Studies on Novel Sulfidation from Carbonyl Compounds and Organosulfur Compounds Using an Indium Compound and a Hydrosilane and Its Applications

(インジウム化合物とヒドロシランによるカルボニル化合物と有機硫黄化合物を用いた新規スルフィド合成法とその応用に関する研究)

東京理科大学大学院　理工学研究科
工業化学専攻　博士後期課程

宮﨑　隆弘

Preface

The studies presented in this thesis have carried out under the direction of Associate Professor Dr. Norio Sakai at the Department of Pure and Applied Chemistry, Faculty of Science and Technology, Tokyo University of Science (RIKADAI) during 2010-2016.

The objects of this thesis are the studies on novel sulfidation from carbonyl compounds and organosulfur compounds using an indium compound and a hydrosilane and its applications. The author hopes that this basic work described in this thesis contributes to the further development of novel indium(III)-catalyzed reductive sulfidation in organic chemistry, pharmaceutical chemistry, and material science.

Takahiro Miyazaki

Department of Pure and Applied Chemistry

Faculty of Science and Technology

Tokyo University of Science (RIKADAI)

2016

Contents

Chapter 1. General Introduction • **5**

Chapter 2. Indium-Catalyzed Reductive Sulfidation from Carboxylic Acid Derivatives and Thiols • **9**

2-1. Reductive Sulfidation from Carboxylic Acids and Thiols

2-2. Reductive Sulfidation from Esters and Thiols

2-3 Reaction Mechanism

Chapter 3. Reductive Conversion to Benzyl Sulfides from Aromatic Acid or Benzaldehydes with Elemental Sulfur • **46**

3-1. Reductive Conversion from Carboxylic Acids and Elemental Sulfur

3-2. Reductive Conversion from Benzaldehydes and Elemental Sulfur

3-3. Reductive Conversion from Benzyl Alcohols and Elemental sulfur

3-4. Reaction Mechanism

Chapter 4. Conclusion • **60**

List of Publication • **61**

Acknowledgment • **62**

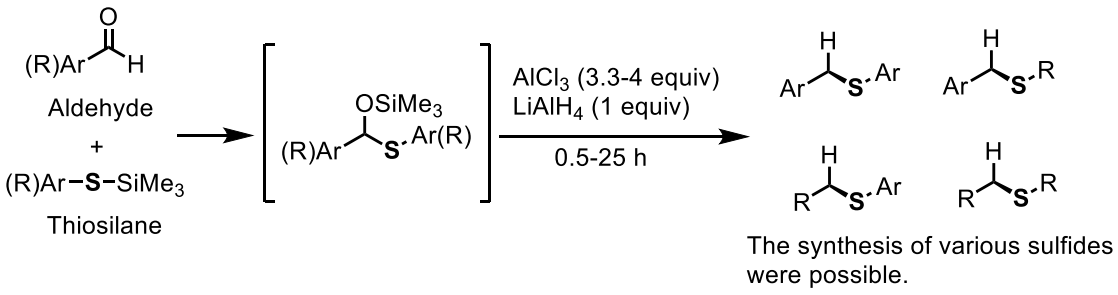
Abbreviations

TMDS	1,1,3,3-tetramethyldisiloxane, $\{Me_2Si(H)OSi(H)Me_2\}$
1,2-DCE	1,2-dichloroethane, $ClCH_2CH_2Cl$

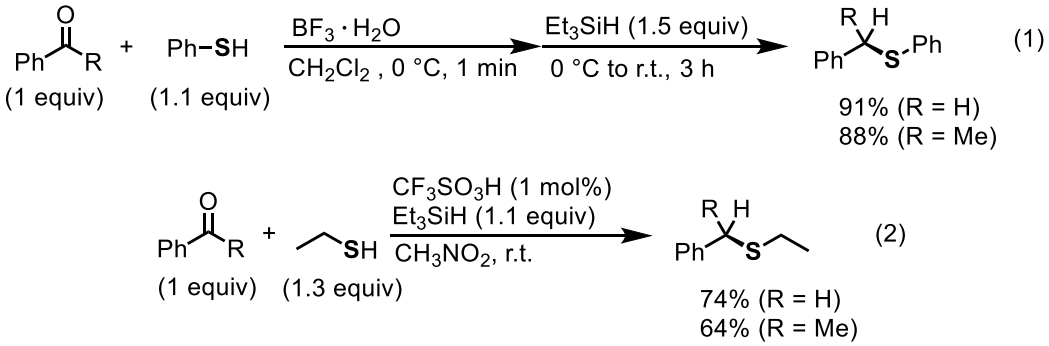
Chapter 1.
General Introduction

General

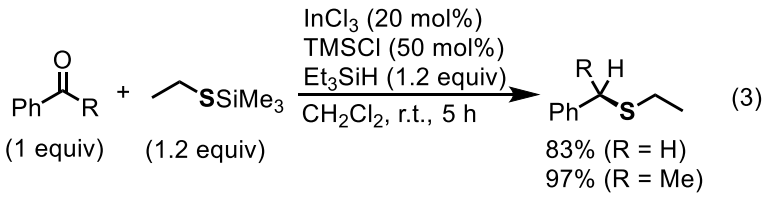
Sulfides have been demonstrated that they show biological activities and pharmacological activities for HIV,[1a] Alzheimer disease,[1b] and cancer.[1c] Also, sulfides were utilized as synthetic intermediates for the natural product synthesis.[2] Therefore, the development of a convenient and an efficient sulfide synthesis is one of the important subjects. For the sulfide synthesis, the sulfidations using thiols as sulfur sources have been reported such as the Williamson-synthesis,[3] the C-S coupling reaction,[4] and the addition of thiols to unsaturated carbon-carbon bond.[5] As another approach to sulfides, Glass reported the first example of a reductive sulfidation using aldehydes and thiosilanes.[6] Since reductive sulfidation could be applied to not only aromatic and aliphatic aldehydes but also aromatic and aliphatic thiosilanes, the synthesis of a variety of sulfides was possible.



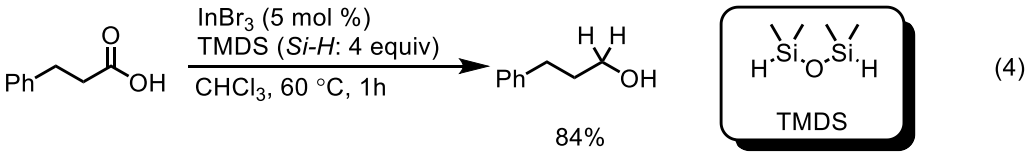
Instead of ignitable $LiAlH_4$, Et_3SiH as a stable hydrosilane has been utilized for the sulfidation. For example, Olar *et al*. reported a two-step conversion from an aldehydes or ketones and a thiols to sulfides by using a mixture of $BF_3•H_2O$ and Et_3SiH (Eq. 1).[7] Recently, Roth *et al*. accomplished an one-step synthesis of sulfides using a catalytic amount of CF_3SO_3H (Eq. 2).[8] However, these reactions reqired to use severe reaction conditions involving a strong acid.



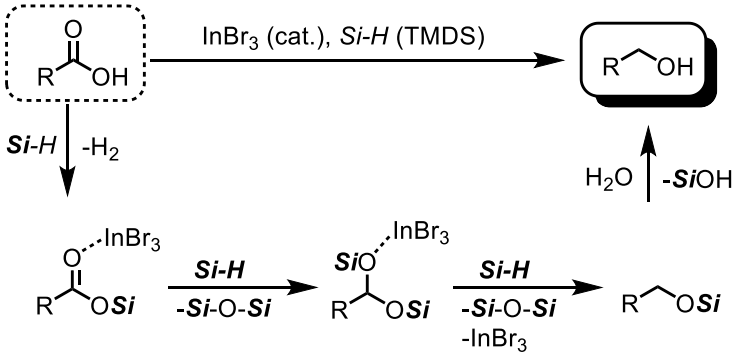
On the other hand, Mukaiyama and co-workers found a milder reductive sulfidation using catalytic amounts of $InCl_3$ and TMSCl (Eq. 3).[9] Since an indium halide showed low heterophilicity toward an oxygen, a nitrogen, and a sulfur atom, it could efficiently function as catalysts.



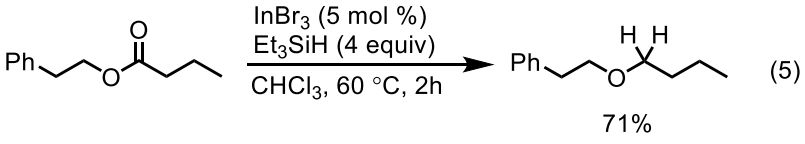
In this context, our group reported an indium-catalyzed reductive conversion of carboxylic acids[10] to alcohols respectively (Eq. 4). Contrary to conventional methods using $LiAlH_4$, the indium-catalyzed reduction used milder hydrosilanes.



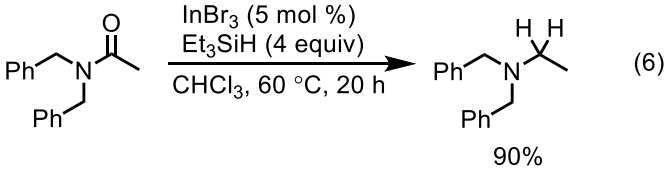
The reason for the reduction proceeded under a mild conditions was unclear. Our group assumed that a carboxylic acid was converted into a silylester and a carbonyl group on the formed silylester was activated by $InBr_3$ to produce a silyl acetal. The silylacetal interacted with $InBr_3$ to form a silylether, which underwent hydrolysis to produce a corresponding alcohol.



As applications, our group reported the selective reduction of esters[11] or amides[12] using an indium halide and a hydrosilane. For example, an ester was treated with an $InBr_3$ catalyst and Et_3SiH, an ether was obtained (Eq. 5). By using similar conditions, a conversion of an amide into an amine was accomplished. These results indicated that the reductive system was compatible with hetero atoms (Eq. 6).

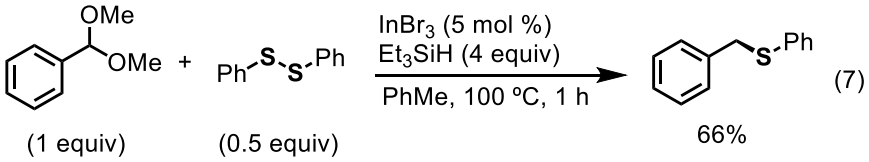


(5)



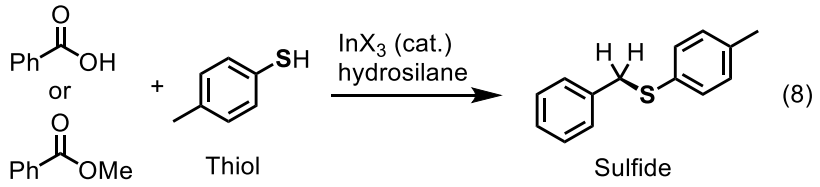
(6)

Also, we found that $InBr_3$ activated both two C-O bonds of an acetal and an S-S bond on a disulfide to afford the corresponding sulfides (Eq. 7).[13]



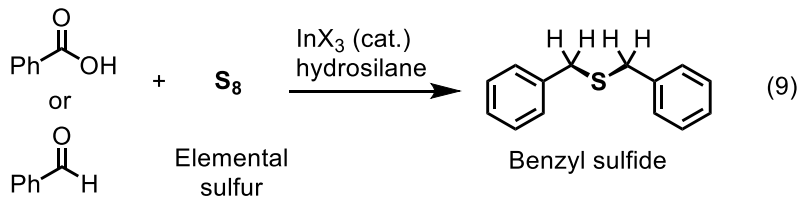
(7)

Based on some examples shown Eq. 7, *Chapter 2* describes a one-step sulfide synthesis from carboxylic acids or its derivatives and thiols using an indium catalyst and a hydrosilane (Eq. 8).



(8)

Chapter 3 deal with the conversion from benzoic acids or benzaldehydes and an elemental sulfur to dibenzyl sulfides (Eq. 9).



(9)

References

(1) (a) Kaldor, S. W.; Kalish, V. J.; Davies, J. F.; Shetty, B. V.; Fritz, J. E.; Appelt, K.; Burgess, J. A.; Campanale, K. M.; Chirgadze, N. Y.; Clawson, D. K.; Dressman, B. A.; Hatch, S. D.; Khalil, D. A.; Kosa, M. B.; Lubbehusen, P. P.; Muesing, M. A.; Patick, A. K.; S. H. Reich.; Su, K. S.; Tatlock, J. H. *J. Med. Chem*. **1997**, *40*, 3979. (b) Liu, G.; Huth, J. R.; Plejniczak, E. T.; Mendoza, R.; DeVries, P.; Leitza, S.; Reilly, E. B.; Okasinski, G. F.; Fesik, S. W.; von Geldern, T. W. *J. Med. Chem*. **2001**, *44*, 1202. (c) De Martino, G.; Edler, M. C.; La Regina, G.; Coluccia, A.; Barbera, M. C.; Barrow, D.; Nicholson, R. I.; Chiosis, G.; Brancale, A.; Hamel, E.; Artico, M.; Silvestri, R. *J. Med. Chem*. **2006**, *49*, 947.

(2) For example see (a) Endo, A.; Yanagisawa, A.; Abe, M.; Tohma, S.; Kan, T.; Fukuyama, T. *J. Am. Chem. Soc*. **2002**, *124*, 6552. (b) Watanabe, H.; Nakada, M. *J. Am. Chem. Soc*. **2008**, *130*, 1150. (c) Takabatake, K.; Nishi, I.; Shindo, M.; Shishido, K. *J. Chem. Soc., Perkin Trans. 1*, **2000**, 1807.

(3) Koval', I. V. *Russ. J. Org. Chem*. **2007**, 43, 319.

(4) Beletskaya, I. P.; Ananikov, V. P. *Chem. Rev*. **2011**, *111*, 1596.

(5) Castarlenas, R.; Di Giuseppe, A.; Pérez-Torrente, J. J.; Oro, L. A. *Angew. Chem. Int. Ed.* **2013**, *52*, 211.

(6) Glass, R. S. *Synth. Commun*. **1976**, *6*, 47.

(7) Olah, G. A.; Wang, Q.; Trivedi, N. J.; Surya Prakash, G. K. *Synthesis* **1992**, 465.

(8) Gellert, B. A.; Kahlcke, N.; Feurer, M.; Roth, S. *Chem. Eur. J*. **2011**, *17*, 12203.

(9) Mukaiyama, T.; Ohno, T.; Nishimura, T.; Han, J. S.; Kobayashi, S. *Bull. Chem. Soc. Jpn.* **1991**, *64*, 2524.

(10) Sakai, N.; Kawana, K.; Ikeda, R.; Nakaike, Y.; Konakahara, T. *Eur. J. Org. Chem*. **2011**, 3178.

(11) Sakai, N.; Moriya, T.; Konakahara, T. *J. Org. Chem.* **2007**, *72*, 5929.

(12) Sakai, N.; Fujii, K.; Konakahara, T. *Tetrahedron Lett*. **2008**, *49*, 6873.

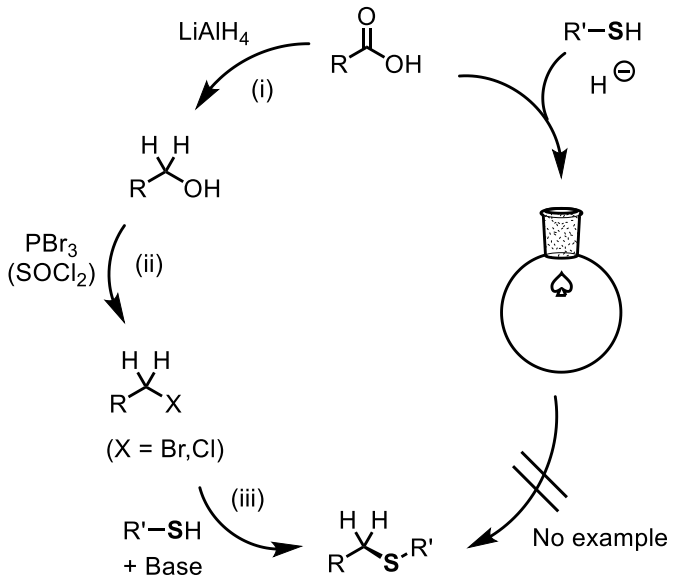
(13) Sakai, N.; Moritaka, K.; Konakahara, T. *Eur. J. Org. Chem*. **2009**, 4123.

Chapter 2.
Indium-Catalyzed Reductive Sulfidation from Carboxylic Acid Derivatives and thiol

Introduction

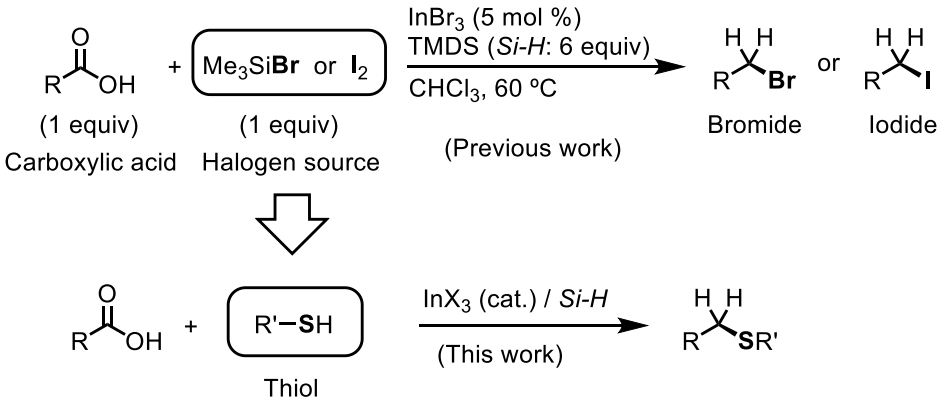
Carboxylic acids are inexpensive, stable in the air and utilized in the Fischer esterification,[1] the Hell-Volhard-Zelinskii reaction,[2] and the Schmidt reaction.[3] Therefore, carboxylic acid is versatile substrates in organic synthesis. Conventional synthesis of sulfides from carboxylic acids, involves the followed 3-reactions, which are :(i) the reduction of a carboxylic acid to an alcohol, (ii) the halogenation of an alcohol to a halide, (iii) the substitution of a halide with a thiol (Scheme 1). We postulated that a one- step reductive sulfidation from carboxylic acids, which has not been reported would reduce the experimental operations involving preparation and purification of the intermediates.

Scheme 1. Conversion of Carboxylic Acids to Sulfides



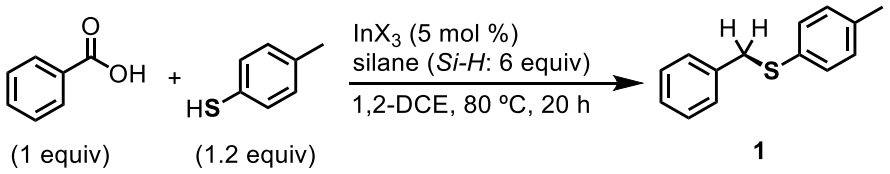
Sakai's group reported on reductive conversion from carboxylic acids to bromides[4] or iodides[5] using TMSBr or I_2 in the presence of a catalytic amount of $InBr_3$ and TMDS (Scheme 2). In this context, the author elucidate that thiols as a nucleophile, instead of halogen sources would react with carboxylic acids to give sulfides. Herein, the details of the experiment are described.

Scheme 2. Indium-Catalyzed Reductive Conversion Using Carboxylic Acids

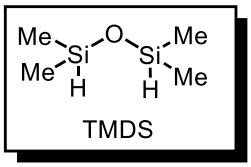


Initially, examinations of reaction conditions were conducted using benzoic acid and *p*-toluenethiol as a model substrate in the presence of 5 mol% of indium (III) halide and 6 equiv (*Si-H*) of a hydrosilane in 1,2-dichloroethane (1,2-DCE) at 80 ºC for 20 h (Table 1). The reaction combined with $InBr_3$ and Et_3SiH did not occurred (entry 1). The use of $PhMe_2SiH$ and $PhSiH_3$ instead of Et_3SiH affored the desired product in moderate yields (entries 2 and 3). Similarly, a more inexpensive hydrosilane, TMDS than $PhSiH_3$ led to high yield (entry 4). When the amount of TMDS was decreased to 4 equiv. (*Si-H*), the yield was slightly reduced (entry 5). Other indium catalysts such as $InCl_3$, $In(OTf)_3$ and $In(OH)_3$, were not effective (entries 6-8). Consequently, it was found that a combination of $InBr_3$ and TMDS effectively promoted the expected sulfidation (entry 4).

