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Reductive Sulfidation

Indium-Catalyzed Reductive Sulfidation of Esters by Using Thiols: An Approach to the Diverse Synthesis of Sulfides

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Abstract: A new reductive preparation of unsymmetrical sulfides from esters and thiols in the presence of InI_3 and either 1,1,3,3-tetramethyldisiloxane (TMDS) or $PhSiH_3$ as the reductant was developed. This protocol was applied to not only benzoic acid esters that have a methoxy, methyl, chloro, bromo, iodo, or trifluoromethyl group on the aromatic ring but also aliphatic acid esters with either aromatic or aliphatic thiols. A reaction mechanism is proposed by using Hammett plot results and several control experiments.

Introduction

Carbon–sulfur bond formation is an important area of organic chemistry because of the synthetic versatility of the products, including sulfides (thioethers), the structure of which is found in biologically and pharmacologically active compounds.[1] Thiols (mercaptans) are one of the more popular sulfidation reagents, and a variety of synthetic methods that use them for C–S bond formation have been developed.[2] Typically, *C*-sulfidation reactions that use thiols involve the substitution of alkyl halides or pseudo-halides by "RS" nucleophiles, which is known as a Williamson-type sulfide synthesis.[3] The coupling of aryl or alkenyl halides with thiols by using transition metals, an Ullmann-type reaction, is also known as a powerful strategy for thioether preparation, particularly an C_{aryl}-sulfidation.[4] The addition of the S–H bond of thiols to unsaturated C–C bonds of alkenes,[5] alkynes,[6] or allenes[7] is another procedure that is used for thioether formation. This type of reaction offers one of the most efficient routes to prepare sulfides in terms of atom economy.

Carbonyl compounds can also be employed as substrates for thioetherification reactions with thiols. Recently, decarboxylative C–S cross-coupling reactions between carboxylic acids and thiols with a transition-metal catalyst were developed to form thioethers.[8] Several research groups have employed a reductive approach to thioethers by using thiols and carbonyl compounds, such as aldehydes[9] or ketones.[10] In 2012, we reported that carboxylic acids are also available for this type of transformation when used with an indium/hydrosilane reducing system.[11] In this reaction, a variety of aromatic/aliphatic carboxylic acids can be used to produce sulfides, which are formed from the corresponding O,S- or S,S-acetal key intermediates (Figure 1). On the basis of a plausible mechanism of the reaction, we envision using esters as substrates for a reductive sulfidation reaction with thiols, as similar O,S- or S,S-acetal intermediates could be generated from esters. To the best of our knowledge, this reductive approach to thioethers from esters and thiols is unexplored.

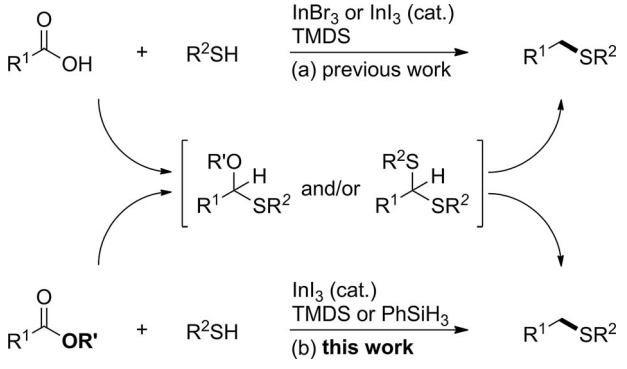

Figure 1. Reductive preparation of sulfides from (a) carboxylic acids with thiols and (b) esters with thiols.

We disclose, herein, the full details of a new reductive catalytic construction of thioethers from esters and thiols. This present reaction is efficiently promoted by InI_3 with either 1,1,3,3-tetramethyldisilazane (TMDS) or $PhSiH_3$ as a reducing reagent to afford a variety of sulfides from aromatic/aliphatic carboxylic acid esters and aryl/alkyl thiols (Figure 1). In addition, several mechanistic investigations have suggested that either an O,S- or S,S-acetal is formed during the reaction as an intermediate, and a negative slope in the Hammett plot indicates the existence of a cationic intermediate in the rate-limiting step.

