropanethioate (**8k**):* viscous pale yellow liquid, ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.20 (d, J = 6.6 Hz, 6H), 3.93 (s, 2H), 5.04–5.07 (m, 1H), 7.42–7.57 (m, 3H), 7.91–7.95 (m, 2H);^{13}C NMR ($CDCl_3$, 75 MHz): δ 21.6, 46.3, 69.1, 128.3, 128.5, 128.7, 133.6, 167.1, 192.7; EI MS (m/z): 222 (M^+). Anal. Calcd for $C_{12}H_{14}O_2S$: C, 64.83; H, 6.35; S, 14.42. Found: C, 64.73; H, 6.45; S, 14.39.
*O-tert-Butyl 3-oxo-3-phenylpropanethioate (**8m**):* viscous pale yellow liquid, ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.25(s, 9H), 3.95(s, 2H), 7.45–7.58 (m, 3H), 7.91–7.94 (m, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz): 26.1, 46.5, 69.9, 128.5, 128.7, 128.9, 133.7, 167.3, 192.9; EI MS (m/z): 236 (M^+). Anal. Calcd for $C_{13}H_{16}O_2S$: C, 66.07; H, 6.82; S, 13.57. Found: C, 66.15; H, 6.75; S, 13.49.