Table 1. Screenings of Indium Catalysts and Hydrosilanes



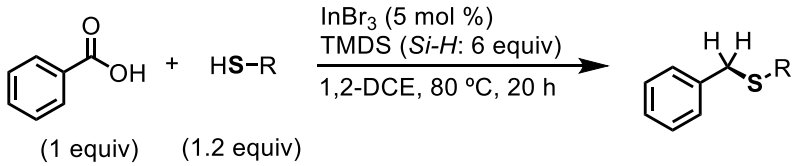
entry	InX_3	silane	GC yield of sulfide (%)
1	$InBr_3$	Et_3SiH	0
2	$InBr_3$	$PhMe_2SiH$	51
3	$InBr_3$	$PhSiH_3$	94
4	**$InBr_3$**	**TMDS**	**97 (91)[a]**
5	$InBr_3$	TMDS	84[b]
6	$InCl_3$	TMDS	0
7	$In(OTf)_3$	TMDS	0
8	$In(OH)_3$	TMDS	0

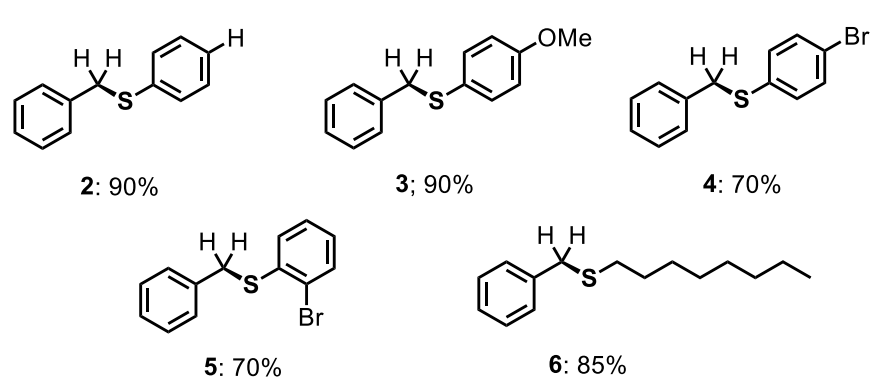


[a] Isolated yield.
[b] TMDS (*Si-H*: 4 equiv) was used.

The scope and limitations were examined under the optimized conditions (Table 2). Initially, a variety of benzenethiols were appied to the reaction system. The reaction of benzoic acid with benzenethiol afforded benzyl phenyl sulfide (**2**) in 90%.

Table 2. Examination of Benzene Thiols

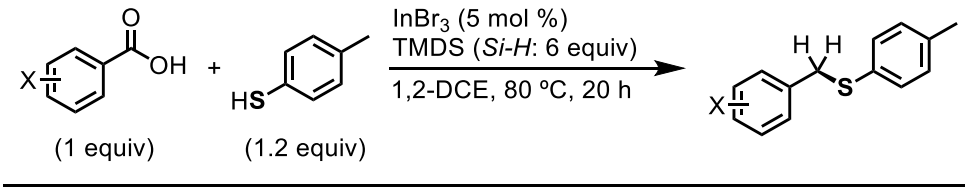


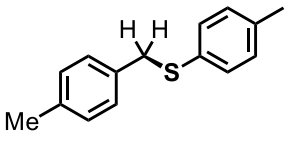


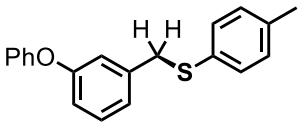
p-Methoxybenzenethiol gave corresponding sulfides **3** in a high yield. This result indicated that $InBr_3$ would not lost the catalytic activity by the combination of the oxgen atom on a methoxy group. With *p*-bromobenzenethiol, corresponding sulfide **4** was obtained in 70%. When using *o*-bromo benzene, the yield of **5** was the same as that of **4**, which showed the locations of a bromo group on the benzene ring did not affect the yields. Moreover, this reaction could be applied to not only benzenethiols but also an aliphatic thiol, 1-octanethiol to give sulfide **6** in a high yiled.

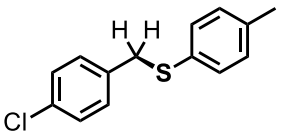
The generality using a variety of benzoic acids was examined (Table 3). *p*-Methylbenzoic acid and *m*-phenoxybenzoic acid were applied to the present reaction system, resulting in sulfide **7** and **8** in 74%, 93% respectively. In the case of substrates having a chloro group as an electron-withdrawing group, sulfides **9**-**11** were obtained in moderate yields with no relation to the locations of a chloro group. On the other hand, *o*-bromobenzoic acid led to decrease the yield of **12** slightly. When *o*-iodobenzoic acid was treated with InI_3, instead of $InBr_3$, the corresponding sulfide **13** was formed in good yield. *p*-Trifluoromethyl benzoic acid could be applied to the reaction system, giving sulfide **14** in good yield.

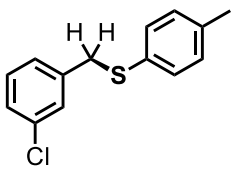
Table 3. Examination of Benzoic Acids

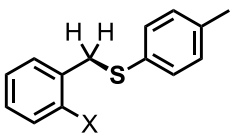


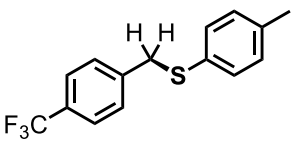

7: 74%


8: 93%


9: 74%


10: 80%

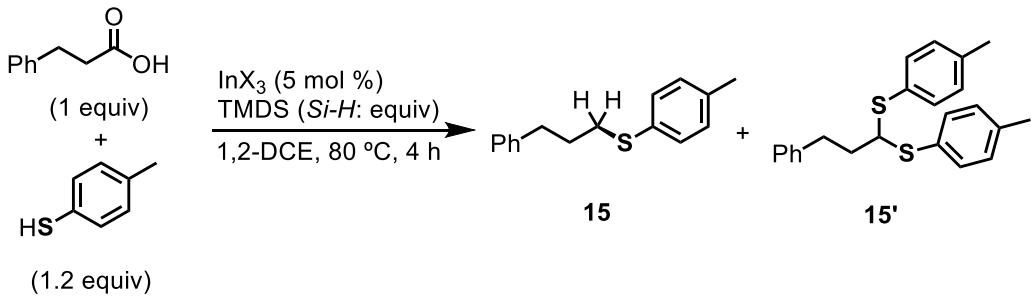

11: 78% (X = Cl)
12: 63% (X = Br)
13: 82% (X = I)[a]


14: 70%

[a] InI_3 was used.

An aliphatic carboxylic acid, instead of an aromatic carboxylic acid, was investigated (Table 4). Initially, examinations of reaction conditions were conducted using 3-phenylpropionic acid and *p*-toluenethiol as a model substrate in the presence of 5 mol % of $InBr_3$ and TMDS. With 5 mol % of $InBr_3$ and 8 equiv. (*Si-H*) of TMDS, the sulfide **15** was obtained in a low yield along with thioacetal **15'** in 58% yield (entry 1). To diminish the formation of thioacetal **15'**, InI_3, instead of $InBr_3$, was used. As a result, thioacetal **15'** was not formed, instead, the sulfide **15** was obtained in 97% yield (entry 2). On the other hand, when the amount of TMDS decreased to 6 equiv (*Si-H*), the formation of thioacetal **15'** was observed (entry 3).

Table 4. Re-Examination of Reaction Conditions Using 3-Phenylpropionic Acid

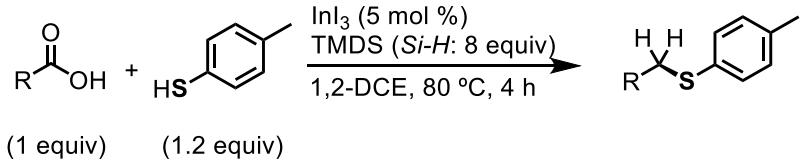


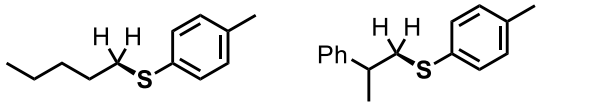
entry	InX_3	TMDS (*Si-H*: equiv)	GC yield (%)	
			15	**15'**
1	$InBr_3$	8	33	58
2	**InI_3**	**8**	**(97)[a]**	**0**
3	InI_3	6	60	35

[a] Isolated yield.

The scope and limitations using a variety of aliphatic carboxylic acids and *p*-toluenethiol were examined (Table 5). Initially, the use of a fatty acid resulted in a corresponding sulfide **16** in good yield. Also, in the case with a carboxylic acid having a branched carbon chain, the expected sulfide **17** was formed. Moreover, aliphatic carboxylic acids having a naphthyl skeleton or a bromo group at *p*-position on the benzene ring gave sulfides **18** and **19** in moderate yields. These results indicated that a steric effect of carboxylic acids had no effect on the product yields.

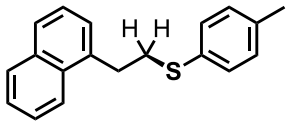
Table 5. Sulfidation of Aliphatic Carboxylic Acids with *p*-Toluene Thiol



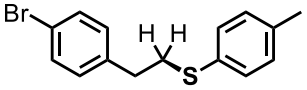


16: 80%

17: 91%



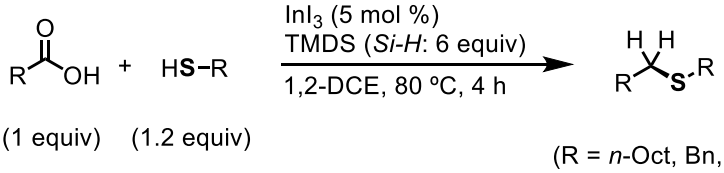
18: 77%

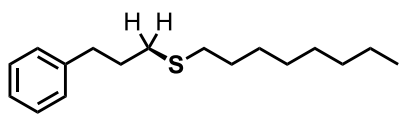


19: 67%

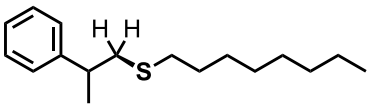
The generality of the sulfidation using aliphatic carboxylic acids and aliphatic thiols was conducted (Table 6). When 3-phenylpropionic acid reacted with 1-octanethiol, an alkyl sulfide **20** was obtained in a 94% yield.

Table 6. Sulfidation of Aliphatic Carboxylic Acids with Aliphatic Thiols

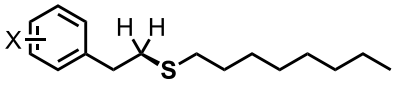




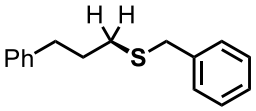
20: 94%



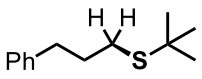
21: 90%



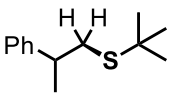
22: 74% (X = *o*-Me)
23: 53% (X = *p*-OH)
24: NR (X = *p*-NH_2)



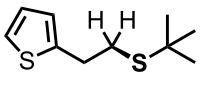
25: 72%



26: 88%



27: 85%

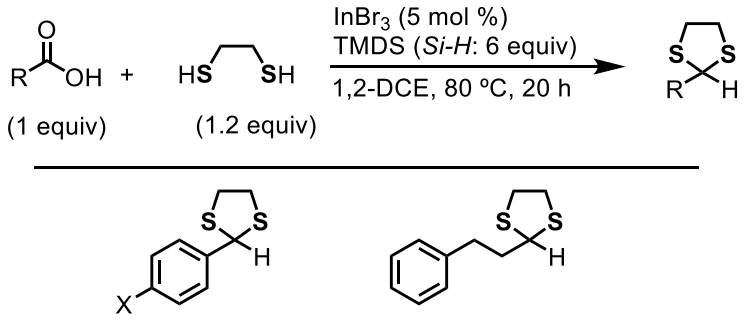


28: 70%

A carboxylic acid having a branched carbon chain was compatible with the reaction system to produce the sulfide in a high yield. Also, when carboxylic acids having a substituent on the benzene ring were examined, not only sulfide **22** having a methyl group at *o*-position but also sulfide **23** bearing a hydroxyl group at a *p*-position was formed. On the other hand, 4-aminophenylacetic acid was not applicable to this reducing system. When 3-phenylpropionic acid was treated with benzyl mercaptan or *tert*-butyl mercaptan, sulfides **25** and **26** were obtained in good yields. Interestingly, a bulky sulfide **27** was formed from a branched carboxylic acid and a thiol. Similarly, in the case of a carboxylic acid having a thiophene moiety, a corresponding sulfide **28** was obtained.

As further applications, the reactions using 1,2-ethenedithiol were examined (Table 7). When benzoic acid reacted with 1,2-ethanedithiol under the optimal conditions, the cyclic thioacetal **29** was obtained in a 96% yield. With substrates bearing a methyl group or a methoxy group at a *p*-position on the benzene ring, the product yields of thioacetals **30** and **31** slightly decreased in comparison with benzoic acid. In the case with 3-phenylpropionic acid, the expected product **32** was formed. Thus far, the synthesis of cyclic thioacetals is limited to thioacetalizations of aldehydes or ketones using dithiols. The presented method is the first example using carboxylic acids and 1,2-ethanedithiol.

Table 7. Applications with 1,2-Ethandithiol

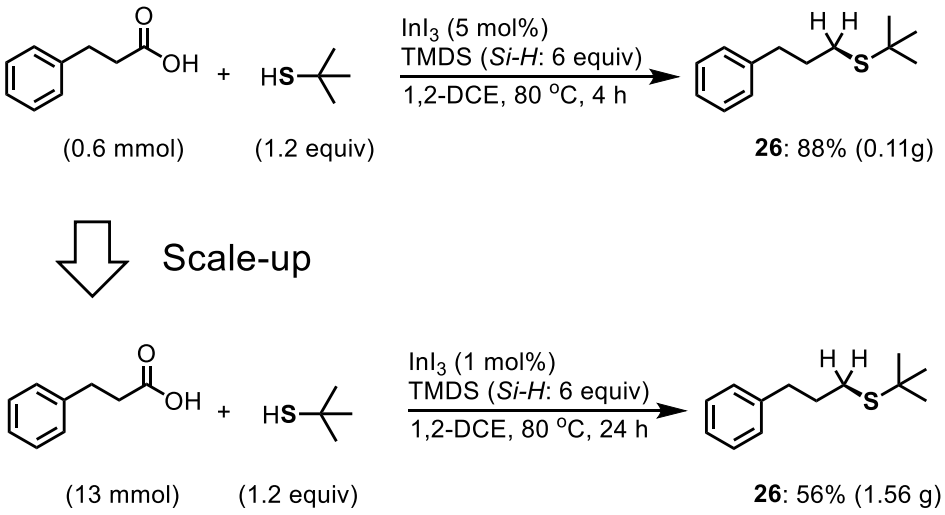


29: 96% (X = H)
30: 83% (X = Me)
31: 67% (X = MeO)

32: 91%

To examine the utility of the reaction system, a scale-up experiment was conducted (Scheme 3). Initially, 3-phenylpropionic acid reacted (0.6 mmol) with *tert*-butyl mercaptan in the presence of 5 mol % of InI_3 and 6 equiv (*Si-H*) of TMDS in 1,2-DCE at 80 ºC for 4 h, sulfide **26** was obtained in an 88% yield (0.11 g). Then, the scale increased to 13 mmol scale. Also, equivalent of InI_3 decreased to 1 mol % because InI_3 is an expensive metal compound. When the reaction was stirred for 24 h, the corresponding sulfide **26** was obtained in a 56% yield (1.56 g). The result indicated that a significant decrease in the scale-up experiment was not observed.

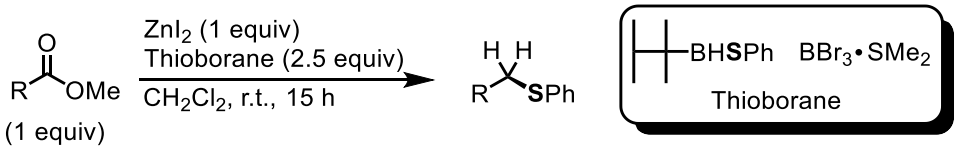
Scheme 3. Examination of a Scale-up Experiment



2-2. Reductive Sulfidation from Esters and Thiols

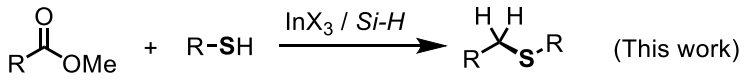
To date, the reductive sulfidation using carboxylic acids has not been reported. On the other hand, in 1987, Kim *et al.* reported only example of the synthesis of sulfides from esters and a thioboran in the presence of ZnI_2 (Scheme 4).[6] However, this example needs a stoichiometric amount of a Lewis acid and the troublesome use of a thioborane.

Scheme 4. Only Example of a Reductive Sulfidation from Esters



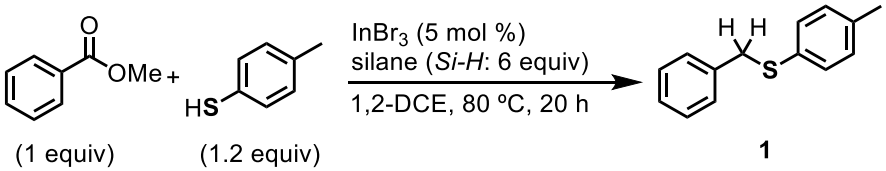
Therefore, the development of a methodology with a catalytic amount of a Lewis acid and without preparing both a reducing reagent and a sulfur source, has been required. The author anticipated that indium-catalyzed reductive sulfidation from esters and thiols would improve the problems of Kim' example shown above. Herein, the details are reported (Scheme 5).

Scheme 5. Indium-Catalyzed Reductive Sulfidation from Esters and Thiols



Initially, screening of hydrosilanes (*Si-H*: 6 equiv) was conducted using methyl benzoate and *p*-toluenethiol as a model substrate in the presence of 5 mol % of $InBr_3$ in 1,2-DCE at 80 ºC for 20 h (Table 8). When Et_3SiH was used, a decrease in the starting ester was observed. However, the expected sulfide **1** was not obtained (entry 1). Hydrosilanes bearing both a methyl group and a phenyl group resulted in low yields (entries 2 and 3). In the case with $PhSiH_3$, the product yield increased slightly (entry 4). Furthermore, TMDS remarkably promoted the present sulfidation to give sulfide **1** in an 86% yield (entry 5). The results showed that TMDS was the best hydrosilane for this conversion.

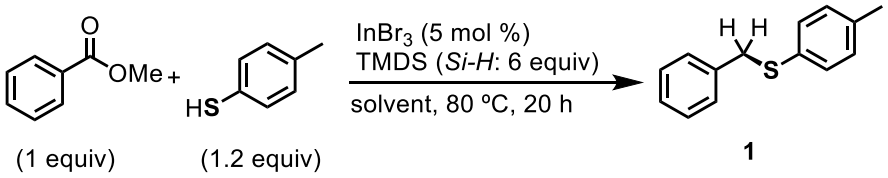
Table 8. Screenings of Silanes



entry	silane	Conversion (%)	GC yield of sulfide (%)
1	Et_3SiH	48	0
2	Ph_2MeSiH	70	6
3	$PhMe_2SiH$	74	18
4	$PhSiH_3$	70	41
5	**TMDS**	**86**	**86**

To study solvent effects, screenings of various solvents were attempted (Table 9). When chloroformwas applied, a slight decrease of yield was observed (entry 2). Toluene did not increase the product yield (entry 3). Also, protic solvents, such as MeCN, THF, EtOH and MeOH, were ineffective to the sulfidation (entries 4-7).