Results and Discussion

1. Aromatic Esters and Aromatic Thiols as Substrates

The optimization of the reaction conditions for the sulfidation was carried out by using methyl benzoate and *p*-toluenethiol (1.2 equiv.) as model substrates in 1,2-dichloroethane (1,2-DCE)

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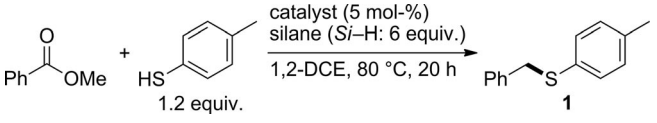
at 80 °C. First, we screened for the hydrosilane in the reaction (Table 1). When $InBr_3$ was combined with Et_3SiH, the sulfidation was ineffective (Table 1, Entry 1). When hydrosilanes such as Me_2PhSiH and $MePh_2SiH$ were used, the desired thioether **1** was formed in low yield (Table 1, Entries 2 and 3). However, thioether **1** was obtained in a 41 % yield when $PhSiH_3$ was employed in the reaction (Table 1, Entry 4). Interestingly, when the hydrosiloxane 1,1,3,3-tetramethyldisiloxane (TMDS) was used as the reducing reagent, thioether **1** was obtained in 86 % yield (Table 1, Entry 5). Next, change of the Lewis acid to aluminum bromide did not result in the desired sulfidation reaction (Table 1, Entry 6).[12] Also, zinc bromide had a lower catalytic activity than indium bromide (Table 1, Entry 7). Using the nonpolar solvent toluene in the sulfidation reaction provided thioether **1** in a 72 % yield (Table 1, Entry 8), whereas using acetonitrile did not allow for the expected sulfidation to proceed and resulted in the recovery of the starting ester (Table 1, Entry 9). Gratifyingly, the use of InI_3, a stronger Lewis acid, improved the product yield to 89 % without the recovery of the starting ester (Table 1, Entry 10). Moreover, when the amount of TMDS was increased to 8 equiv. (*Si*–H), the amount of thioether **1** increased to an almost quantitative yield (Table 1, Entry 11).

Table 1. Optimization for reductive condensation of an ester with a thiol.[a]

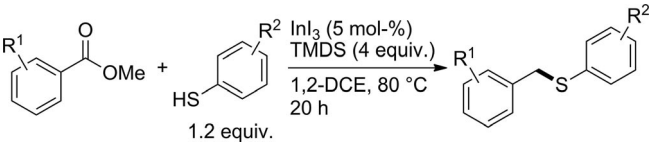


Entry	Catalyst	Silane	Conversion [%][b]	Yield [%][b]
1	$InBr_3$	Et_3SiH	48	0
2	$InBr_3$	Me_2PhSiH	74	18
3[c]	$InBr_3$	$MePh_2SiH$	70	6
4	$InBr_3$	$PhSiH_3$	70	41
5	$InBr_3$	TMDS	86	86
6	$AlBr_3$	TMDS	11	0
7	$ZnBr_2$	TMDS	24	20
8[c]	$InBr_3$	TMDS	77	72
9[d]	$InBr_3$	TMDS	<1	0
10	InI_3	TMDS	>99	89
11[e]	InI_3	TMDS	>99	96 (90)[f]

[a] Reagents and conditions: methyl benzoate (0.6 mmol), *p*-toluenethiol (0.72 mmol), InI_3 (0.03 mmol), TMDS (1.8 mmol), 1,2-DCE (0.6 mL), 80 °C, 20 h. [b] Determined by GC analysis. [c] Toluene was used as the solvent. [d] MeCN was used as the solvent at 60 °C. [e] TMDS (*Si*–H, 8 equiv.) was used. [f] Isolated yield in parentheses.

To expand the generality of the sulfidation, the reaction was then carried out with various aromatic esters and aromatic thiols under the optimal conditions (Table 2). The reaction of methyl benzoate with *p*-methoxybenzenethiol gave the corresponding thioether **2** in 72 % yield (Table 2, Entry 1). On the other hand, the use of *p*-chlorobenzenethiol led to thioether **3** in a decreased yield (Table 2, Entry 2). Bromo-substituted benzenethiols were also employed, but the reaction with the *ortho*-substituted derivative was more influenced by steric factors than that of the *para*-substituted benzenethiol (Table 2, Entries 3 and 4). A substituent on the benzene ring of the methyl benzoate had only a slight effect on the transformation, and corresponding thioethers **6**–**8** were produced in relatively good yields (Table 2, Entries 5–7). Also, methyl benzoates that contain a chlorine atom gave thioethers **9**–**11** in moderate yields, regardless of the position of the chloro group, whereas the use of *o*-bromobenzoate led to a decrease in the yield of **12** (Table 2, Entries 8–11). Ethyl benzoate with an iodine atom at the *para* position was also compatible with the reaction and produced thioether **13** in 66 % yield (Table 2, Entry 12). However, the sulfidation reaction with methyl *o*-iodobenzoate led to a low conversion into thioether **14** along with a 16 % generation of sulfide **1**, which indicates that deiodination had occurred as a side reaction (Table 2, Entry 13). When the reaction was carried out with aromatic esters that have the strong electron-withdrawing trifluoromethyl group, the formation of the corresponding thioether **15** was rather low (Table 2, Entry 14).

Table 2. Reaction of methyl benzoates with aryl mercaptans.[a]

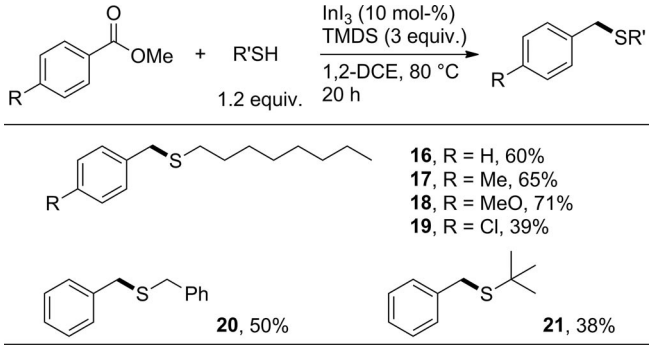


Entry	R^1	R^2	Product	Yield [%][b]
1	H	*p*-MeO	**2**	72
2	H	*p*-Cl	**3**	29
3	H	*p*-Br	**4**	68
4	H	*o*-Br	**5**	36
5	*p*-Me	*p*-Me	**6**	81
6	*p*-MeO	*p*-Me	**7**	72
7	*m*-PhO	*p*-Me	**8**	67
8	*p*-Cl	*p*-Me	**9**	60
9	*m*-Cl	*p*-Me	**10**	55
10	*o*-Cl	*p*-Me	**11**	57
11	*o*-Br	*p*-Me	**12**	34
12[c]	*p*-I	*p*-Me	**13**	66
13	*o*-I	*p*-Me	**14**	35[d]
14	*p*-CF_3	*p*-Me	**15**	40

[a] Reagents and conditions: methyl ester (0.6 mmol), thiol (0.72 mmol), InI_3 (0.03 mmol), TMDS (2.4 mmol), 1,2-DCE (0.6 mL), 80 °C, 20 h. [b] Isolated yields. [c] An ethyl ester was used as a substrate. [d] Deiodination occurred as a side reaction, and product **1** was also generated in a 16 % GC yield.

2. Aromatic Esters and Aliphatic Thiols as Substrates

The sulfidation of aromatic esters with aliphatic thiols, instead of aromatic thiols, was examined next (Scheme 1). For instance, when methyl benzoate was treated with 1-octanethiol under our optimized reaction conditions, the desired thioether **16** was obtained in 60 % yield. The reactions between esters that contain an electron-donating group such as a methyl or methoxy group and octanethiol gave thioethers **17** and **18** in good yields. On the other hand, when methyl *p*-chlorobenzoate was used, the yield of thioether **19** decreased to 39 %. As an extension, benzylthiol (benzyl mercaptan) or *tert*-butylthiol (*tert*-butyl mercaptan) gave expected thioethers **20** and **21** in 50 and 38 % yield, respectively.

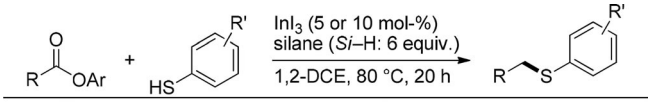


Scheme 1. Reaction of methyl benzoates with alkyl mercaptans. Regents and conditions: methyl ester (0.6 mmol), thiol (0.72 mmol), InI_3 (0.06 mmol), TMDS (1.8 mmol), 1,2-DCE (0.6 mL), 80 °C, 20 h.

3. Aliphatic Esters and Aromatic Thiols as Substrates

The sulfidation reaction between aliphatic esters and aromatic thiols was then investigated (Table 3). On the basis of the previous results, we conducted the reaction of methyl 3-phenylpropionate with *p*-toluenethiol under the optimal conditions, and, contrary to our expectations, the formation of the desired thioether **22** was not observed (see Table S1). We then anticipated that the aryl esters of an aliphatic acid could be employed, as aryloxy is a better leaving group than methoxy. After investigating the reaction conditions several times, we found that with regard to the aryl esters of 3-phenylpropionic acid, the use of either *p*-chlorophenyl ester and $PhSiH_3$ (conditions A) or phenyl ester and TMDS (conditions B) effectively improved the sulfidation reaction and gave corresponding thioether **22** in yields of 76 and 74 % (Table 3, Entries 1 and 2), respectively.