Table 9. Investigation of Solvent Effects



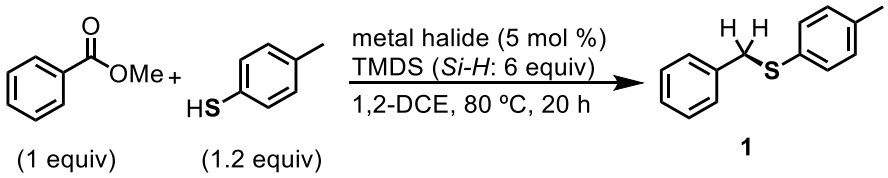
(1 equiv) (1.2 equiv) **1**

entry	solvent	Conversion (%)	GC yield of sulfide(%)
1	**1,2-DCE**	**86**	**86**
2	$CHCl_3$	81[a]	74[a]
3	PhMe	77	72
4	MeCN	0[a]	0[a]
5	THF	0[a]	0[a]
6	EtOH	0[a]	0[a]
7	MeOH	0[a]	0[a]

[a] 60 ºC. [b] Room temperature.

To improve a yield of sulfide **1**, screenings of catalysts were examined (Table 10). As group 13 metal compound, aluminum bromide did not afford the product (entry 2). Also, zinc bromide did not improve the yield (entry 3). On the other hand, when using InI_3, the starting ester was perfectly consumed, the product yield significantly increased (entry 4). Moreover, when the equivalent of TMDS increased to 8 equiv, the improvement of the yield was observed (entry 5).

Table 10. Examination of Catalysts

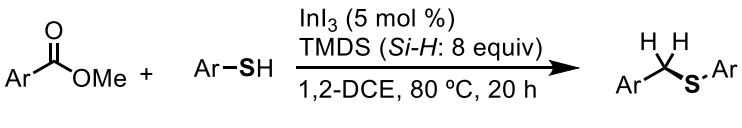


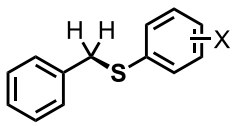
entry	InX_3	Conversion (%)	GC yield of sulfide (%)
1	**$InBr_3$**	**86**	**86**
2	$AlBr_3$	11	0
3	$ZnBr_2$	24	20
4	InI_3	99	89
5	InI_3	99	96[a] (90)[a,b]

[a] TMDS (*Si-H*: 8 equiv) was used. [b] Isolated yield.

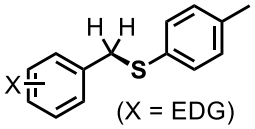
The sulfidation using a variety of aromatic esters and aromatic thiols is shown in Table 11. For the results of aromatic thiols, when using *p*-methoxybenzenethiol and *p*-bromobenzenethiol, the expected **3** and **4** were obtained in good yields. Uses of *o*-bromobenzenethiol and *p*-chlorobenzenethiol led to the decrease in the product yields of **5** and **33**.

Table 11. Sulfidation of Aromatic Esters with Aromatic Thiols



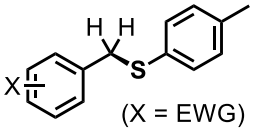


3: 72% (X = *p*-OMe)
4: 68% (X = *p*-Br)
5: 36% (X = *o*-Br)
33: 29% (X = *p*-Cl)



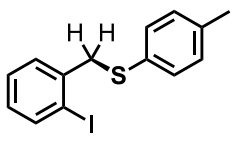
(X = EDG)

7: 81% (X = *p*-Me)
34: 72% (X = *p*-MeO)
8: 67% (X = *m*-PhO)

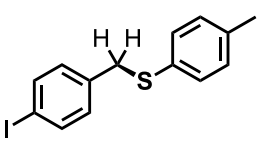


(X = EWG)

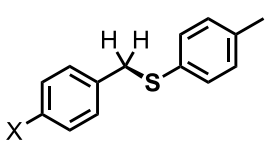
9: 60% (X = *p*-Cl)
10: 55% (X = *m*-Cl)
11: 57% (X = *o*-Cl)
12: 34% (X = *o*-Br)



13: 35%[a]



35: 66%[b]



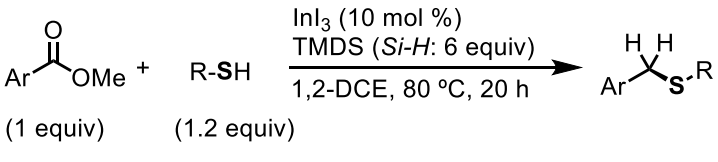
14: 40% (X = CF_3)
36: 0% (X = NO_2)

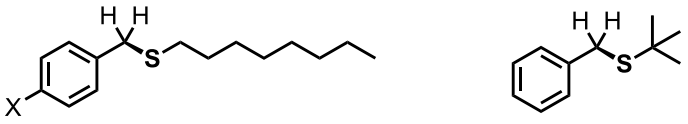
[a] The deiodinated product, benzyl *p*-tolyl suifide was obtained in 16% (GC yield).
[b] An ethyl ester as a substrate was used. The deiodinated product was not detected.

Also, examinations of benzoic acid methyl ester were conducted. Substrates having a methyl, methoxy, and phenoxy group gave sulfides **7**, **34** and **8** in good yields. Esters bearing a chloro group resulted in moderate yields of **9**-**11** with no relation to a position of a substituent. In the case with methyl *o*-bromobenzoate, the yield of **12** decreased. Similarly, methyl *o*-iodobenzoate led to a low yield of **13**. The cause of decreasing the yield is the formation of the deiodinated product **1** in 16% yield with sulfide **13**. When ethyl *p*-iodobenzoate was used, the deiodinated product **1** was not detected, and sulfide **35** was formed in a 66 yield. As a strong electron-withdrawing group, the use of an ester having a trifluoromethyl group gave corresponding sulfide **14** in a 40% yield. On the other hand, when methyl *p*-nitrobenzoate was treated with the optimal conditions, the reaction system became to be a complicated mixture, and the expected product **36** was not formed at all.

An aliphatic thiol, instead of an aromatic thiol, was applied to the reaction system (Table 12). When methyl benzoate reacted with 1-octanethiol, the corresponding sulfide **6** was obtained in a moderate yield. In the case with esters bearing a methyl or a methoxy group, the product yield of **37** and **38** increased slightly in comparison with methyl benzoate. A substrate having a chloro group at the *p*-position resulted in a low yield of **39**. As another aliphatic thiol, *tert*-butyl mercaptan gave sulfide **40** in a 38% yield.

Table 12. Sulfidation of Aromatic Esters with Aliphatic Thiols

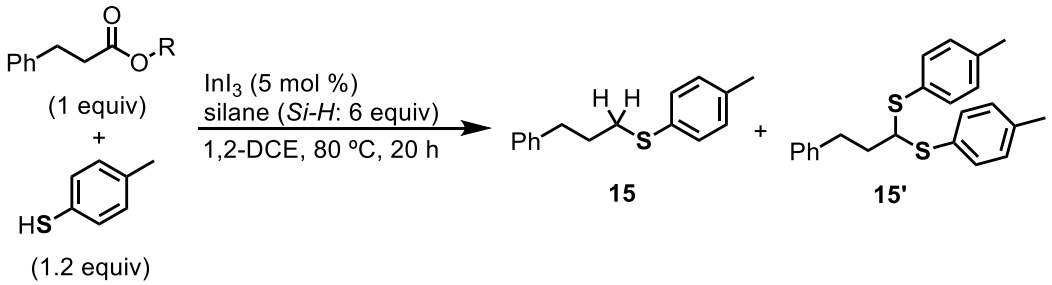




6: 60% (X = H) **38**: 71% (X = OMe) **40**: 38%
37: 65% (X = Me) **39**: 39% (X = Cl)

Applications to aliphatic esters instead of aromatic esters were attempted (Table 13). Initially, examinations of reaction conditions were conducted using esters derived from 3-phenyl propionic acid and *p*-toluene thiol as a model substrate in the presence of 5 mol % of InI_3 and 6 equiv (*Si-H*) of a hydrosilane. When methyl 3-phenylpropionate was treated with TMDS, thioacetal **15'** was formed in a 73% yield along with sulfide **15** in a 12% yield (entry 1). To increase the ability of the leaving group on the ester, a pheny ester instead of methyl ester was applied. Consequently, the expected sulfide was selectively obtained in a 74% yield (entry 2). On the other hand, when a phenyl ester reacted with $PhSiH_3$, a decrease of the product yield was observed (entry 3). Also, the use of *p*-chlorophenyl ester, instead of a phenyl ester, and $PhSiH_3$ increased the yield of sulfide (entry 4). Finally, even though the amount of InI_3 was increased to 10 mol %, a thioacetal was not formed (entry 5). From the results shown above, it was found that entry 2 and entry 5 were determined to be the best reaction conditions for this sulfidation.

Table 13. Re-Examination using Aliphatic Esters Derived from 3-Phenylpropionic Acid



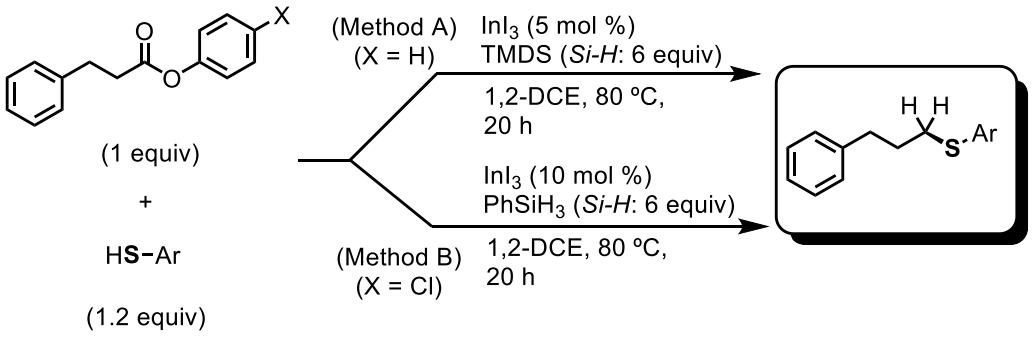
entry	R	silane	yield of **5**[a]	yield of **5'**[a]
1	Me	TMDS	12	73
2	**Ph**	**TMDS**	**(74)**[b]	**0**
3	Ph	$PhSiH_3$	44	3
4	*p*-ClC_6H_4	$PhSiH_3$	84	14
5	***p*-ClC_6H_4**	**$PhSiH_3$**	**(76)**[b,c]	**0**

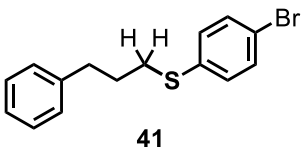
[a] GC yield. [b] Isolated yield. [c] InI_3 (10 mol %) was used.

With benzene thiols, instead of *p*-toluenethiol, the generality was examined (Table 14). The condition using a phenyl ester was regareded as Method A and the other conditions using a *p*-chlorophenyl ester was regarded as Method B. *p*-bromobenzenethiol afforded sulfide **41** in a 92%

yield using Method B. In the case of *o*-bromobenzene, a steric effect have no effect on the yield to afford a sulfide **42** in an 88% yield using Method B. A benzenethiol bearing a methoxy group at the *p*-position produced a sulfide **43** in a 63% yield using Method A. These results showed that Method B could applicable to benzene thiols bearing a bromo group, by contrast, Method A was better conditions for sulfidation with *p*-methoxybenzenethiol.

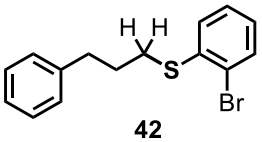
Table 14. Sulfidation of Aliphatic Esters with Aromatic Thiols





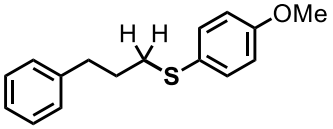
41

Method A: 34%
Method B: 92%



42

Method A: 29%[a]
Method B: 88%



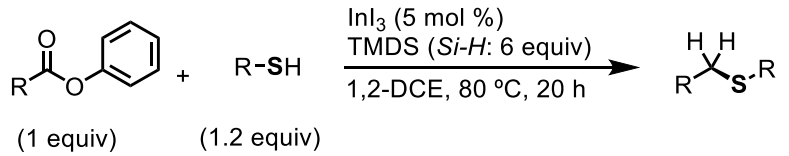
43

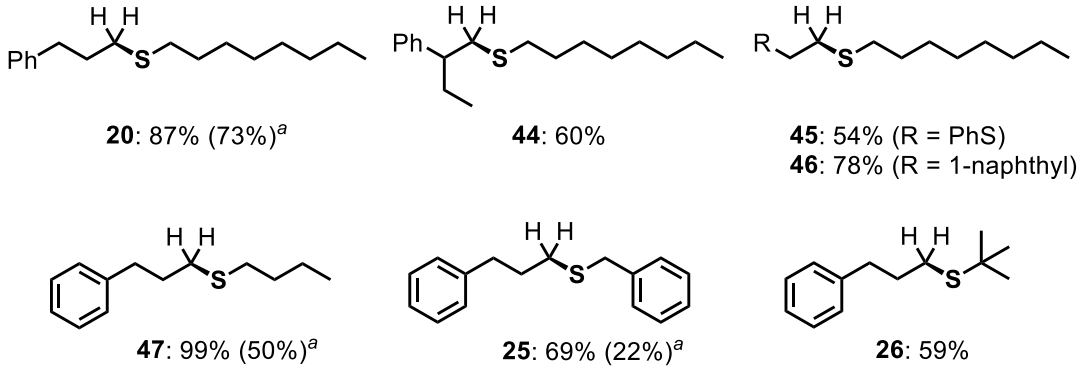
Method A: 63%
Method B: 44%

[a] NMR yield.

The sulfidation using aliphatic esters and aliphatic thiols was conducted (Table 15). When phenyl 3-propionate reacted with 1-octane thiol, a corresponding sulfide **20** was obtained in a high yield. An ester having a branched carbon chain resulted in a moderate yield of **44**. Substrates bearing a sulfide moiety or naphthyl skeleton gave sulfides **45** and **46** in 54% and 78%, respectively. Also, phenyl 3-phenylpropionate reacted with 1-butanethiol, instead of 1-octanethiol, to afford sulfide **47** in a high yield. In the case of *tert*-butyl mercaptan and benzyl mercaptan, the corresponding sulfides **25** and **26** were obtained in moderate yields.

Table 15. Sulfidation of Aliphatic Esters with Aliphatic Thiols

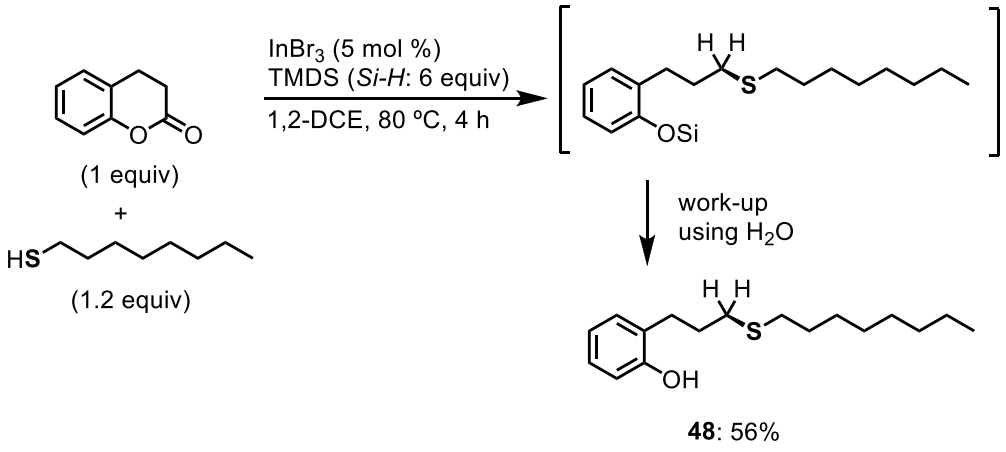




[a] Methyl ester was used.

As applications, the sulfidation using a cyclic ester was examined (Scheme 6). The cyclic ester, 3,4-dihydrocoumarin was treated with 1-octanethiol in the presence of 5 mol % of $InBr_3$ and 6 equiv. (*Si-H*) of TMDS. Consequently, the sulfide **48** having a hydroxyl group at *o*-position on the benzene ring was obtained. This result indicated that a ring-opening reaction proceeded to produce the sulfide bearing a siloxy group on the benzene ring.

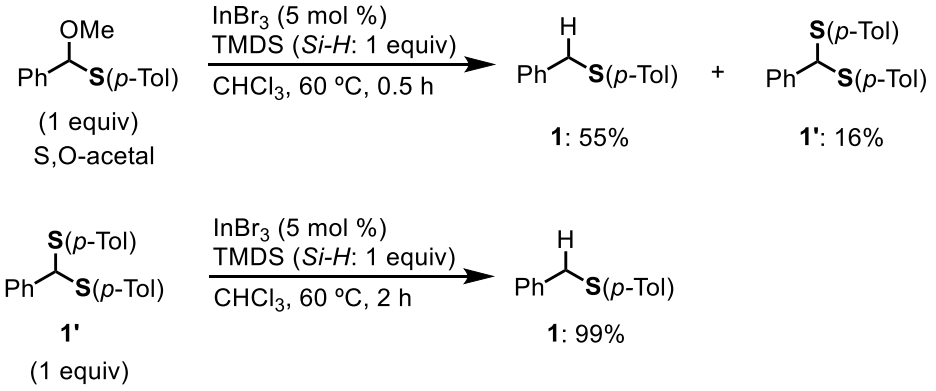
Scheme 6. Application Using a Cyclic ester



2-3 Reaction Mechanism

To clarify the reaction mechanism, several control experiments were conducted. Initially, the role of a sulfur-containing intermediate was investigated. The aouthor expected that an *S,O*-acetal would exist as an intermediate and the reduction of an *S,O*-acetal was attempted (Scheme 7). The prepared *S,O*-acetal was treated with 1 equiv. (*Si-H*) of TMDS in the presence of 5 mol % of $InBr_3$ in $CHCl_3$ at 60 ºC for 0.5 h. Contrary to my expectation, thioacetal **1'** was formed in a 16% yied along with sulfide **1**. From the result of Scheme 9, a thioacetal **1'** was reduced to give sulfide **1** in a quantitative yield.

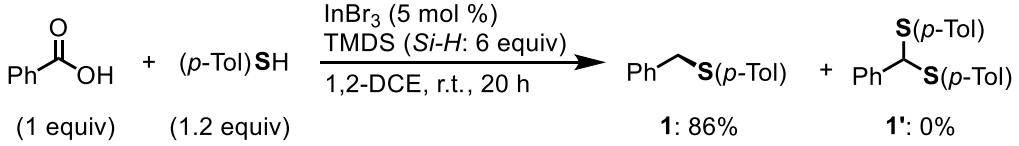
Scheme 7. Reduction of a *S,O*-acetal



Alghough the existence of an *S,O*-acetal as an intermediate was unclear, these results indicated that there is two reaction pathes: (i) a single-step direct conversion of an *S,O*-acetal to a sulfide , (ii) two-step conversions of an *S,O*-acetal to a sulfide via a thioacetal.

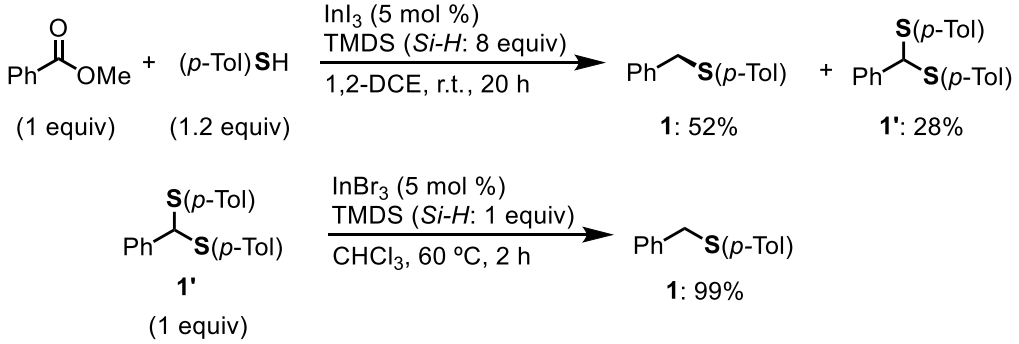
Benzoic acid reacted with *p*-toluenethiol in the presence of 5 mol % of $InBr_3$ and 6 equiv (*Si-H*) of TMDS at room temperature to give sulfide **1** in an 86% yield (Scheme 8).