Table 3. Reaction of aliphatic esters with aryl mercaptans.[a]



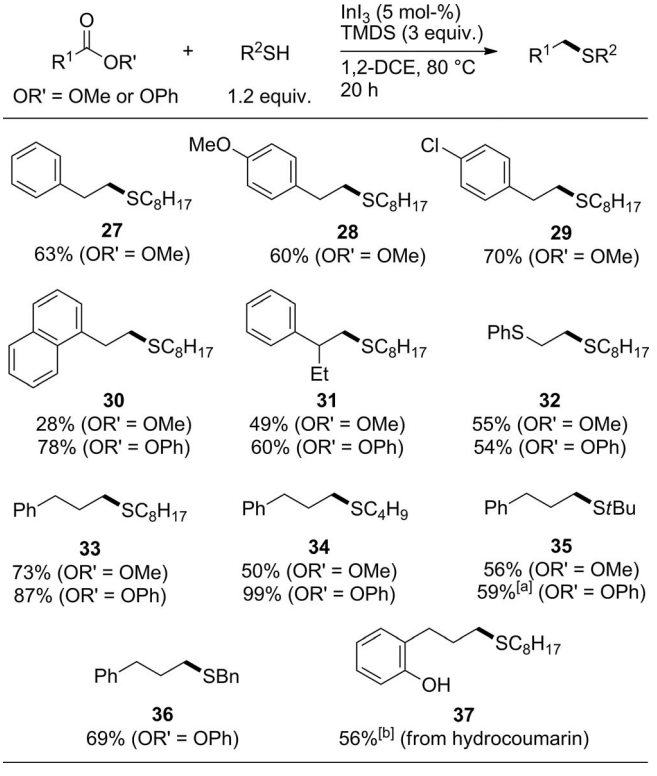
Entry	Conditions	Product	Yield [%][b]
1	A	**22**	76
2	B		74
3	A	**23**	44[c]
4	B		63
5	A	**24**	92
6	B		34
7	A	**25**	88
8	B		29[c]
9	A	**26**	59
10	B		57

[a] Reagents and conditions A: *p*-chlorophenyl ester (ArO = *p*-ClC_6H_4O, 0.6 mmol), thiol (0.72 mmol), InI_3 (0.06 mmol), $PhSiH_3$ (1.2 mmol), 1,2-DCE (0.6 mL), 80 °C, 20 h. Reagents and conditions B: phenyl ester (ArO = PhO, 0.6 mmol), thiol (0.72 mmol), InI_3 (0.03 mmol), TMDS (1.8 mmol), 1,2-DCE (0.6 mL), 80 °C, 20 h. [b] Isolated yields. [c] NMR yield.

In the case of *p*-methoxybenzenethiol, the expected product **23** was formed in moderate yield under both reaction conditions (Table 3, Entries 3 and 4). On the other hand, when benzenethiols with a bromine atom at either the *para* or *ortho* position were subjected to conditions A, the yields of sulfides **24** and **25** highly improved to 92 and 88 % yield, respectively (Table 3, Entries 5 and 7). In contrast, using conditions B resulted in remarkably decreased yields of the same sulfides (Table 3, Entries 6 and 8). Aryl esters that have a naphthyl group on the aliphatic acid portion were also subjected to both sets of reaction conditions to give the corresponding thioether **26** in yields of 59 and 57 %, respectively (Table 3, Entries 9 and 10).

4. Aliphatic Esters and Aliphatic Thiols as Substrates

The one-pot preparation of thioether derivatives from the methyl or phenyl aliphatic esters and aliphatic thiols was then investigated as another application (Scheme 2). In most cases, the desired sulfidation reaction proceeded smoothly to produce the corresponding thioethers in good to excellent yields. The reactions of the phenylacetic acid ester derivatives with 1-octanethiol gave the desired thioethers **27**–**30** in yields of 28–78 %. In addition, the esters of an aliphatic acid that contains a branched carbon chain or PhS moiety were employed to the sulfidation with 1-octanethiol to afford **31** and **32**. Combinations of 3-phenylpropionic acid esters with several aliphatic thiols gave sulfides **33**–**36** in relatively good yields. When the

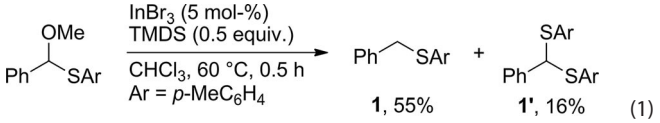


Scheme 2. Reaction of aliphatic esters with alkyl mercaptans. Reagents and conditions: ester (0.6 mmol), thiol (0.72 mmol), InI_3 (0.03 mmol), TMDS (1.8 mmol), 1,2-DCE (0.6 mL), 80 °C, 20 h. [a] GC yield. [b] $InBr_3$ (5 mol-%) and TMDS (1.8 mmol) were employed over 4 h.

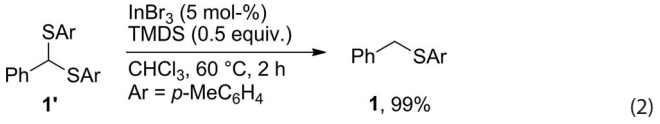
cyclic ester hydrocoumarin was used as the substrate, $InBr_3$ functioned as a better catalyst than InI_3 to give ring-opened sulfide **37**. Unfortunately, this sulfidation approach could not be applied to an ester such as methyl cinnamate, which has a conjugated alkene system.

5. Mechanistic Studies of the Reductive Thioetherification

Our 2012 report of an indium-catalyzed reductive thioetherification of carboxylic acids with thiols revealed the reaction intermediates to be either O,S- or S,S-acetals.[11] The same mechanism is expected to generate similar intermediates from esters. To further understand this transformation, several control experiments were conducted with either the O,S- or S,S-acetal as the starting substrate. The reaction of a benzylic O,S-acetal with 0.5 equiv. of TMDS in $CHCl_3$ in the presence of a catalytic amount of $InBr_3$, a weaker Lewis acid than InI_3, at 60 °C for 0.5 h produced thioether **1** and the corresponding S,S-acetal **1′** in 55 and 16 % yield, respectively [Equation (1)]. Thioether **1** was also smoothly generated in quantitative yield from S,S-acetal **1′** and an $InBr_3$/TMDS system [Equation (2)].

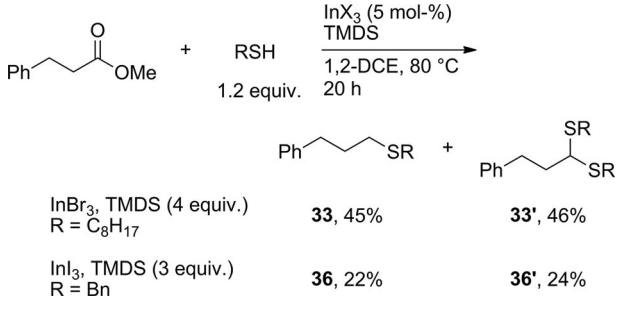


(1)



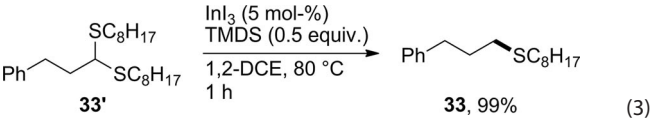
(2)

Similar studies were then conducted by using a combination of 3-phenylpropionic acid ester and an alkylthiol. Consequently, both the corresponding S,S-acetal **33′** and **36′** along with thioether **33** and **36**, respectively, were observed under the standard reaction conditions (Scheme 3). Moreover, the reductive conversion of S,S-acetal **33′** into thioether **33** proceeded smoothly by using an InI_3/TMDS system [Equation (3)]. These results strongly indicate that O,S- and S,S-acetals are relevant intermediates.



Scheme 3. Control experiments.

To further explore the reaction mechanism, the relative rates for the reductive sulfidation reactions of several *p*-substituted



(3)

methyl benzoates with *p*-toluenethiol in the presence of InI_3 and TMDS in $CDCl_3$ were determined by ^1H NMR spectroscopic analysis. The results (Hammett plot) appear in Figure 2, and the negative ρ value ($\rho = -1.31$) implies that a cationic intermediate is involved in the rate-limiting step.

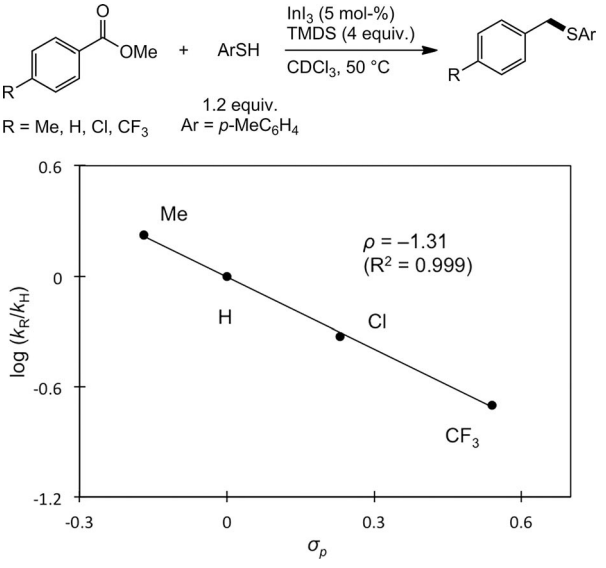
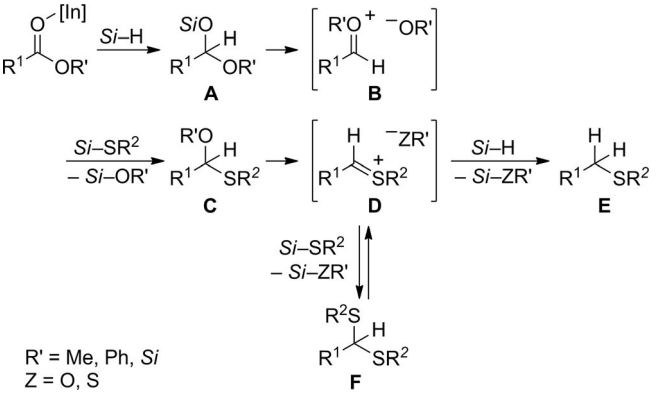


Figure 2. Hammet plot for the InI_3-catalyzed reductive sulfidation of the *p*-substituted methyl benzoates p-$RC_6H_4CO_2Me$ (R = Me, H, Cl, CF_3).