Scheme 8. Control experiment Using Benzoic Acid



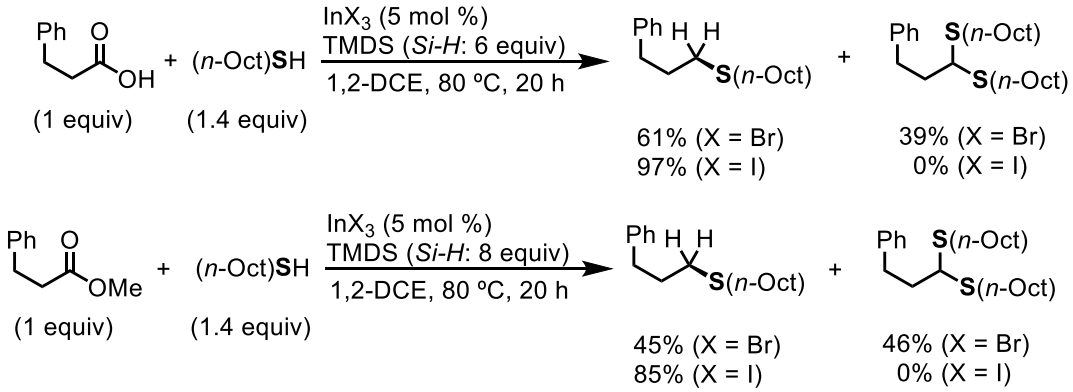
On the other hand, in the case with methyl benzoate using 5 mol % of InI_3 and 8 equiv (*Si-H*) of TMDS, thioacetal **1'** was formed in a 28% yield along with sulfide **1**. Also, the prepared thioacetal **1'** was treated with 5 mol % of $InBr_3$ (5 mol %) and 1 equiv. (*Si-H*) of TMDS to give a sulfide **1** in a 99% yield. Those results indicated that an aromatic thioacetal would exist as an intermediate (Scheme 9).

Scheme 9. Control Experiments Using Methyl Benzoate



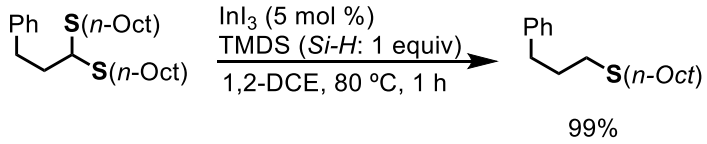
Also, the formation of a thioacetal intermediate was examined using 3-phenylpropionic acid and methyl 3-phenyl propionate. When 3-phenylpropionic acid reacted with 1-octanethiol in the presence of 5 mol % of $InBr_3$ and 6 equiv. (*Si-H*) of TMDS, thioacetal **20'** was formed in a 39 % yield. On the other hand, by using InI_3 instead of $InBr_3$, a thioacetal **20'** disappeared, instead, giving sulfide **20** in a 97% yield selectively. Similar results were observed using methyl 3-phenylpropionate (Scheme 10).

Scheme 10. Control Experiments Using an Aliphatic Carboxylic Acid and an Aliphatic Thiol.



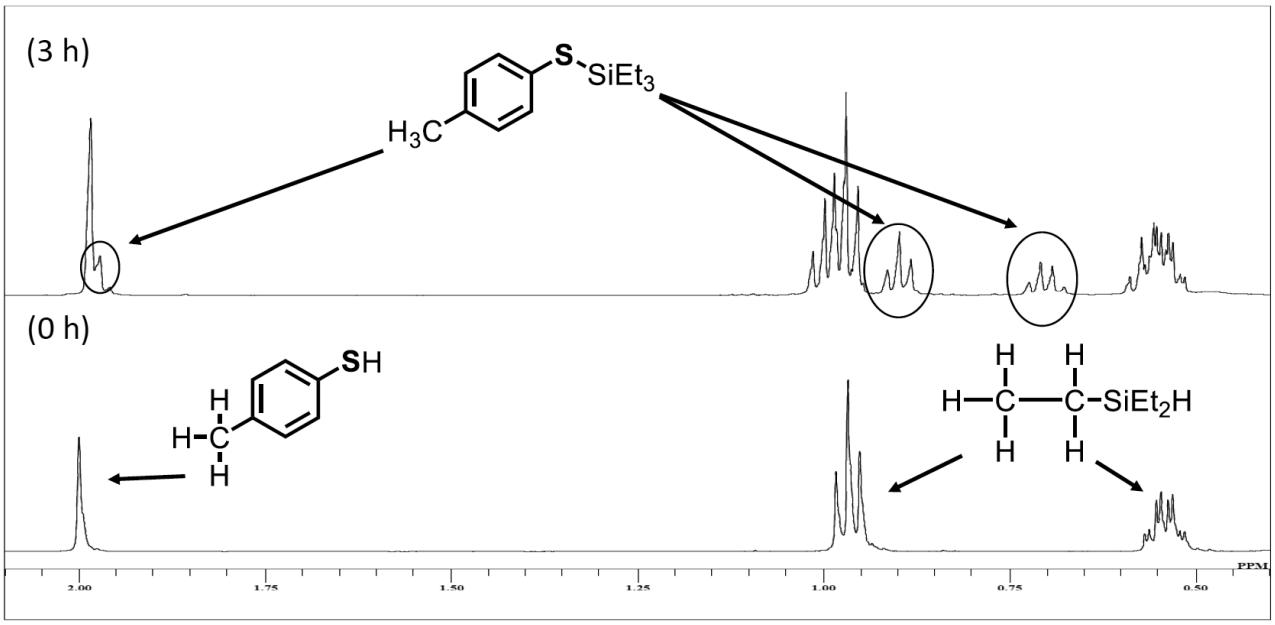
The prepared thioacetal **20'** was then treated with 5 mol % of InI_3 and 1 equiv. (*Si-H*) of TMDS to afford sulfide **20** in a 99% (Scheme 11). These results showed that an aliphatic thioacetal would exist as an intermediate.

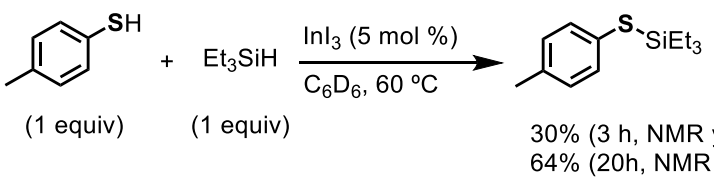
Scheme 11. Reduction of a Thioacetal



The generation of a thiosilane was examined with *p*-toluenethiol and Et_3SiH in d_6-benzene. A catalytic amount of InI_3 was added to the reaction mixture, and the formation of the new peaks in NMR was observed with NMR (Figure 1).

Figure 1. NMR monitor Using a Thiol and a Hydrosilane

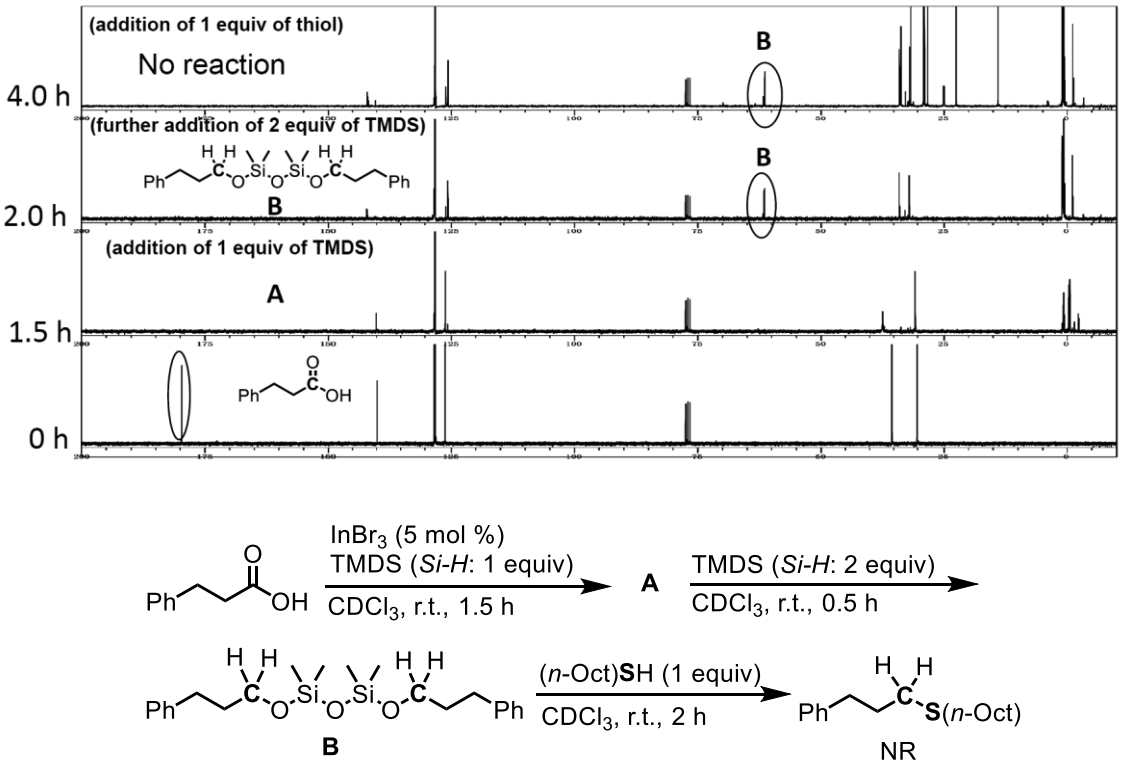




Consequently, when the reaction mixture reacted for 3 h, the new peaks derived from thiosilane were observed. Also, a NMR yield of thiosilane was to be 30% (Scheme 7). When the mixture was treated for 20 h, the yield of the thiosilane increased to 64%. These results indicated that a thiosilane would be in-situ formed from a thiol and a hydrosilane in the presence of the indium compound.

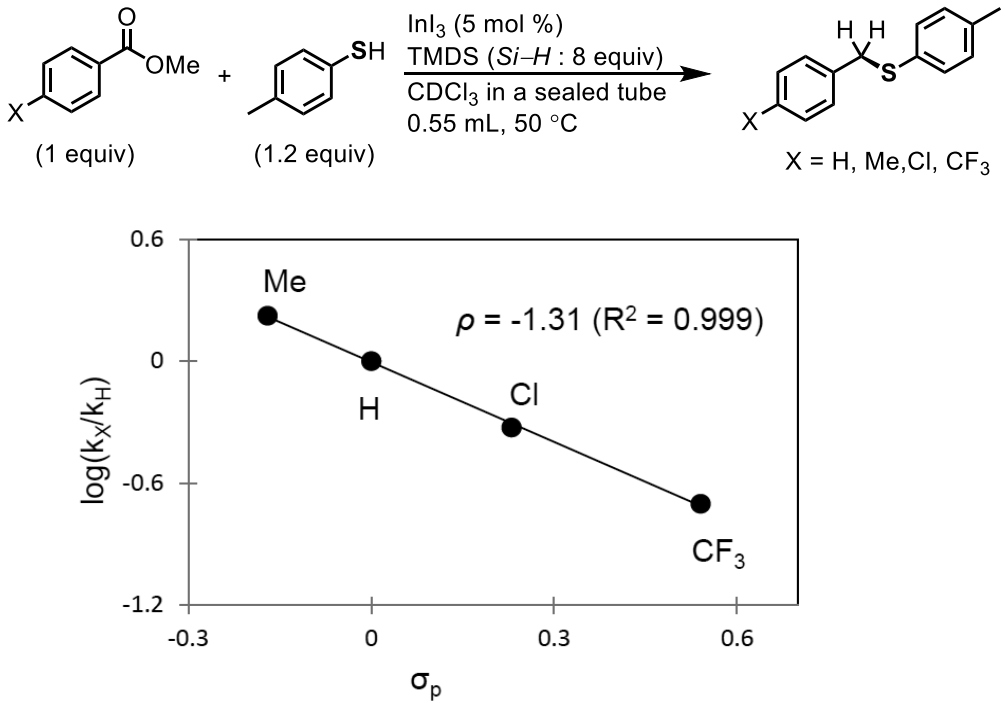
A reaction path from an aliphatic silyl ether to a sulfide was examined (Figure 2). To prepare an aliphatic silyl ether, a NMR monitor was conducted. When 3-phenylpropionic acid was treated with 5 mol % of $InBr_3$ and 1 equiv. (*Si-H*) of TMDS, the peak derived from a carbonyl carbon disappeared. However, the formed product **A** could not be characterized. Then, 2 equiv (*Si-H*) of TMDS was added to the reaction mixture to form an aliphatic silyl ether **B**. When the aliphatic silyl ether reacted with 1-octanethiol, the desired sulfidation did not occur. Therefore, an aliphatic silyl ether was not converted into sulfide **20**.

Figure 2. Examination of a Conversion from an Aliphatic Silylether to a Sulfide



To investigate the rate-determining step, the control experiments to draw a Hammett plot were conducted (Figure 3). Initially, the rate constants were examined using various methyl benzoates and *p*-toluenethiol in the presence of 5 mol % of InI_3 and 8 equiv. (*Si-H*) of TMDS in *d*-chloroform at 50 ºC. On the basis of the calculated rate constants and the substituent constants quoted from the reference,[7] a Hammett plot was drawn. Consequently, the graph in a Hammett plot showed a negative slope (ρ = -1.31). This result suggested that a benzyl cation would exist at the rate-determing step.

Figure 3. Investigation of Substituent Effects

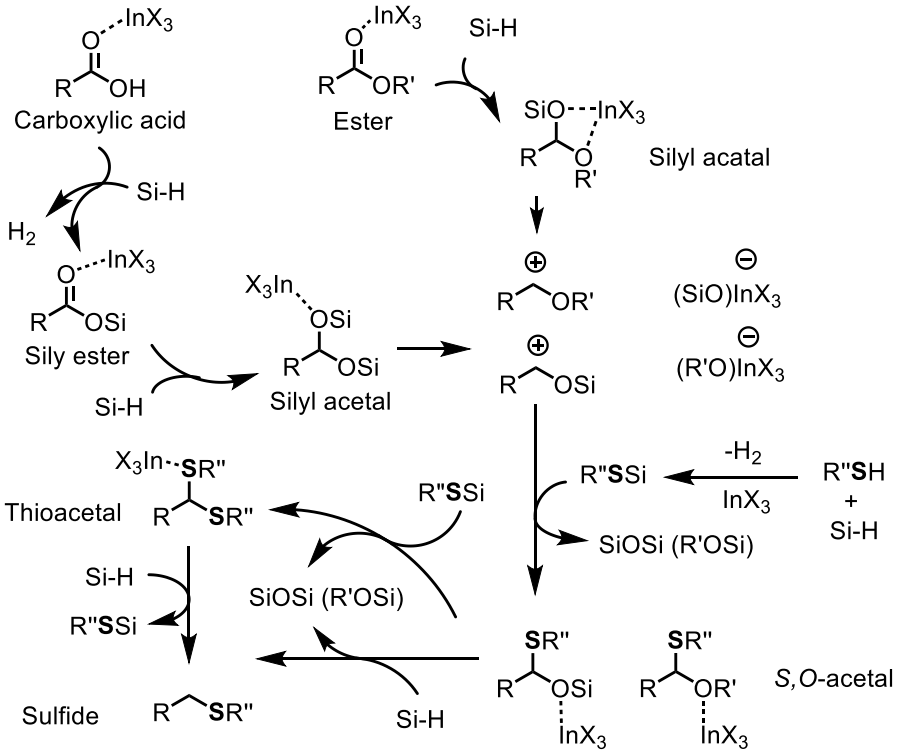


Based on above control experiments shown above, the plausible mechanism is shown in Scheme 12. This reaction mechanism is composed of the hydrosilylation and the sulfidation. For the hydrosilylation, a carboxylic acid reacted with a silane to produce a silyl ester with the liberation of H_2. The formed silyl ester was reduced by other hydrosilane to give a silyl acetal. One C-O bond on the silyl acetal was activated by an indium catalyst to afford a cation species. The mechanism from a carboxylic acid to a cation species was quoted from the reference.[8]

In the case of an ester, an ester reacted with a hydrosilane to afford a silyl acetal. Based on a

Hammett plot, the silyl acetal was activated by an indium catalyst, and a cation species was formed. For a sulfidation, a thiosilane derived from a thiol and a silane attacked the formed cation species to produce an *S,O*-acetal. The *S,O*-acetal activated by an indium catalyst reacted with a hydrosilane to affored a sulfide. As another path, an *S,O*-acetal was converted into a thioacetal, followed by reduction with a hydrosilane to form a sulfide.

Scheme 12. Plausible Mechanism



Conclusion

The author have demonstrated the first reductive sulfidations from carboxylic acids and thiols in the presence of 5 mol % of $InBr_3$ or InI_3 and 6 or 8 equiv (*Si-H*) of TMDS to produce 26 examples of sulfides. As appricatios, the thioacetalization from carboxylic acids and 1,2-ethanedithiol was also found and a gram-scale synthesis of a sulfide was performed.

The indium-catalyzed reductive sulfidation could be applied to esters as carbonyl compounds. In comparison with only Zn-promoted reductive sulfidation from esters and a thioborane, the present reductive sulfidation used a catalytic amount of a Lewis acid. Also, the present sulfidation requires only commercially available TMDS, $PhSiH_3$ and thiols. Therefore, it was not necessary the use of troublesome sulfur source and reducing reagent.

The author examined the reaction mechanism by NMR, GC and following results were found; (i) a generation of a thiosilane, (ii) a formation of thioacetal, (iii) existence of a cation species by a Hammett plot were observed.

This reaction drives with a catalytic amount of indium catalyst and the sulfidations could proceed under relatively milder conditions in comparison with the conventional methods.

Experimental Section

General Information

All were carried out under a N_2 atmosphere, unless otherwise noted. 1,2-dichloroethane (1,2-DCE) was freshly distilled from P_2O_5 prior to use. All indium salts were commercially available and were used without further purification. Silanes were used without further purification. Reactions were monitored by TLC analysis of reaction aliquots. Thin-layer chromatography (TLC) was performed on silica gel 60 F_{254}, and the components were located by observation under UV light. Column chromatography was also performed using silica gel. ^1H NMR spectra were measured at 500 (or 300) MHz using tetramethylsilane as an internal standard. ^{13}C NMR spectra were measured at 125 (or 75) MHz using the center peak of chloroform (77.0 ppm) as an internal standard. High resolution mass spectra were measured using NBA (3-nitrobenzylalcohol) as a matrix.

General procedure for the synthesis of sulfides from carboxylic acids

To a freshly distilled dichloroethane solution (0.60 mL) in a scew-capped vial under N_2 atmosphere were successively added a magnetic stirrer bar, a carboxylic acid (0.60 mmol), a thiol (0.72 mmol), $InBr_3$ (0.030 mmol, 11 mg), and $[Me_2Si(H)]_2O$ (1.8 mmol, 3.2 x 10^2 μ L). The vial was sealed with a cap contained a PTFE septum. During heating of the reaction mixture at 80 ºC (bath temperature), the reaction was monitored by TLC until consumption of the starting thiol. After the reaction, the resulting mixture was quenched with H_2O (3.0 mL). The aqueous layer was extracted with $CHCl_3$ (5.0 mL x 3), the combined organic phases were dried over anhydrous Na_2SO_4, filtered, and then evaporated under reduced pressure. The crude product was purified by a preparative TLC (SiO_2 / hexane) to give the corresponding sulfide.

General procedure for the synthesis of sulfides from aromatic esters and aromatic thiols

To a freshly distilled dichloroethane solution (0.60 mL) in a screw-capped vial under a N_2 atmosphere were successively added a magnetic stirrer bar, an aromatic ester (0.60 mmol), an aromatic thiol (0.72 mmol), InI_3 (0.030 mmol, 15 mg), and TMDS (2.4mmol, 4.2 x 10^2 μL). The vial was sealed with a cap that contained a PTFE septum. During heating of the reaction mixture at 80 °C (bath temperature), the reaction was monitored via TLC until consumption of the starting carboxylic acid. After the reaction, the resultant mixture was quenched with H_2O (3.0 mL). The aqueous layer was extracted with $CHCl_3$ (5.0 mL × 3), the combined organic phases were dried over anhydrous Na_2SO_4, filtered, and then evaporated under reduced pressure. The crude product was purified by silicagel column chromatography (hexane/AcOEt = 99 : 1) to give the corresponding sulfide.

General procedure for the synthesis of methyl esters

A carboxylic acid (5 mmol), sulfuric acid (1 mL) and a magnetic stirrer bar were successively added to distilled methanol (20 mL). The solution was stirred under reflux for 2 h. After the reaction, the resultant solution was neutralized with $NaHCO_3$ aqueous solution. The aqueous layer was

extracted with AcOEt (10 mL), the combined organic phases were dried over anhydrous Na_2SO_4, filtered, and then evaporated under reduced pressure to afford the corresponding methyl ester.

General procedure for the synthesis of phenyl esters

A carboxylic acid (5 mmol), phenol (5 mmol, 4.7×10^2 mg), *N,N*-dimethyl-4-aminopyridine (0.63 mmol, 7.6×10 mg) and a magnetic stirrer bar were successively added to distilled dichloromethane. *N,N*-dicyclohexylcarbodiimide (5.0 mmol, 1.0×10^3 mg) was add to the solution. The solution was stirred overnight at 0 °C to room temperature. After the reaction, the resultant mixture was filtered off. Then, the filtrate was evaporated under reduced pressure. The crude product was purified via silica gel column chromatography (hexane/AcOEt = 9 : 1) to afford the corresponding phenyl ester.

General procedure for the synthesis of 4-chlorophenyl esters

A carboxylic acid (5 mmol), phenol (5 mmol, 4.7×10^2 mg), *N,N*-dimethyl-4-aminopyridine (0.63 mmol, 7.6×10 mg), *N,N*-dicyclohexylcarbodiimide (5 mmol, 1.0×10^3 mg) were used as substrates. The experimental operation for the synthesis of 4-chlorophenyl esters is the same as that of phenyl ester.

Experiments for drawing the Hammett plot

InI_3 (0.030 mmol, 15 mg), an aromatic ester (0.60 mmol), *p*-toluenethiol (0.72 mmol, 89 mg) and 1,1,2,2-tetrachloroethane (0.20 mmol, 34 mg) as an internal standard substance were successively added to a chloroform-*d* (0.55 mL). The solution was heated at 50 °C. ^{1}H NMR spectra were measured at 500 MHz using tetramethylsilane as an internal standard (0.00 ppm) at intervals of ten minutes. Based on integrated value of an ester and an internal standard substance, a concentration [A] of an ester was calculated. To evaluate a rate constant k, the concentration [A] and a corresponding reaction time (t) were adapted to a following equation: $\ln([A]_0/[A]) = k(t)$. With four valuated rate constants and substituent constants[7], the Hammett plot was drawn.

Spectral data

Benzyl *p*-tolyl sulfide (1)[9]

A colorless oil; ^{1}H NMR (500.2 MHz, $CDCl_3$) δ 2.30 (s, 3H), 4.06 (s, 2H), 7.05-7.06 (m, 2H), 7.20-7.21 (m, 2H), 7.23-7.27 (m, 5H); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 21.0, 39.7, 127.0, 128.4, 128.8, 129.6, 130.7, 132.4, 136.5, 137.8; MS (EI): *m/z* 214 (M^+).

Benzaldehyde di(*p*-tolyl) thioacetal (1')[10]

A white solid; mp 78.0-79.5 °C (lit.[10] 78-79 °C) ^{1}H NMR (500.2 MHz, $CDCl_3$) δ 2.29 (s, 6H), 5.31 (s, 1H), 7.04 (d, *J* = 7.5 Hz, 4H), 7.22-7.25 (m, 7H), 7.32 (d, *J* = 7.0 Hz, 2H); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 21.1, 61.3, 127.83, 127.85, 128.3, 129.5, 130.8, 133.1, 138.0, 140.0; MS (FAB): *m/z* 335 (M^+-H).

Benzyl phenyl sulfide (2)[11]

A white solid; mp 38.5-38.9 ºC (lit.[10]40-41 ºC); ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.09 (s, 2H), 7.14-7.29 (m, 10H); ^{13}C NMR (125 MHz, $CDCl_3$) δ38.9, 126.2, 127.1, 128.4, 128.75, 128.76, 129.7, 136.3, 137.4; MS (FAB): *m/z* 200 (M^+).

Benzyl *p*-methoxyphenyl sulfide (3)[12]

A colorless oil; ^{1}H NMR (500.2 MHz, $CDCl_3$) δ 3.76 (s, 3H), 3.97 (s, 2H), 6.78 (d, *J* = 9.0 Hz, 2H), 7.18 (d, *J* = 9.0 Hz, 2H), 7.20-7.25 (m, 5H); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 41.2, 55.3, 114.4, 126.0, 126.9, 128.3, 128.9, 134.1, 138.1, 159.2; MS (EI): *m/z* 230 (M^+).

Benzyl *p*-bromophenyl sulfide (4)[13]

A colorless oil; ^{1}H NMR (500.2 MHz, $CDCl_3$) δ 4.08 (s, 2H), 7.14 (d, *J* = 8.5 Hz, 2H), 7.23-7.30 (m, 5H), 7.35 (d, *J* = 8.5 Hz, 2H); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 39.1, 120.3, 127.3, 128.5, 128.8,

131.4, 131.8, 135.4, 137.0; MS (EI): *m/z* 278 (M^+).

Benzyl *o*-bromophenyl sulfide (5)[14]

A colorless oil; ^{1}H NMR (500.2 MHz, $CDCl_3$) δ 4.14 (s, 2H), 7.00-7.03 (m, 1H), 7.20-7.26 (m, 3H), 7.30 (t, *J* = 7.5 Hz, 2H), 7.35 (d, *J* = 7.0 Hz, 2H), 7.54 (d, *J* = 8.0 Hz, 1H); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 37.9, 123.6, 126.9, 127.4, 127.7, 128.6, 128.8, 128.9, 132.9, 136.1, 137.8; MS (EI): *m/z* 278 (M^+, 100%).

Benzyl octyl sulfide (6)[15]

A colorless oil; ^{1}H NMR (500.2 MHz, $CDCl_3$) δ 0.88 (t, *J* = 7.0 Hz, 3H), 1,25-1.35 (m, 10H), 1.55 (quin, *J* = 7.5 Hz, 2H), 2.40 (t, *J* = 7.5 Hz, 2H), 3.70 (s, 2H), 7.22-7.26 (m, 1H), 7.30-7.31 (m, 4H); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 14.1, 22.6, 28.9, 29.1, 29.16, 29.19, 31.4, 31.8, 36.3, 126.8, 128.4, 128.8, 138.7; MS (EI): *m/z* 236 (M^+).

***p*-Methylbenzyl *p*-tolyl sulfide (7)**

A colorless oil; ^{1}H NMR (500.2 MHz, $CDCl_3$) δ 2.30 (s, 3H), 2.31 (s, 3H), 7.05-7.08 (m, 4H), 7.16 (d, *J* = 8.0 Hz, 2H), 7.21 (d, *J* = 8.0 Hz, 2H); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 21.0, 21.1, 128.7, 129.1, 129.6, 130.4, 132.7, 134.6, 136.4, 136.7; HRMS (FAB): Calcd for $C_{15}H_{16}S$: 228.0973, Found 228.0971.

***m*-Phenoxybenzyl *p*-tolyl sulfide (8)**

A colorless oil; ^{1}H NMR (500.2 MHz, $CDCl_3$) δ 2.30 (s, 3H), 4.00 (s, 2H), 6.86 (d, *J* = 7.5 Hz, 1H), 6.88 (s, 1H), 6.94 (d, *J* = 8.5 Hz, 2H), 7.01 (d, *J* = 7.5 Hz, 1H), 7.05 (d, *J* = 8.0 Hz, 2H), 7.09 (t, *J* = 7.5 Hz, 1H), 7.19 (d, *J* = 8.5 Hz, 2H), 7.23 (t, *J* = 8.0 Hz, 1H), 7.31 (t, *J* = 8.0 Hz, 2H); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 21.1, 39.6, 117.6, 118.8, 119.2, 123.2, 123.7, 129.6, 129.67, 129.69, 131.0, 132.0, 136.7, 139.9, 157.06, 157.10; HRMS (FAB): Calcd for $C_{20}H_{18}OS$: 306.1078, Found: 306.1085.

***p*-Chlorobenzyl *p*-tolyl sulfide (9)**[16]

A colorless oil; ^{1}H NMR (500.2 MHz, $CDCl_3$) δ 2.31 (s, 3H), 4.00 (s, 2H), 7.06 (d, *J* = 8.0 Hz, 2H), 7.16 (d, *J* = 8.0 Hz, 2H), 7.18 (d, *J* = 8.0 Hz, 2H), 7.23 (d, *J* = 8.0 Hz, 2H); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 21.0, 39.2, 128.5, 129.7, 130.1, 131.1, 131.7, 132.8, 136.5, 136.9; MS (EI): *m/z* 248 (M^+).

***m*-Chlorobenzyl *p*-tolyl sulfide (10)**

A colorless oil; ^{1}H NMR (500.2 MHz, $CDCl_3$) δ 2.30 (s, 3H), 4.00 (s, 2H), 7.07 (d, *J* = 8.0 Hz, 2H), 7.10-7.11 (m, 1H), 7.16-7.20 (m, 4H), 7.23-7.24 (m, 1H); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 21.0, 39.4, 126.9, 127.2, 128.9, 129.6, 129.7, 131.1, 131.7, 134.1, 137.0, 139.9; HRMS (FAB): Calcd for $C_{14}H_{13}ClS$: 248.0427, Found 248.0427.

***o*-Chlorobenzyl *p*-tolyl sulfide (11)**

A colorless oil; ^{1}H NMR (500.2 MHz, $CDCl_3$) δ 2.31 (s, 3H), 4.16 (s, 2H), 7.07 (d, *J* = 8.0 Hz, 2H), 7.12-7.18 (m, 3H), 7.23 (d, *J* = 8.0 Hz, 2H), 7.36 (d, *J* = 8.0 Hz, 1H); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 21.1, 37.7, 126.7, 128.5, 129.59, 129.62, 130.7, 131.5, 131.8, 134.0, 135.5, 137.0; HRMS (FAB): Calcd for $C_{14}H_{13}ClS$: 248.0427, Found 248.0431.

.

***o*-Bromobenzyl *p*-tolyl sulfide (12)**

A pale yellow oil; ^{1}H NMR (500.2 MHz, $CDCl_3$) δ 2.31 (s, 3H), 4.16 (s, 2H), 7.06-7.10 (m, 3H), 7.15-7.18 (m, 2H), 7.23 (d, *J* = 8.5 Hz, 2H), 7.55 (d, *J* = 8.0 Hz, 1H); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 21.1, 40.4, 124.5, 127.3, 128.7, 129.6, 130.7, 131.5, 131.8, 132.9, 137.0, 137.1; HRMS (FAB): Calcd for $C_{14}H_{13}BrS$: 291.9921, Found 291.9933.

***o*-Iodobenzyl *p*-tolyl sulfide (13)**

A colorless oil; ^{1}H NMR (500.2 MHz, $CDCl_3$) δ 2.32 (s, 3H), 4.14 (s, 2H), 6.91 (t, *J* = 8.0 Hz,

1H), 7.08 (d, J = 8.0 Hz, 2H), 7.17-7.21 (m, 2H), 7.24 (d, J = 8.0 Hz, 2H), 7.84 (d, J = 8.0 Hz, 1H); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 21.1, 45.4, 100.6, 128.2, 128.8, 129.6, 130.0, 131.6, 131.7, 137.1, 139.7, 140.2; HRMS (FAB): Calcd for $C_{14}H_{13}IS$: 339.9783, Found 339.9788.

_p_-Tolyl _p_-trifluoromethyl sulfide (14)[17]

A colorless solid;mp 90.1-91.1 °C (lit.[17] 89-91 °C) ^{1}H NMR (300.4 MHz, $CDCl_3$) δ 2.31 (s, 3H), 4.07 (s, 2H), 7.06 (d, J = 8.4 Hz, 2H), 7.19 (d, J = 8.4 Hz, 2H), 7.33 (d, J = 8.4 Hz, 2H), 7.51 (d, J = 8.4 Hz, 2H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 21.0, 39.5, 124.1 (q, J_{C-F} = 271.6 Hz), 125.3 (q, J_{C-F} = 3.7 Hz), 129.0, 129.2 (d, J_{C-F} = 32.3 Hz), 129.7, 131.2, 131.4, 137.2, 142.1 (d, J_{C-F} = 1.3 Hz); MS (EI): *m/z* 282 (M^+).

3-Phenylpropyl _p_-tolyl sulfide (15)[18]

A colorless oil; ^{1}H NMR (500.2 MHz, $CDCl_3$) δ 1.93 (quin, J = 7.5 Hz, 2H), 2.31 (s, 1H), 2.74 (t, J = 7.5 Hz, 2H), 2.87 (t, J = 7.5 Hz, 2H), 7.08 (d, J = 8.0 Hz, 2H), 7.15-7.20 (m, 3H), 7.23 (d, J = 8.0 Hz, 2H), 7.27 (t, J = 7.5 Hz, 2H); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 21.0, 30.7, 33.6, 34.6, 125.9, 128.4, 128.5, 129.6, 130.0, 132.6, 136.0, 141.4; MS (EI): *m/z* 242 (M^+).

Pentyl _p_-tolyl sulfide (16)[19]

A colorless oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.89 (t, J = 7.5 Hz, 3H), 1.32 (quint, J = 7.5 Hz, 2H), 1.39 (quint, J = 7.5 Hz, 2H), 1.62 (quint, J = 7.5 Hz, 2H), 2.87 (t, J = 7.5 Hz, 2H), 7.09 (d, J = 8.5 Hz, 2H), 7.24 (d, J = 8.5 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 13.9, 20.9, 22.2, 28.9, 31.0, 34.3, 129.6, 129.7, 133.1, 135.8; MS (FAB): *m/z* 195 (M^++H).

2-Phenylpropyl _p_-tolyl sulfide (17)[20]

A yellow oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.38 (d, J = 7.0 Hz, 3H), 2.31 (s, 3H), 2.94 (sext, J = 7.0 Hz, 1H), 2.99-3.03 (dd, J = 8.5 Hz, 1H), 3.16-3.20 (dd, J = 6.5 Hz, 1H), 7.08 (d, J = 8.0 Hz, 2H), 7.19 (d, J = 8.0 Hz, 2H), 7.21-7.24 (m, 3H), 7.29-7.32 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$)

δ 20.9, 21.0, 39.4, 42.8, 126.5, 126.9, 128.5, 129.7, 129.9, 132.9, 136.0, 145.6; MS (FAB): *m/z* 242 (M^+).

2-(1-Naphthyl)ethyl *p*-tolyl sulfide (18)

A colorless oil; ^{1}H NMR (500.2 MHz, $CDCl_3$) δ 2.33(s, 3H), 3.22 (t, *J* = 8.0 Hz, 2H), 3.34 (t, *J* = 8.0 Hz, 2H), 7.12 (d, *J* = 8.5 Hz, 2H), 7.30-7.34 (m, 3H), 7.38 (t, *J* = 7.5 Hz, 1H), 7.44-7.48 (m, 2H), 7.72 (d, *J* = 8.5 Hz, 1H), 7.83 (d, *J* = 9.0 Hz, 1H), 7.88 (d, *J* = 8.5 Hz, 1H); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 21.0, 33.1, 35.2, 123.4, 125.49, 125.53, 126.0, 126.4, 127.2, 128.8, 129.7, 130.4, 131.6, 132.3, 133.8, 136.34; HRMS (FAB): Calcd for $C_{19}H_{18}S$: 328.9976, Found: 328.9955.

2-(*p*-Bromophenyl)ethyl *p*-tolyl sulfide (19)

A pale yellow oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.32 (s, 3H), 2.83 (t, *J* = 7.5 Hz, 2H), 3.07 (t, *J* = 7.5 Hz, 2H), 7.03 (d, *J* = 8.0 Hz, 2H), 7.10 (d, *J* = 8.0 Hz, 2H), 7.26 (d, *J* = 8.0 Hz, 2H), 7.39 (d, *J* = 8.0 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 21.0, 35.0, 35.6, 120.2, 129.7, 130.3, 131.4, 131.5, 132.1, 136.4, 139.1; HRMS (ESI): Calcd for $C_{15}H_{15}BrS$ (M^++Na): 328.9976, Found: 328.9955.

Octyl 3-phenylpropyl sulfide (20)

A colorless oil; ^{1}H NMR (500.2 MHz, $CDCl_3$) δ 0.88 (t, *J* = 7.0 Hz, 3H), 1.27-1.36 (m, 10H), 1.56 (quin, *J* = 7.5 Hz, 2H), 1.90 (quin, *J* = 7.5 Hz, 2H), 2.48-2.53 (m, 4H), 2.71 (t, *J* = 7.5 Hz, 2H), 7.18-7.19 (m, 3H), 7.28-7.29 (m, 2H); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 14.1, 22.6, 28.9, 29.16, 29.18, 29.7, 31.2, 31.4, 31.8, 32.1, 34.8, 125.8, 128.3, 128.4, 141.6; Anal. Calcd for $C_{17}H_{28}S$: C, 77.20; H, 10.67, Found: C, 77.27; H, 10.93.

3-Phenylpropionaldehyde dioctyl thioacetal (20')

A colorless oil; ^{1}H NMR (500.2 MHz, $CDCl_3$) δ 0.88 (t, *J* = 7.0 Hz, 6H), 1.27-1.37 (m, 20 H), 1.52-1.59 (m, 4H), 2.09 (q, *J* = 7.0 Hz, 2H), 2.52-2.57 (m, 2H), 2.62-2.67 (m, 2H), 2.85 (t, *J* = 7.5 Hz, 2H), 3.69 (t, *J* = 7.0 Hz, 1H), 7.17-7.21 (m, 3H), 7.24-7.29 (m, 2H); ^{13}C NMR (125.8 MHz,

$CDCl_3$) δ 14.1, 22.6, 29.0, 29.2, 29.4, 30.1, 31.8, 33.4, 37.7, 51.0, 125.9, 128.4, 128.5, 141.2; Anal. Calcd for $C_{25}H_{44}S_2$: C, 73.46; H, 10.85, Found: C, 73.40; H, 10.91.

α-Methylphenethyl octyl sulfide (21)

A colorless oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.88 (t, *J* = 7.0 Hz, 3H), 1.26-1.33 (m, 10H), 1.36 (d, *J* = 7.0 Hz, 3H), 1.50-1.56 (m, 2H), 2.43 (t, *J* = 7.5 Hz, 2H), 2.65-2.70 (dd, *J* = 8.0 Hz, 1H), 2.77-2.80 (dd, *J* = 6.5 Hz, 1H), 2.94 (sext, *J* = 7.0 Hz, 1H), 7.20-7.22 (m, 3H), 7.31 (t, *J* = 7.5 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.1, 21.0, 22.6, 28.9, 29.16, 29.17, 29.7, 31.8, 32.8, 40.2, 40.8, 126.4, 126.9, 128.4, 146.0; HRMS (FAB): Calcd for $C_{17}H_{29}S$: 265.1990, Found 265.1989.

2-(*o*-Methylphenyl)ethyl octyl sulfide (22)

A colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ; 0.88 (t, *J* = 6.6 Hz, 3H), 1.27-1.40 (m, 10 H), 1.60 (quint, *J* = 7.5 Hz, 2 H), 2.32 (s, 3H), 2.55 (t, *J* = 7.5 Hz, 2 H), 2.68-2.73 (m, 2H), 2.85-2.90 (m, 2 H), 7.12-7.16 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.1, 19.2, 22.6, 28.9, 29.1, 29.2, 29.6, 31.8, 32.26, 32.28, 33.8, 126.0, 126.4, 128.9, 130.2, 135.8, 138.8; HRMS (ESI): Calcd for $C_{17}H_{28}S$ (M^++Na): 287.1809, Found: 287.1796.