A plausible pathway is shown in Scheme 4. The observation of S,S-acetals and the reactivity of both O,S- and S,S-acetals suggest that these species constitute the intermediates in this sulfidation reaction series. These intermediates can be formed by the initial hydrosilylation of the ester activated by an indium compound to produce silyl acetal **A**. The elimination of an alkoxide anion from the acetal proceeds to generate the corresponding intermediate **B**, which undergoes a substitution with a thiosilane, generated from a thiol and hydrosilane, to produce O,S-acetal **C**.[13] The departure of the alkoxide leaving group



Scheme 4. Plausible reaction mechanism.

from acetal **C** produces cationic intermediate **D**, which can proceed through two possible reaction pathways: (1) one leads to final sulfide **E** by a second hydrosilylation and (2) the other leads to S,S-acetal **F** through the thiosilane. Either cationic intermediate **B** or **D** can appear in the rate-limiting step on the basis of the negative slope of the Hammett plot.

Conclusions

We have demonstrated an unprecedented sulfidation reaction between esters and thiols through a new reductive system. Compared with conventional methods for sulfidation, our developed procedure uses easily handled reagents, such as esters, indium iodide, and a hydrosilane, and enables a practical and straightforward sulfidation under milder reaction conditions. Methyl benzoates that contain a methyl, methoxy, halogen, or trifluoromethyl group can tolerate the present reduction system, with the exception of methyl 2-iodobenzoate. The approach can be applied to not only aromatic esters and aromatic thiols but also aliphatic esters and aliphatic thiols. Moreover, the use of aryl esters, instead of methyl esters, led to an increase in product yields and the elimination of thioacetal byproducts. Work regarding further applications of this method and a further explanation of the reaction mechanism is ongoing in our laboratory.

Experimental Section

General Methods: All reactions were carried out under N_2, unless otherwise noted. 1,2-Dichloroethane was freshly distilled from P_2O_5 prior to use. All indium compounds were commercially available and used without further purification. The hydrosilanes were used without further purification. The reaction progress was monitored by TLC analysis of reaction aliquots. Column chromatography was performed with silica gel. The ^{1}H NMR spectroscopic data were recorded at 500 (or 300) MHz with tetramethylsilane as an internal standard (δ = 0.00 ppm). The ^{13}C NMR spectroscopic data were measured at 125 (or 75) MHz by using the center peak of deuterated chloroform (δ = 77.0 ppm) as the internal standard. High-resolution mass spectra were measured by using NBA (3-nitrobenzyl alcohol) as a matrix.

General Procedure for the Synthesis of Sulfides from Aromatic Esters and Aromatic Thiols: To a freshly distilled 1,2-dichloroethane solution (0.60 mL) in a screw-capped vial under N_2 were successively added a magnetic stir bar, an aromatic ester (0.60 mmol), an aromatic thiol (0.72 mmol), InI_3 (0.030 mmol, 15 mg), and TMDS (2.4 mmol, 4.2×10^2 μL). The vial was sealed with a cap that contained a polytetrafluoroethylene (PTFE) septum. The reaction mixture was heated at 80 °C (bath temperature), and the progress was monitored by TLC analysis until the starting carboxylic acid was consumed. Upon completion, the reaction was quenched with H_2O (3.0 mL), and the aqueous layer was extracted with $CHCl_3$ (3 × 5.0 mL). The combined organic phases were dried with anhydrous Na_2SO_4, filtered, and then concentrated under reduced pressure. The crude product was purified by silica gel column chromatography (hexane/AcOEt, 99:1) to give the corresponding sulfide.

***p*-Iodobenzyl *p*-Tolyl Sulfide (13):** ^{1}H NMR (500.2 MHz, $CDCl_3$): δ = 2.30 (s, 3 H), 3.96 (s, 2 H), 6.97 (d, *J* = 8.5 Hz, 2 H), 7.06 (d, *J* = 8.5 Hz, 2 H), 7.57 (d, *J* = 8.5 Hz, 2 H) ppm. ^{13}C NMR (125.8 MHz, $CDCl_3$): δ = 21.0, 39.3, 92.4, 129.7, 130.7, 131.0, 131.7, 136.9, 137.6 ppm. HRMS (EI): calcd. for $C_{14}H_{13}IS$ $[M]^+$ 339.9783; found 339.9778.