2-(*p*-Hydroxyphenyl)ethyl octyl sulfide (23)

A colorless oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.88 (t, *J* = 7.0 Hz, 3H), 1.27-1.36 (m, 10H), 1.58 (quint, *J* = 7.5 Hz, 2H), 2.52 (t, *J* = 7.5 Hz, 2H), 2.72 (t, *J* = 8.0 Hz, 2H), 2.81 (t, *J* = 8.0 Hz, 2H), 5.25 (brs, 1H), 6.76 (d, *J* = 8.5 Hz, 2H), 7.06 (d, *J* = 8.5 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 14.1, 22.6, 28.9, 29.1, 29.2, 29.6, 31.8, 32.2, 33.9, 35.4, 115.3, 129.5, 132.9, 154.0; HRMS (ESI): Calcd for $C_{16}H_{26}OS$ (M^+-H): 265.1626, Found: 265.1618.

Benzyl 3-phenylpropyl sulfide (25)

A colorless oil; ^{1}H NMR (500.2 MHz, $CDCl_3$) δ 1.86 (quin, *J* = 7.5 Hz, 2H), 2.42 (t, *J* = 7.5 Hz, 2H), 2.66 (t, *J* = 7.5 Hz, 2H), 3.68 (s, 2H), 7.12-7.29 (m, 10H); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ

30.6, 30.8, 34.8, 36.2, 125.8, 126.8, 128.3, 128.42, 128.43, 128.8, 138.5, 141.5; MS (EI); Anal. Calcd for $C_{17}H_{28}S$: C, 77.20; H, 10.67; S, 12.12, Found: C, 77.27; H, 10.93.

***tert*-Butyl 3-phenylpropyl sulfide (26)**

A colorless oil; ^{1}H NMR (300.5 MHz, $CDCl_3$) δ 1.31 (s, 9H), 1.90 (quin, J = 7.5 Hz, 2H), 2.54 (t, J = 7.5 Hz, 2H), 2.72 (t, J = 7.5 Hz, 2H), 7.18-7.20 (m, 3H), 7.25-7.30 (m, 2H); ^{13}C NMR (75.6 MHz, $CDCl_3$) δ 27.6, 31.0, 31.4, 35.1, 41.9, 125.8, 128.3, 128.4, 141.6; HRMS (ESI): Calcd for $C_{13}H_{20}S$ (M^++Na): 231.1183, Found: 231.1170.

***tert*-Butyl α-methylphenethyl sulfide (27)**

A colorless oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.30 (s, 9H), 1.36 (d, J = 7.0 Hz, 3 H), 2.66-2.70 (dd, J = 8.5 Hz, 1H), 2.78-2.81 (dd, J = 6.0 Hz, 1H), 2.91 (sext, J = 7.0 Hz, 1 H), 7.19-7.25 (m, 3H), 7.29-7.32 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 21.3, 30.9, 36.7, 40.5, 42.0, 126.4, 126.8, 128.4, 146.3; HRMS (ESI): Calcd for $C_{13}H_{20}S$ (M^++Na): 231.1183, Found: 231.1170.

2-[2-[(2-Methyl-2-butyl)thio]ethyl]-thiophene (28)

A colorless oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.34 (s, 9H), 2.83 (t, J = 7.5 Hz, 2H), 3.08 (t, J = 7.5 Hz, 2H), 6.85 (d, J = 3.5 Hz, 1H), 6.93 (t, J = 4.5 Hz, 1H), 7.14 (d, J = 5.0 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 30.3, 30.7, 31.0, 42.3, 123.4, 124.7, 126.7, 143.5; HRMS (EI); Calcd for $C_{10}H_{16}S_2$ (M^+): 200.0694, Found: 200.0671.

2-Phenyl-1,3-dithiolane (29)[21]

A colorless oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.32-3.36 (m, 2H), 3.48-3.51 (m, 2H), 5.64 (s, 1H), 7.26 (t, J = 7.5 Hz, 1H), 7.31 (t, J = 7.5 Hz, 2H), 7.52 (d, J = 7.5 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 40.2, 56.2, 127.9, 128.0, 128.4, 140.2; MS (EI): *m/z* 182 (M^+, 100%).

2-(4-Methylphenyl)-1,3-dithiolane (30)[21]

A white solid; mp 58.0-58.5 ºC (lit.[21] 58-59 ºC); ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.32 (s, 3H), 3.31-3.36 (m, 2H), 3.45-3.50 (m, 2H), 5.62 (s, 1H), 7.11 (d, *J* = 8 Hz, 2H), 7.41 (d, *J* = 8 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 21.1, 40.1, 56.1, 127.8, 129.1, 137.1, 137.8; MS (FAB): *m/z* 196 (M^+-H).

2-(4-Methoxylphenyl)-1,3-dithiolane (31)[21]

A white solid; mp 60.2-61.0 ºC (lit.[21] 64-65 ºC); ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.31-3.36 (m, 2H), 3.45-3.50 (m, 2H), 3.78 (s, 3H), 5.63 (s, 1H), 6.83 (d, *J* = 9.0 Hz, 2H), 7.45 (d, *J* = 9.0 Hz, 2H) ; ^{13}C NMR (125 MHz, $CDCl_3$) δ 40.1, 55.2, 56.0, 113.8, 129.1, 131.7, 159.3; MS (FAB): *m/z* 213 (M^++H, 100%).

2-Phenyl-[1,3]dithiolane (32)

A colorless oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.12 (q, *J* = 7.0 Hz, 2H), 2.77 (t, *J* = 7.0 Hz, 2H), 3.17-3.217 (m, 2H), 3.222-3.27 (m, 2H), 4.43 (t, *J* = 7.0 Hz, 1H), 7.18-7.19 (m, 3H), 7.29 (d, *J* = 8.0 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 35.2, 38.3, 41.0, 52.7, 126.0, 128.4, 128.5, 140.8; Anal. Calcd for $C_{11}H_{14}S_2$: C, 62.81; H, 6.71; S, 30.49, Found: C, 63.14; H, 6.93.

Benzyl *p*-chlorophenyl sulfide (33)[12]

A pale yellow solid; mp 48.5-49.8 °C (lit.[12] 57.6-58.4 °C) ^{1}H NMR (500.2 MHz, $CDCl_3$) δ 4.07 (s, 2H), 7.20-7.28 (m, 9H); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 39.3, 127.3, 128.5, 128.8, 128.9, 131.4, 132.5, 134.7, 137.1; MS (EI): *m/z* 234 (M^+, 100%).

***p*-Methoxybenzyl *p*-tolyl sulfide (34)**[16]

A colorless oil; ^{1}H NMR (297.6 MHz, $CDCl_3$) δ 2.30 (s, 3H), 3.77 (s, 3H), 4.02 (s, 2H), 6.80 (d, *J* = 8.6 Hz, 2H), 7.06 (d, *J* = 7.7 Hz, 2H), 7.16-7.22 (m, 2H); ^{13}C NMR (75.6 MHz, $CDCl_3$) δ 21.0, 39.1, 55.2, 113.8, 129.5, 129.7, 129.9, 130.6, 132.6, 136.4, 158.6; MS (EI): *m/z* 244 (M^+).

_p_-Iodobenzyl _p_-tolyl sulfide (35)

A white solid; mp 93.8-94.6 °C ^{1}H NMR (500.2 MHz, $CDCl_3$) δ 2.30 (s, 3H), 3.96 (s, 2H), 6.97 (d, J = 8.5 Hz, 2H), 7.06 (d, J = 8.5 Hz, 2H), 7.18 (d, J = 8.5 Hz, 2H), 7.57 (d, J = 8.5 Hz, 2H); ^{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; HRMS (EI); Calcd for $C_{14}H_{13}IS$ (M^+): 339.9783, Found: 339.9778.

_p_-Methylbenzyl octyl sulfide (37)[22]

A pale yallow oil; ^{1}H NMR (300.5 MHz, $CDCl_3$) δ 0.88 (t, J = 7.5 Hz, 3H), 1.25-1.30 (m, 10H), 1.55 (quin, J = 7.5 Hz, 2H), 2.33 (s, 3H), 2.40 (t, J = 7.5 Hz, 2H), 3.67 (s, 2H), 7.11 (d, J = 7.8 Hz, 2H), 7.20 (d, J = 7.8 Hz, 2H); ^{13}C NMR (75.6 MHz, $CDCl_3$) δ 14.1, 21.1, 22.6, 28.9, 29.15, 29.17, 29.2, 31.3, 31.8, 35.9, 128.7, 129.1, 135.6, 136.4; MS (EI): *m/z* 250 (M^+).

_p_-Methoxylbenzyl octyl sulfide (38)[22]

A pale yellow oil; ^{1}H NMR (500.2 MHz, $CDCl_3$) δ 0.88 (t, J = 7.0 Hz, 3H), 1.25-1.35 (m, 10H), 1.54 (quin, J = 7.5 Hz, 2H), 2.39 (t, J = 7.5 Hz, 2H), 3.66 (s, 2H), 3.79 (s, 3H), 6.84 (d, J = 8.5 Hz, 2H), 7.22 (d, J = 8.5 Hz, 2H); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 14.1, 22.6, 28.9, 29.13, 29.14, 29.21, 31.3, 31.8, 35.6, 55.2, 113.8, 129.8, 130.6, 158.5; MS (EI): *m/z* 266 (M^+).

_p_-Chlorobenzyl octyl sulfide (39)[22]

A pale yellow oil; ^{1}H NMR (500.2 MHz, $CDCl_3$) δ 0.88 (t, J = 7.5 Hz, 3H), 1.25-1.33 (m, 10H), 1.54 (quin, J = 7.5 Hz, 2H), 2.39 (t, J = 7.5 Hz, 2H), 3.66 (s, 2H), 7.23-7.28 (m, 4H); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 14.1, 22.6, 28.8, 29.1, 31.4, 31.8, 32.8, 35.62, 35.63, 128.6, 130.1, 132.6, 137.2; MS (EI): *m/z* 270 (M^+-H).

Benzyl _tert_-butyl sulfide (40)[23]

A colorless oil; ^{1}H NMR (300.5 MHz, $CDCl_3$) δ 1.35 (s, 9H), 3.76 (s, 2H), 7.20-7.35 (m, 5H); ^{13}C NMR (75.6 MHz, $CDCl_3$) δ 30.9, 33.4, 42.8, 126.7, 128.4, 128.9, 138.5; MS (EI): *m/z* 180 (M^+).

4-Bromophenyl 3-phenylpropyl sulfide (41)[24]

A colorless oil; ^{1}H NMR (300.5 MHz, $CDCl_3$) δ 1.94 (quin, *J* = 7.5 Hz, 2H), 2.73 (t, *J* = 7.5 Hz, 2H), 2.88 (t, *J* = 7.5 Hz, 2H), 7.12-7.38 (m, 9H); ^{13}C NMR (75.6 MHz, $CDCl_3$) δ 30.4, 32.8, 34.6, 119.5, 126.0, 128.40, 128.44, 130.5, 131.8, 135.8, 141.0; MS (EI): *m/z* 306 (M^+).

2-Bromophenyl 3-phenylpropyl sulfide (42)

A colorless oil; ^{1}H NMR (500.2 MHz, $CDCl_3$) δ 2.02 (quin, *J* = 7.5 Hz, 2H), 2.79 (t, *J* = 7.5 Hz, 2H), 2.92 (t, *J* = 7.5 Hz, 2H), 6.70 (t, *J* = 7.5 Hz, 1H), 7.14 (d, *J* = 8.0 Hz, 1H), 7.18-7.24 (m, 4H), 7.29 (t, *J* = 7.5 Hz, 2H), 7.53 (d, *J* = 8.0 Hz, 1H); ^{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; HRMS (EI): Calcd for $C_{15}H_{15}BrS$ (M^+): 306.0078, Found: 306.0076.

4-methoxyphenyl 3-phenylpropyl sulfide (43)

A colorless oil; ^{1}H NMR (500.2 MHz, $CDCl_3$) δ 1.89 (quin, *J* = 7.5 Hz, 2H), 2.72 (t, *J* = 7.5 Hz, 2H), 2.81 (t, *J* = 7.5 Hz, 2H), 3.78 (s, 3H), 6.83 (d, *J* = 8.5 Hz, 2H), 7.14-7.19 (m, 3H), 7.26 (t, *J* = 7.5 Hz, 2H), 7.32 (d, *J* = 8.5 Hz, 2H); ^{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; HRMS (EI); Calcd for $C_{16}H_{18}OS$ (M^+): 258.1078, Found: 258.1079.

Octyl 2-phenylbutyl sulfide (44)

A colorless oil; ^{1}H NMR (500.2 MHz, $CDCl_3$) δ 0.79 (t, *J* = 7.0 Hz, 3H), 0.88 (t, *J* = 7.0 Hz, 3H), 1.25-1.32 (m, 10H), 1.51 (quin, *J* = 7.5 Hz, 2H), 1.57-1.63 (m, 1H), 1.88-1.93 (m, 1H), 2.40 (t, *J* = 7.5 Hz, 2H), 2.62-2.68 (m, 1H), 2.73-2.80 (m, 2H), 7.17-7.23 (m, 3H), 7.29-7.32 (m, 2H); ^{13}C NMR (125.8 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; HRMS (FAB): Calcd for $C_{18}H_{31}S$ (M^++H): 279.2146, Found: 279.2142.

2-(Octylthio)ethyl phenyl sulfide (45)

A colorless oil; ^{1}H NMR (500.2 MHz, $CDCl_3$) δ 0.88 (t, *J* = 7.5 Hz, 3H), 1.26-1.35 (m, 10H), 1.54 (quin, *J* = 7.5 Hz, 2H), 2.52 (t, *J* = 7.5 Hz, 2H), 2.70-2.74 (m, 2H), 3.08-3.11 (m, 2H), 7.20 (t, *J* = 7.5 Hz, 1H), 7.29 (t, *J* = 8.0 Hz, 2H), 7.36 (d, *J* = 8.0 Hz, 2H); ^{13}C NMR (125.8 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: Calcd for $C_{16}H_{26}S_2$ (M^+): 282.1476, Found: 282.1495.

2-(1-Naphthyl)ethyl octyl sulfide (46)

A colorless oil; ^{1}H NMR (500.2 MHz, $CDCl_3$) δ 0.88 (t, *J* = 7.0 Hz, 3H), 1.27-1.37 (m, 10H), 1.59 (quin, *J* = 7.5 Hz, 2H), 2.56 (t, *J* = 7.5 Hz, 2H), 2.88 (t, *J* = 8.0 Hz, 2H), 3.34 (t, *J* = 8.0 Hz, 2H), 7.36 (t, *J* = 7.0 Hz, 1H), 7.40 (d, *J* = 7.5 Hz, 1H), 7.45-7.53 (m, 2H), 7.73 (d, *J* = 8.0 Hz, 1H), 7.85 (d, *J* = 8.0 Hz, 1H), 8.01 (d, *J* = 8.0 Hz, 1H); ^{13}C NMR (125.8 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; HRMS (EI): Calcd for $C_{20}H_{28}S$ (M^+): 300.1912, Found: 300.1913.

Butyl 3-phenylpropyl sulfide (47)[23]

A colorless oil; ^{1}H NMR (297.6 MHz, $CDCl_3$) δ 0.91 (t, *J* = 7.4 Hz, 3H), 1.39 (sext, *J* = 7.4 Hz, 2H), 1.55 (quin, *J* = 7.4 Hz, 2H), 1.90 (quin, *J* = 7.4 Hz, 2H), 2.49-2.54 (m, 4H), 2.72 (t, *J* = 7.4 Hz, 2H), 7.17-7.30 (m, 5H); ^{13}C NMR (75.6 MHz, $CDCl_3$) δ 13.7, 22.0, 31.2, 31.4, 31.71, 31.73, 34.8, 125.8, 128.3, 128.4, 141.6; MS (EI): *m/z* 209 (M^++H, 100%).

2-[3-(Octylthio)propyl]-phenol (48)

A colorless oil; ^{1}H NMR (300.4 MHz, $CDCl_3$) δ 0.88 (t, *J* = 6.9 Hz, 3H), 1.27-1.37 (m, 10H), 1.57 (quin, *J* = 7.5 Hz, 2H), 1.92 (quin, *J* = 6.9 Hz, 2H), 2.49-2.56 (m, 4H), 2.74 (t, *J* = 7.2 Hz, 2H), 5.86 (s, 1H), 6.78-6.88 (m, 2H), 7.06-7.11 (m, 2H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 14.1, 22.6, 28.2, 28.9, 29.1, 29.2, 29.5, 31.1, 31.8, 31.9, 115.7, 120.6, 127.2, 127.3, 130.3, 154.0; HRMS (EI): Calcd for $C_{17}H_{28}OS$ (M^+): 280.1861, Found: 280.1863.

References

(1) Otera, J. *Chem. Rev*. **1993**, *93*, 1449.

(2) Sweet, R. S.; Estes, F. L. *J. Org. Chem.* **1956**, *21*, 1426.

(3) (a) Sasaki, T.; Eguchi, E.; Toru, T. *J. Org. Chem*. **1970**, *35*, 4109. (b) Moriconi, E.; Stemnski, M. *J. Org. Chem.* **1972**, *37*, 2035.

(4) Moriya, T.; Yoneda, S.; Kawana, K.; Ikeda, R.; Konakahara, T.; Sakai, N. *Org. Lett*. **2012**, *14*, 4842.

(5) Moriya, T.; Yoneda, S.; Kawana, K.; Ikeda, R.; Konakahara, T.; Sakai, N. *J. Org. Chem*. **2013**, *78*, 10642.

(6) Kim, S.; Kim, S. S. *Tetrahedron Lett.* **1987**, *28*, 1913.

(7) Hansch, C.; Leo, A.; Taft, R. W. *Chem. Rev*. **1991**, *91*, 165.

(8) Inamoto, Y.; Nishimoto, Y.; Saito, T.; Yasuda, M.; Baba, A. *Chem. Lett*. **2013**, 1551.

(9) Bryliakov, K. P.; Talsi, E. P. *Eur. J. Org. Chem*. **2011**, 4693.

(10) Kakimoto, M.; Seri, T.; Imai, Y. *Synthesis* **1987**, 164.

(11) Itoh, T.; Mase, T. *Org. Lett*. **2004**, *6*, 4587.

(12) Shi, Y.; Cai, Z.; Guan, P.; Pang, G. *Synlett* **2011**, 2090.

(13) Ham, J.; Yang, I.; Kang, H. *J. Org. Chem.* **2004**, *69*, 3236.

(14) Barry, N.; Brondel, N.; Lawrence, S. E.; Maguire, A. R. *Tetrahedron* **2009**, *65*, 10660.

(15) Tanaka, K.; Ajiki, K. *Org. Lett*. **2005**, *7*, 1537.

(16) Ding, Q.; Cao, B.; Yuan, J.; Liu, X.; Peng, Y. *Org. Biomol. Chem*. **2011**, *9*, 748.

(17) Santoni, G.; Mba, M.; Bonchio, M.; Nugent, W. A.; Zonta, C.; Licini, G. *Chem. Eur. J.* **2010**, *16*, 645.

(18) Blakemore, P. R.; Burge, M. S. *J. Am. Chem. Soc*. **2007**, *129*, 3068.

(19) Reddy, V. P.; Kumar, A. V.; Swapna, K.; Rao, K. R. *Org. Lett*. **2009**, *11*, 1697.

(20) Movassagh, B.; Navidi, M. *ARKIVOC* **2008**, 47.

(21) Hajipour, A. R.; Pourmousavi, S. A.; Ruoho, A. E. *Org. Prep. Rroced. Int*. **2007**,

39, 403.

(22) Tanner, D. D.; Koppula, S.; Kandanarachchi, P. *J. Org. Chem*. **1997**, *62*, 4210.

(23) Sakai, N.; Moritaka, K.; Konakahara, T. *Eur. J. Org. Chem*. **2009**, 4123.

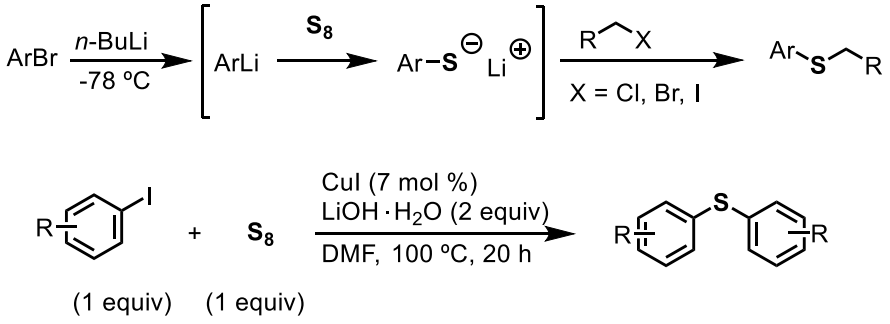
(24) Capozzi, M. A. M.; Centrone, C.; Fracchiolla, G.; Naso, F.; Cardellicchio, C. *Eur. J. Org. Chem*. **2011**, 4327.

Chapter 3.
Reductive Conversion to Benzyl Sulfides from Aromatic Carboxylic acids and Benzaldehydes with Elemental Sulfur

Introduction

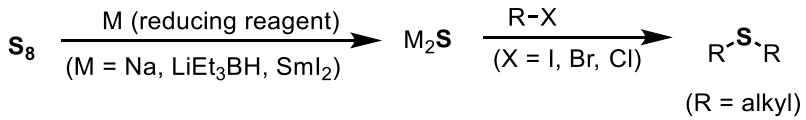
Elemental sulfur has many excellent properties, such as stability, nontoxicity, odorless, and an inexpensive substance. Therefore, the organic synthesis using elemental sulfur is versatile due to the advantages shown above. Among them, synthesis of aryl sulfides using elemental sulfur has been reported (Scheme 1).[1] For example, as a representative method, an organolithium compound reacted with elemental sulfur to produce a thiolate, followed by a substitution with an alkyl halide to give an unsymmetrical sulfide.[2] Recently, one-pot conversion from an aryl iodide and elemental sulfur to a diaryl sulfide using a copper catalyst and a strong base was reported.[3]

Scheme 1. Synthesis of Aryl Sulfides Using Elemental Sulfur



Except for alkyl triflormethyl sulfides,[4] the synthese of dialkyl sulfides using elemental sulfur has been reportrd (Scheme 2). For example, elemental sulfur was treated with a reducing reagent, such as Na,[5a] $LiEt_3BH$,[5b] SmI_2,[5c] to produce a metal sulfide, followed by a substitution with an alkyl halide to give dialkyl sulfide.

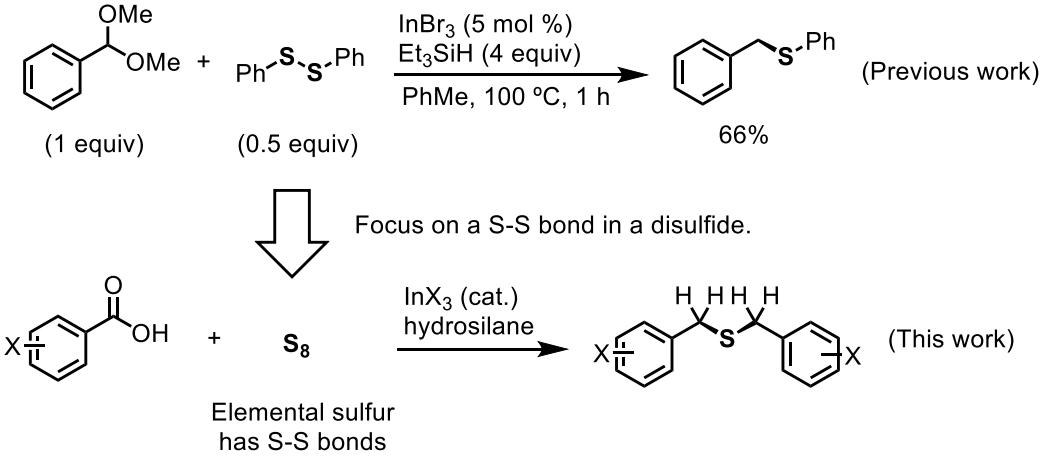
Scheme 2. Synthesis of Alkyl Sulfides Using Elemental Sulfur



However, these reactions need to use ignitable and unstable reducing reagents. Therefore, one-pot synthesis of dialkyl sulfides using elemental sulfur and a milder reducing reagent has been demanded.

In a previous work of Sakai's group, the synthesis of sulfide using acetals and disulfides in the presence of 5 mol % of $InBr_3$ and 4 equiv. of Et_3SiH was reported.[6] The author focused on a weak S-S bond in a sulfide. Elemental sulfur has S-S bonds and would act as a good sulfur source (Scheme 3). If it is possible to prepare dibenzyl sulfides from benzoic acids and an elemental sulfur with a hydrosilane, the use of troublesome handling reducing reagents could be avoided.

Scheme 3. Application to the Synthesis of Sulfides Using Elemental Sulfur

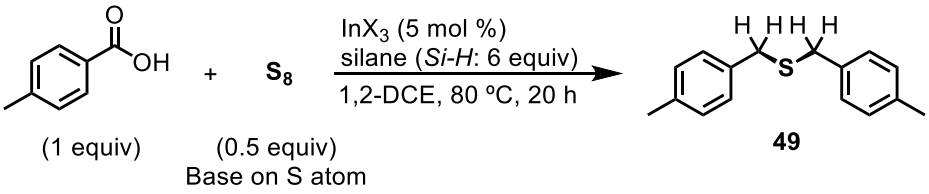


3-1. Reductive Conversion from Carboxylic acids and Elemental Sulfur

Initially, screenings of indium catalysts and hydrosilanes was conducted using *p*-toluic acid and elemental sulfur in 1,2-DCE at 80 ºC for 20 h (Table 1). When $(EtO)_3SiH$ and Et_3SiH were combined with a catalytic amount of $InBr_3$ respectively, both cases did not produce the expected sulfide **49** at all (entries 1 and 2). In the case with $PhMe_2SiH$, a low yield of the symmetrical sulfide

was detected (entry 3). When TMDS was used, the product yield increased slightly (entry 4). Interestingly, a combination of InI_3 and TMDS gave the expected sulfide in a good yield (entry 5).

Table 1. Screenings of Silanes

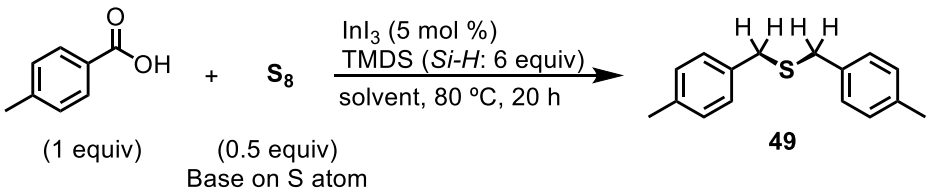


InX_3	silane	GC yield (%)
$InBr_3$	$(EtO)_3SiH$	0
$InBr_3$	Et_3SiH	0
$InBr_3$	$PhMe_2SiH$	15
$InBr_3$	TMDS	27
InI_3	**TMDS**	**74(56)[a]**

[a] Isolated yield.

Also, screenings of solvents were examined (Table 2). When toluene was applied, the yield of the sulfide decreased in comparison with 1,2-DCE (entry 2). Polar solvents, such as CH_3CN, DMF, and EtOH, were ineffective to the reaction (entry 3-5). These result showed that 1,2-DCE was the optimal solvent for this sulfidation.

Table 2. Examination of Solvent Effects

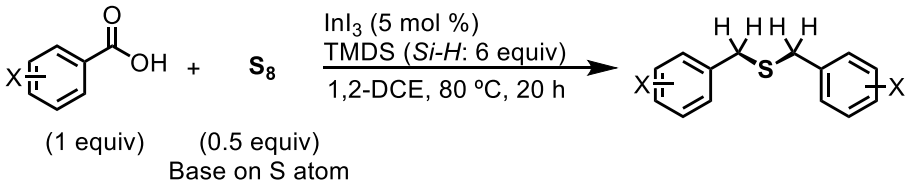


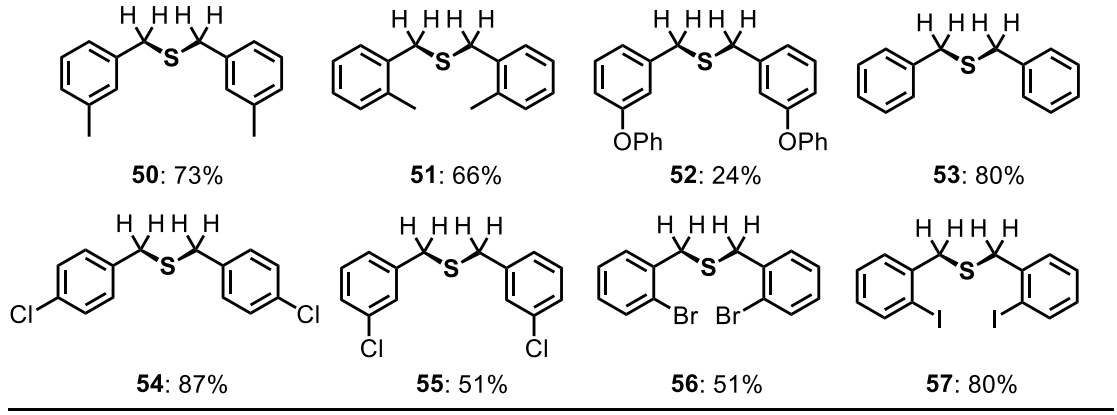
solvent	GC yield (%)
1,2-DCE	**(56)[a]**
PhMe	38
CH_3CN	0
DMF	0
EtOH	0

[a] Isolated yield.

With the optimal conditions, the synthesis of various dibenzyl sulfides was examined (Table 3). Benzoic acids having a methyl group at *m*- or *o*- position on the benzene ring gave sulfides **50** and **51** in moderate yields.

Table 3. Sulfidation from Benzoic Acids with Elemental Sulfur



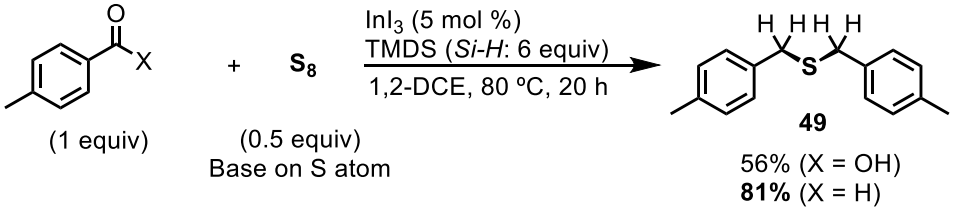


Although *m*-phenoxybenzoic acid was applied, only 24% of a sulfide **52** was obtained. Benzoic acid was converted into benzyl sulfide (**53**) in a good yield. In the case with *p*-chloro benzoic acid, the yield of **54** increased slightly. Using of *m*-chloro and *o*-bromobenzoic acid produced corresponding sulfides **55** and **56** in moderate yields. Substrate bearing an iodo group at *o*-position gave sulfide **57** in an 80% yield.

3-2. Reductive Conversion from Benzaldehydes and Elemental Sulfur

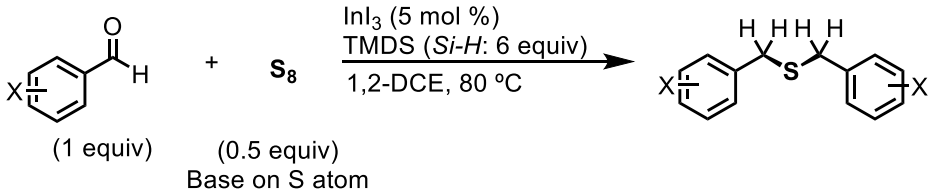
The author found that *p*-toluic acid reacted with elemental sulfur in the presence of 5 mol % of InI_3 and 6 equiv. (*Si-H*) of TMDS to afford a benzyl sulfide **49** in a 56% yield. When *p*-tolualdehyde, instead of *p*-toluic acid, was applied, the improvement of the product yield was observed (Scheme 4). Therefore, in the hope of increase in the product yield, the sulfidation from benzaldehydes and elemental sulfur was examined.

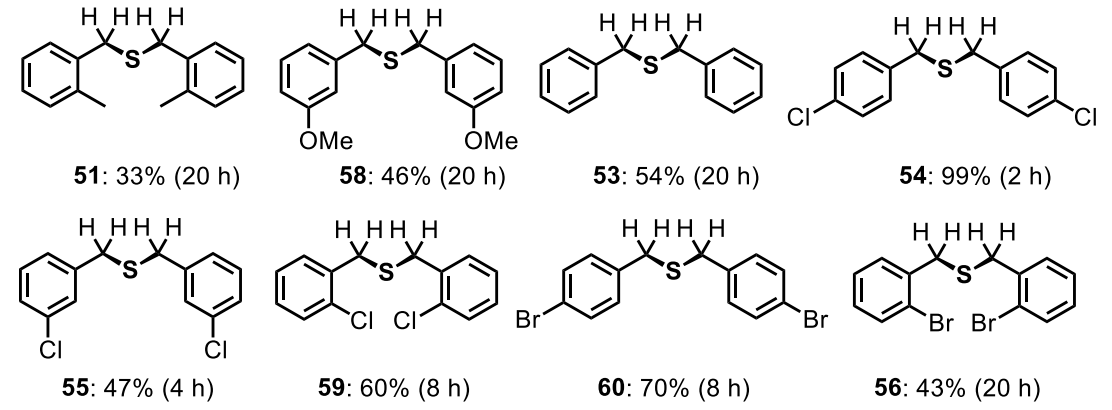
Scheme 4. Synthesis of a Dibenzyl Sulfide Using a Benzaldehyde instead of a Benzoic Acid.



The extension of the synthesis of benzyl sulfides using benzaldehydes was conducted (Table 4). *o*-Tolualdehyde and *m*-anisaldehyde gave sulfides **51** and **58** in low yields. Similarly, benzaldehyde led to decrease the yield of dibenzyl sulfide (**53**) compared with benzoic acid. On the other hand, *p*-chloro benzaldehyde was converted into sulfide **54** in a quantitative yield. Also, benzaldehydes bearing a chloro group at *m*- or *o*- position produced sulfides **55** and **59** in moderate yields. In the case with *p*-bromo and *o*-bromobenzaldehyde, the corresponding sulfides were obtained in 70% and 43%, respectively.

Table 4. Sulfidation of Benzaldehydes with Elemental Sulfur

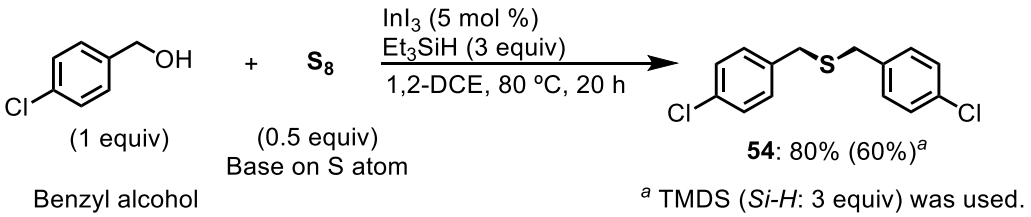




3-3. Reductive Conversion from Benzyl alcohols and Elemental Sulfur

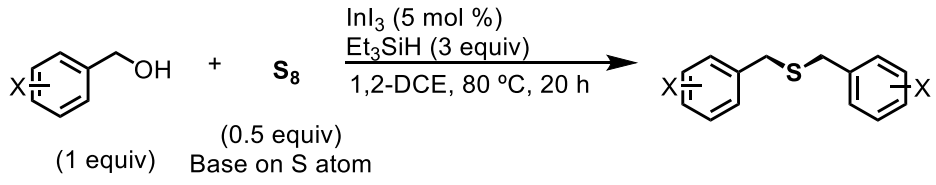
As applications, the sulfidation using benzyl alcohols that were prepared by reductions of either benzoic acids or benzaldehydes were examined with elemental sulfur. When *p*-chloro benzyl alcohol was treated with elemental sulfur in the presence of 5 mol % of InI_3 and 3 equiv of Et_3SiH to produce a dibenzyl sulfide in an 80% yield (Scheme 5).

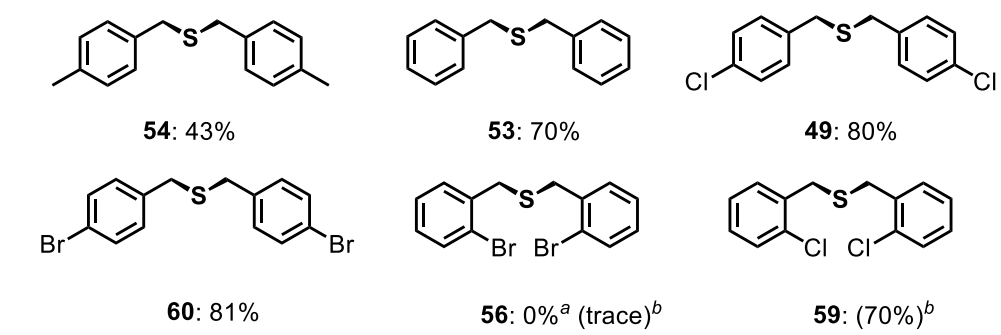
Scheme 5. Application Using a Benzyl Alcohol



The sulfidations using various benzyl alcohols are shown in Table 5. In the case of TMDS, instead of Et_3SiH, the product yield decreased to give the sulfide in a 60% yield. Therefore, a benzyl alcohol could be applied to the reaction system. Electron effects of substituents were examined using various benzyl alcohols. When benzyl alcohol was used, dibenzyl sulfide (**53**) was obtained in a moderate yield. When *p*-methyl benzyl alcohol was used, the yield of a sulfide **49** decreased slightly.

Table 5. Sulfidation of Benzyl Alcohol with an Elemental Sulfur





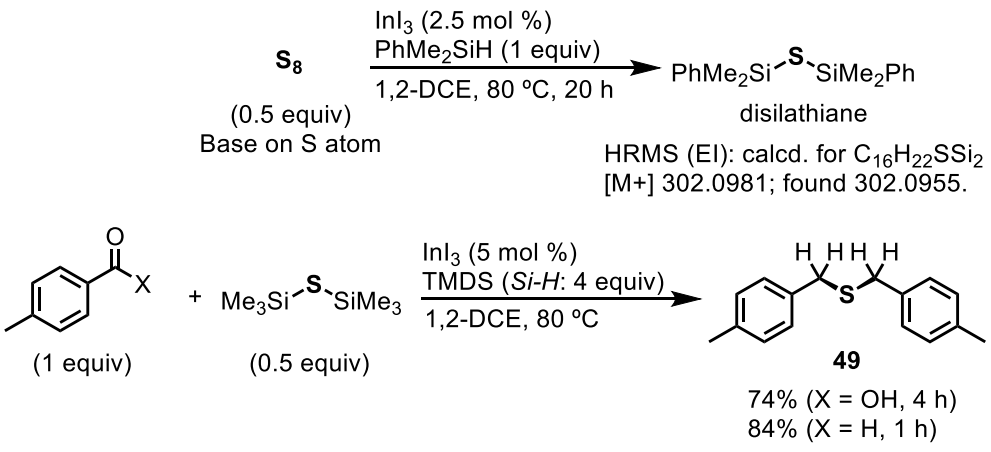
[a] Bis (*o*-bromobenzyl) ether was obtained in 99%. [b] TMDS (*Si-H*: 3 equiv) was used.

These results indicated that an electron-withdrawing effect of a chloro group would increase the yield of sulfide **54**. Similarly, a substrate bearing a bromo group at *p*-position afforded sulfide **60** in 81% yield. On the other hand, with *o*-bromobenzyl alcohol, the expected sulfide was not obtained and the corresponding dibenzyl ether was formed in a quantitative yield. The reason for the formation of the dibenzyl ether was unclear at this present. Interestingly, in the case with *o*-chloro benzyl alcohol, the corresponding sulfide **56** was obtained in a 70 % yield. From the results shown above, a steric effect of a bromo group would have an effect on the product yields.