4-Methoxyphenyl 3-Phenylpropyl Sulfide (23): ^{1}H NMR (500.2 MHz, $CDCl_3$): δ = 1.89 (quint, *J* = 7.5 Hz, 2 H), 2.72 (t, *J* = 7.5 Hz, 2 H), 2.81 (t, *J* = 7.5 Hz), 3.78 (s, 3 H), 6.83 (d, *J* = 8.5 Hz, 2 H), 7.14–7.19 (m, 3 H), 7.26 (t, *J* = 7.5 Hz, 2 H), 7.32 (d, *J* = 8.5 Hz, 2 H) ppm. ^{13}C NMR (125.8 MHz, $CDCl_3$): δ = 30.7, 34.5, 35.1, 55.3, 114.5, 125.9, 126.4, 128.3, 128.4, 133.1, 141.4, 158.8 ppm. HRMS (EI): calcd. for $C_{16}H_{18}OS$ $[M]^+$ 258.1078; found 258.1079.

2-Bromophenyl 3-Phenylpropyl Sulfide (25): ^{1}H NMR (500.2 MHz, $CDCl_3$): δ = 2.02 (quint, *J* = 7.5 Hz, 2 H), 2.79 (t, *J* = 7.5 Hz, 2 H), 2.92 (t, *J* = 7.5 Hz, 2 H), 6.70 (t, *J* = 7.5 Hz, 1 H), 7.14 (d, *J* = 8.0 Hz, 1 H), 7.18–7.24 (m, 4 H), 7.29 (t, *J* = 7.5 Hz, 2 H), 7.53 (d, *J* = 8.0 Hz, 1 H) ppm. ^{13}C NMR (125.8 MHz, $CDCl_3$): δ = 29.9, 32.0, 34.7, 123.3, 126.1, 126.3, 127.64, 127.65, 128.4, 128.5, 132.9, 138.1, 141.0 ppm. HRMS (EI): calcd. for $C_{15}H_{15}BrS$ $[M]^+$ 306.0078; found 306.0076.

2-(*p*-Methoxyphenyl)ethyl Octyl Sulfide (28): ^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.88 (t, *J* = 7.5 Hz, 3 H), 1.27–1.38 (m, 10 H), 1.58 (quint, *J* = 7.5 Hz, 2 H), 2.52 (t, *J* = 7.5 Hz, 2 H), 2.73 (t, *J* = 7.5 Hz, 2 H), 2.82 (t, *J* = 7.5 Hz, 2 H), 3.78 (s, 3 H), 6.84 (d, *J* = 8.5 Hz, 2 H), 7.12 (d, *J* = 8.5 Hz, 2 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 14.1, 22.6, 28.9, 29.17, 29.18, 29.6, 31.8, 32.3, 33.9, 35.4, 55.2, 113.8, 129.4, 132.8, 158.0 ppm. HRMS (EI): calcd. for $C_{17}H_{28}OS$ $[M]^+$ 280.1861; found 280.1860.

2-(*p*-Chlorophenyl)ethyl Octyl Sulfide (29): ^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.88 (t, *J* = 7.0 Hz, 3 H), 1.27–1.36 (m, 10 H), 1.57 (quint, *J* = 7.5 Hz, 2 H), 2.51 (t, *J* = 7.0 Hz, 2 H), 2.74 (t, *J* = 7.5 Hz, 2 H), 2.85 (t, *J* = 7.5 Hz, 2 H), 7.13 (d, *J* = 8.5 Hz, 2 H), 7.26 (d, *J* = 8.5 Hz, 2 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 14.1, 22.6, 28.9, 29.2, 29.6, 31.8, 32.3, 33.5, 35.6, 128.5, 129.8, 132.0, 139.0 ppm. HRMS (EI): calcd. for $C_{16}H_{25}ClS$ $[M]^+$ 284.1365; found 284.1361.

2-(1-Naphthyl)ethyl Octyl Sulfide (30): ^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.88 (t, *J* = 7.0 Hz, 3 H), 1.27–1.37 (m, 10 H), 1.57 (quint, *J* = 7.5 Hz, 2 H), 2.51 (t, *J* = 7.0 Hz, 2 H), 2.74 (t, *J* = 7.5 Hz, 2 H), 2.85 (t, *J* = 7.5 Hz, 2 H), 7.13 (d, *J* = 8.5 Hz, 2 H), 7.26 (d, *J* = 8.5 Hz, 2 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 14.1, 22.6, 28.9, 29.17, 29.18, 29.7, 31.8, 32.4, 32.9, 33.7, 123.4, 125.50, 125.52, 126.0, 126.3, 127.1, 128.9, 131.6, 133.9, 136.7 ppm. HRMS (EI): calcd. for $C_{20}H_{28}S$ $[M]^+$ 300.1912; found 300.1913.

Octyl 2-Phenylbutyl Sulfide (31): ^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.79 (t, *J* = 7.0 Hz, 3 H), 0.88 (t, *J* = 7.0 Hz, 3 H), 1.25–1.32 (m, 10 H), 1.51 (quint, *J* = 7.5 Hz, 2 H), 1.57–1.63 (m, 1 H), 1.88–1.93 (m, 1 H), 2.40 (t, *J* = 7.5 Hz, 2 H), 2.62–2.68 (m, 1 H), 2.73–2.80 (m, 2 H), 7.17–7.23 (m, 3 H), 7.29–7.32 (m, 2 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 12.0, 14.1, 22.6, 28.3, 28.9, 29.2, 29.6, 31.8, 32.8, 39.1, 48.0, 126.4, 127.6, 128.3, 144.2 ppm. HRMS (FAB): calcd. for $C_{18}H_{31}S$ $[M]^+$ 279.2146; found 279.2142.

2-(Octylthio)ethyl Phenyl Sulfide (32): ^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.88 (t, *J* = 7.5 Hz, 3 H), 1.26–1.35 (m, 10 H), 1.54 (quint, *J* = 7.5 Hz, 2 H), 2.52 (t, *J* = 7.5 Hz, 2 H), 2.70–2.74 (m, 2 H), 3.08–3.11 (m, 2 H), 7.20 (t, *J* = 7.5 Hz, 1 H), 7.29 (t, *J* = 8.0 Hz, 2 H), 7.36 (d, *J* = 8.0 Hz, 2 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 14.1, 22.6, 28.8, 29.1, 29.6, 31.4, 31.8, 32.0, 33.9, 126.4, 129.0, 129.8, 135.4 ppm. HRMS (EI): calcd. for $C_{16}H_{26}S$ $[M]^+$ 282.1476; found 282.1495.

General Procedure for the Synthesis of Methyl Esters: A carboxylic acid (5 mmol), sulfuric acid (1 mL), and a magnetic stir bar were successively added to distilled methanol (20 mL). The solution was stirred and heated at reflux for 2 h. Upon completion of the reaction, the solution was neutralized with an aqueous $NaHCO_3$ so-

lution. The aqueous layer was extracted with AcOEt (10 mL), and the organic phase was dried with anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure to afford the corresponding methyl ester.

General Procedure for the Synthesis of Phenyl Esters: A carboxylic acid (5 mmol), phenol (5.0 mmol, 4.7×10^2 mg), 4-(dimethylamino)pyridine (5.0 mmol, 7.6×10 mg), and a magnetic stir bar were successively added to distilled 1,2-dichloromethane. *N*,*N*′-Dicyclohexylcarbodiimide (5.0 mmol, 1.0×10^3 mg) was added, and the solution was stirred at 0 °C to room temperature overnight. Upon completion of the reaction, the mixture was filtered, and the filtrate was then concentrated under reduced pressure. The crude product was purified by silica gel column chromatography (hexane/AcOEt, 9:1) to afford the corresponding phenyl ester.

Synthesis of the O,S-Acetal [Methoxy(*p*-tolylthio)methyl]benzene: To freshly distilled toluene (0.5 mL) in a screw-capped vial under N_2 were successively added a magnetic stirrer bar, LiBr (0.40 mmol, 3.5×10 mg), benzaldehyde dimethyl acetal (2.0 mmol, 3.0×10^2 mg), and *p*-toluenethiol (2.6 mmol, 3.2×10^2 mg). The contents of the vial were stirred at room temperature for 25 h. Upon completion of the reaction, the solution was neutralized with an aqueous NaOH solution. The aqueous layer was extracted with AcOEt (10 mL), and the organic phase was dried with anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The crude product was purified by silica gel column chromatography (hexane/AcOEt, 99:1) to give the corresponding O,S-acetal, [methoxy(*p*-tolylthio)methyl]benzene. ^{1}H NMR (500.2 MHz, $CDCl_3$): δ = 2.30 (s, 3 H), 3.51 (s, 3 H), 5.65 (s, 1 H), 7.03 (d, J = 8.0 Hz, 2 H), 7.22–7.27 (m, 7 H) ppm. ^{13}C NMR (125.8 MHz, $CDCl_3$): δ = 21.1, 56.5, 91.4, 126.2, 127.8, 128.0, 129.1, 129.4, 134.1, 137.9, 139.4 ppm. HRMS (EI): calcd. for $C_{14}H_{13}S$ [M – CH_3O]$^+$ 213.0738; found 213.0746.

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[12] When the model reaction shown in Scheme 1 was carried out with other Lewis acids, such as $B(C_6F_5)_3$ and $CuBr_2$, the expected sulfide was obtained in small amounts. Also, when $FeCl_3$ was used, the sulfidation did not proceed.

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