3-4. Reaction Mechanism

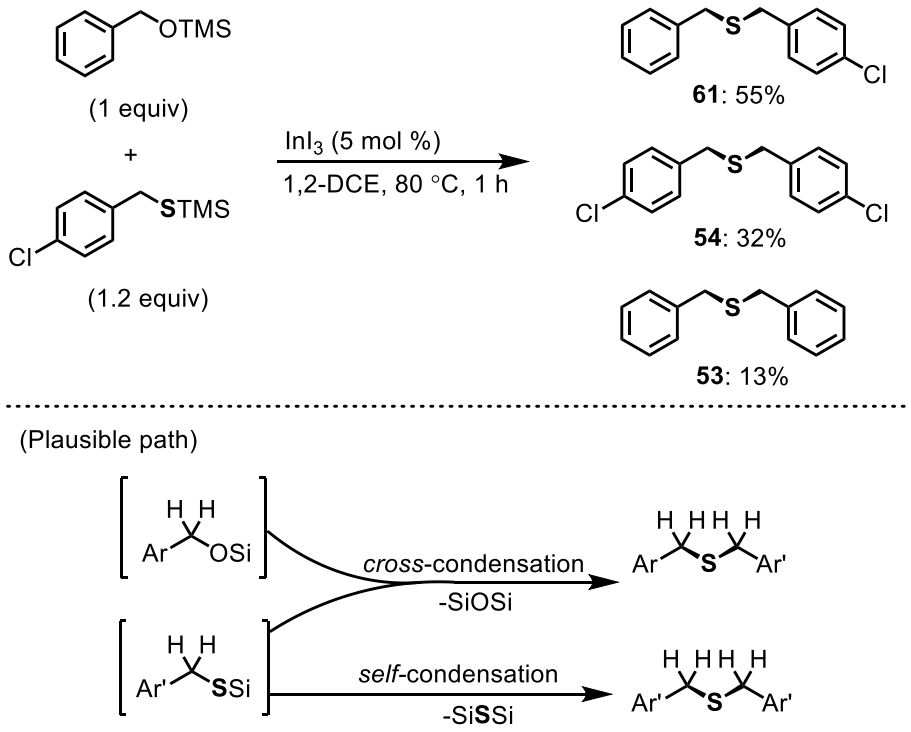
To elucidate the reaction path, several control experiments were conducted. Initially, a sulfur-containing conpound was investigated (Scheme 6). Elemental sulfur reacted with $PhMe_2SiH$ in the presence of InI_3 in 1,2-DCE at 80 ºC for 20 h. The reaction mixture measured using GC-mass spectrometer. Consequently, the mass of the peak was observed at 302.0955 and in good agreement with the exact mass of the corresponding disilathiane (calculated for $C_{16}H_{22}SSi_2$: 302.0981). Also, *p*-toluic acid was treated with a commercially available disilathiane, $Me_3SiSSiMe_3$ to afford sulfide **46** in a 74% yield. Similarly, in the case of *p*-tolualdehyde, the corresponding sulfide **46** was obtained. These results indicated that a disilathiane would function as a sulfur source.

Scheme 6. Examination of a Sulfur-Containing Intermediate



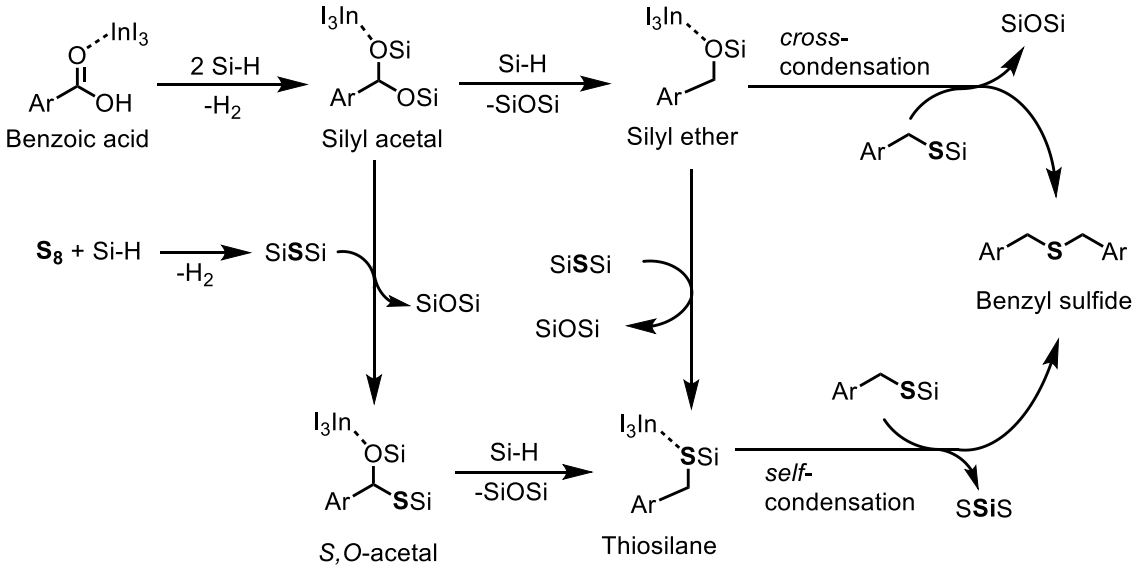
The author expected that a benzyl silyl ether and a benzyl silyl thioether would exist as intermediates, and a plausible reaction path with these intermediates was investigated (Scheme 7). When the silyl ether reacted with the thiosilane in the presence of 5 mol % of InI_3 in 1,2-DCE, 80 ºC for 1 h, the expected unsymmetrical sulfide **61** was formed in a 55% yield. Contrary to my expectation, the symmetrical sulfides **54** and **53** were detected in 32%, 13% yields, respectively. These results indicated that the sulfidation proceeded via not only a *cross*-condensation from a silyl ether and a thiosilane but also a *self*-condensation from two thiosilanes.

Scheme 7. Control Experiment Using a Benzyl Silylether and a Benzyl Silylthioether



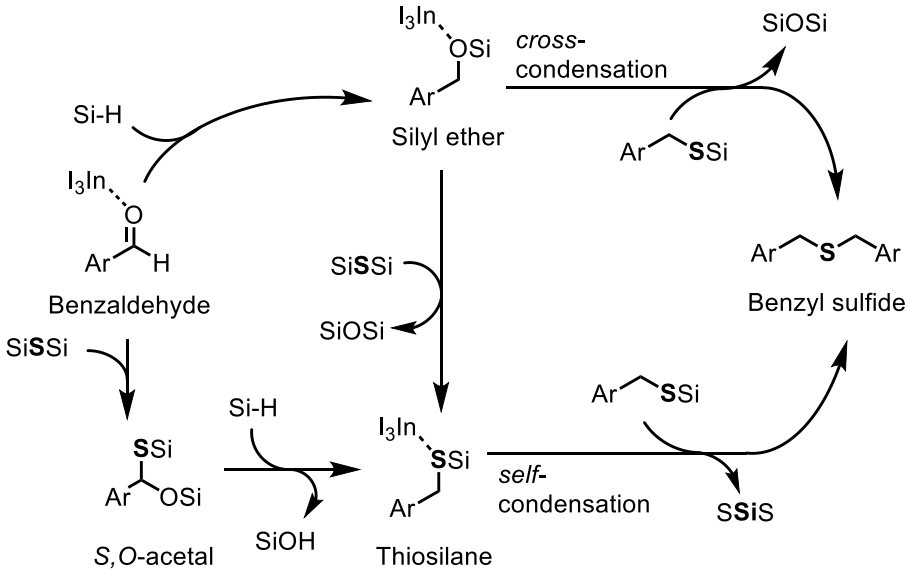
On the basis of the control experiments, a plausible mechanism using a benzoic acid is shown in Scheme 8. A benzoic acid reacted with two silanes to give a silyl acetal. The formed silyl acetal was activated by InI_3 to afford a silyl ether. As another path, a disilathiane formed from elemental sulfur and a silane attacked a central carbon of the silyl acetal, resulting in an *S,O*-acetal. The formed *S,O*-acetal was reduced to produce the thiosilane. The silyl ether and a thiosilane were converted into a final dibenzyl sulfide via a *cross*-condensation and a *self*-condensation.

Scheme 8. Plausible Mechanism for Benzoic Acids



Also, a plausible mechanism using a benzaldehyde is shown in Scheme 9. A benzaldehyde was reduced by a silane to produce a silyl ether. As another path, the benzaldehyde reacted with a disilathiane to give an *S,O*-acetal. The formed *S,O*-acetal was reduced by a silene to afford a thiosilane. Finally, the silyl ether and the thiosilane was converted into a final sulfide via *cross*-condensation and *self*-condensation.

Scheme 9. Plausible Mechanism for Benzaldehydes



Conclusion

The author have demonstrated the first reductive sulfidations from benzoic acids and elemental sulfur in the presence of 5 mol % of InI_3 and 6 equiv (*Si-H*) of TMDS to produce 9 examples of benzyl sulfides up to 97%.

With similar reaction conditions shown above, benzaldehyde instead of benzoic acids were also converted into dibenzyl sulfides in good yields. As applications, the sulfidation was comparable with benzyl alcohols.

When elucidations of reaction mechanisms was conducted by GCMS, a generation of disilathiane was observed. The author found that the reaction proceeded via cross-condensation between benzyl silyl ether and benzyl silyl thioether and self-condensation of benzyl thiosilyl ethers. In ordinary methods, the synthesis of alkyl sulfides, except for alkyl trifluoromethyl sulfides using elemental sulfur, needs ignitable and unstable reducing reagents, such as Na, $LiEt_3BH$ and SmI_2. On the other hand, the indium-catalyzed sulfidation uses a stable and an easy to handle hydrosilane, TMDS as a reducing reagent. Therefore, a dialkyl sulfide synthesis using elemental sulfur can proceed under mild conditions.

Experimental Section

General Method: All Reaction were carried out under a N_2 atomosphere, unless otherwise note. 1,2-Dichloroethane (1,2-DCE) was freshly distilled from P_2O_5 prior to use. All indium compounds were commercially available and were used without further purification. Hydrosilanes were used without further purification. Reactions were monitored by TLC analysis of TLC analysis of reaction aliquots. Thin-layer chromatography (TLC) was performed on silica gel 60 F_{254}, and the components were located by observation under UV light. Column chromatography was also performed using silica gel. ^1H NMR spectra were measured at 500 MHz using tetramethylsilane as an internal standard (0.00 ppm). $^{13}C\{^1H\}$ NMR spectra were measured at 125 MHz using the center peak of chloroform (77.0 ppm). High-resolution mass spectra were measured using NBA (3-nitrobenzylalcohol) as a matrix.

General procedure for the synthesis of sulfides: To a freshly distilled dichloroethane solution (0.60 mL) in a screw-capped vial under N_2 atmosphere were successively added a magnetic stirrer bar, carboxylic acid **1** (0.60 mmol) or aldehyde **4** (0.60 mmol), elemental sulfur (0.30 mmol of S atom, 9.6 mg), InI_3 (0.030 mmol, 15 mg), and TMDS (1.8 mmol, 3.2×10^2 μL). The vial was sealed with a cap that contained a PTFE septum. During heating of the reaction mixture at 80 °C (bath temperature), the reaction was monitored by TLC until consumption of the starting carboxylic acid. After the reaction, the resulting mixture was filtered by a Celite pad, and then evaporated under reduced pressure. The crude product was purified by a preparative TLC (SiO_2, 99/1 = hexane/EtOAc) to give the corresponding sulfide **2**.

Bis(4-methylbenzyl) sulfide (49)[7]

A white solid; mp 73—74 °C; ^{1}H NMR (500.2 MHz, $CDCl_3$) δ 2.33 (s, 6H), 3.56 (s, 4H), 7.11 (d, J = 8.0 Hz, 2H), 7.17 (d, J = 8.0 Hz, 2H); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 21.1, 35.2, 128.9, 129.1, 135.1, 136.5; MS (EI): *m/z* 242 (M^+).

Bis(3-methylbenzyl) sulfide (50)[7]

A colorless oil (General procedure A: 54.3 mg, 73%); ^{1}H NMR (500.2 MHz, DMSO-d_6) δ 2.27 (s, 6H), 3.60 (s, 4H), 7.05—7.19 (m, 8H); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 20.9, 35.2, 125.9, 127.5, 128.3, 129.5, 137.5, 138.2; MS (FAB): *m/z* 242 (M^+).

Bis(2-methylbenzyl) sulfide (51)[7]

A white solid; mp 81—83 °C; ^{1}H NMR (500.2 MHz, $CDCl_3$) δ 2.30 (s, 6H), 3.66 (s, 4H), 7.15—7.21 (m, 8H); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 19.0, 34.2, 125.8, 127.2, 129.6, 130.6, 135.7, 136.8; MS (FAB): *m/z* 242 (M^+).

Bis(3-phenoxybenzyl) sulfide (52)

A colorless oil; ^{1}H NMR (500.2 MHz, $CDCl_3$) δ 3.55 (s, 4H), 6.87 (d, *J* = 8.0 Hz, 2H), 6.93 (s, 2H), 6.98 (d, *J* = 8.0 Hz, 2H), 7.00 (d, *J* = 7.5 Hz, 4H), 7.09 (t, *J* = 7.5 Hz, 2H), 7.23 (t, *J* = 8.0 Hz, 2H), 7.32 (t, *J* = 7.5 Hz, 4H); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 35.3, 117.4, 118.9, 119.2, 123.3, 123.8, 129.69, 129.74, 140.1, 157.0, 157.4; HRMS (FAB): Calcd for $C_{26}H_{23}O_2S$ (M^++H): 399.1419, Found: 399.1425.

Benzyl sulfide (53)[8]

A colorless oil; ^{1}H NMR (500.2 MHz, $CDCl_3$) δ 3.60 (s, 4H), 7.25─7.33 (m, 10H); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 35.5, 126.9, 128.4, 129.0, 138.1; MS (FAB): *m/z* 214 (M^+).

Bis(4-chlorobenzyl) sulfide (54)[9]

A colorless oil; ^{1}H NMR (500.2 MHz, $CDCl_3$) δ 3.53 (s, 4H), 7.19 (d, *J* = 8.5 Hz, 2H), 7.27 (d, *J* = 8.5 Hz, 2H); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 34.8, 128.6, 130.3, 132.8, 136.3; MS (EI): *m/z* 282 (M^+, 100%).

Bis(3-chlorobenzyl) sulfide (55)[7]

A colorless oil (General procedure A: 43.9 mg, 51%, General procedure B: 40.8 mg, 47%); ^{1}H NMR (500.2 MHz, $CDCl_3$) δ 3.55 (s, 4H), 7.14 (d, *J* = 7.0 Hz, 2H), 7.23─7.26 (m, 6H); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 35.1, 127.1, 127.3, 129.0, 129.7, 134.3, 139.9; MS (EI): *m/z* 282 (M^+).

Bis(2-bromobenzyl) sulfide (56)[10]

A white solid; mp 64─66 °C; ^{1}H NMR (500.2 MHz, $CDCl_3$) δ 3.82 (s, 4H), 7.11 (t, *J* = 7.5 Hz, 2H), 7.26 (t, *J* = 7.5 Hz, 2H), 7.37 (d, *J* = 7.5 Hz, 2H), 7.56 (d, *J* = 7.5 Hz, 2H); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 36.4, 124.6, 127.5, 128.7, 130.7, 133.1, 137.2; MS (EI): *m/z* 370 (M^+).

Bis(2-iodobenzyl) sulfide (57)

A white solid (General procedure A: 114.8 mg, 80%); mp 74─75 °C; ^{1}H NMR (500.2 MHz,

$CDCl_3$) δ 3.80 (s, 4H), 6.94 (t, *J* = 7.5 Hz, 2H), 7.30 (t, *J* = 7.5 Hz, 2H), 7.36 (d, *J* = 7.5 Hz, 2H), 7.84 (d, *J* = 7.5 Hz, 2H); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 41.4, 100.9, 128.3, 128.8, 130.1, 139.8, 140.2; HRMS (ESI): Calcd for $C_{14}H_{12}I_2S$ (M^++Na): 488.8647, Found: 488.8641.

Bis(3-methoxybenzyl) sulfide (58)[7]

A colorless oil; ^{1}H NMR (500.2 MHz, $CDCl_3$) δ 3.57 (s, 4H), 3.78 (s, 6H), 6.76−6.87 (m, 6H), 7.21 (t, *J* = 7.8 Hz, 2H); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 35.5, 55.1, 112.5, 114.3, 121.3, 129.3, 139.6, 159.6; MS (EI): *m/z* 274 (M^+).

Bis(2-chlorobenzyl) sulfide (59)[11]

A white solid; mp 41−42 °C; ^{1}H NMR (500.2 MHz, $CDCl_3$) δ; 3.81 (s, 4H), 7.19−7.21 (m, 4H), 7.35−7.37 (m, 4H); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 33.7, 126.8, 128.4, 129.7, 130.7, 134.1, 135.6; MS (EI): *m/z* 282 (M^+).

Bis(4-bromobenzyl) sulfide (60)[11]

A white solid; mp 53−54 °C; ^{1}H NMR (500.2 MHz, $CDCl_3$) δ 3.52 (s, 4H), 7.13 (t, *J* = 8.0 Hz, 4H), 7.43 (t, *J* = 8.0 Hz, 4H); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 34.9, 120.9, 130.6, 131.6, 136.8; MS (EI): *m/z* 370 (M^+).

Benzyl 4-chlorobenzyl sulfide (61)[7]

A yellow oil; ^{1}H-NMR (300.5 MHz, $CDCl_3$) δ 3.54 (s, 2H), 3.58 (s, 2H), 7.18-7.31 (m, 9H); ^{13}C NMR (75.6 MHz, $CDCl_3$) δ 34.8, 35.5, 127.0, 128.48, 128.55, 128.9, 130.2, 132.7, 136.6, 137.8; *m/z* 248 (M^+).

References

(1) (a) Taniguchi, N. *Tetrahedron* **2012**, *68*, 10510. (b) Jiang, Y.; Qin, Y.; Xie, S.; Zhang, X.; Dong, J.; Ma, D. *Org. Lett*. **2009**, *11*, 5250. (c) Arisawa, M.; Ichikawa, T.; Yamaguchi, M. *Org. Lett*. **2012**, *14*, 5318. (d) Yavari, I.; Ghazanfarpour-Darjani, M.; Solgi, Y. *Synlett* **2014**, 1121. (e) Rostami, A.; Rostami, A.; Ghader, A.; Ali Zolfigol, M. *RSC Adv.* **2015**, *5*, 37060. (f) Rostami, A.; Rostami, A.; Ghaderi, A. *J. Org. Chem*. **2015**, *80*, 8694. (g) Wang, X.; Li, Y.; Yuan, Y. *Synthesis* **2013**, 1247.

(2) Ham, J.; Yang, I.; Kang, H. *J. Org. Chem*. **2004**, *69*, 3236.

(3) Chen, H.-Y.; Peng, W.-T.; Lee, Y.-H.; Cheng, Y.-L.; Chen. Y.-J.; Lai, Y.-C.; Jheng, N.-Y.; Chen, H.-Y. *Organometallics* **2013**, *32*, 5514.

(4) (a) Li, J.; Wang, P.; Xie, F.-F.; Yang, X.-G.; Song, X.-N.; Chen, W.-D.; Ren, J.; Zeng, B.-B. *Eur. J. Org. Chem*. **2015**, 3568. (b) Huang, Y.; He, X.; Lin, X.; Rong, M.; Weng, Z. *Org. Lett*. **2014**, *16*, 3284. (c) Chen, C.; Chu, L.; Qing, F.-L. *J. Am. Chem. Soc.* **2012**, *134*, 12454. (d) Zhai, L.; Li, Y.; Yin, J.; Jin, K.; Zhang, R.; Fu, X.; Duan, C. *Tetrahedron* **2013**, *69*, 10262. (e) Chen, C.; Xie, Y.; Chu, L.; Wang, R.-W.; Zhang, X.; Qing, F.-L. *Angew. Chem. Int. Ed*. **2012**, *51*, 2492.

(5) (a) Takata, T.; Saeki, D.; Makita, Y.; Yamada, N.; Kihara, N. *Inorg. Chem*. **2003**, *42*, 3712. (b) Gladysz, J. A.; Wong, V. K.; Jick, B. S. *Tetrahedron* **1979**, *35*, 2329. (c) Ogawa, A.; Takami, N.; Sekiguchi, M.; Sonoda, N.; Hirao, H. *Heteroatom Chem.* **1998**, *9*, 581.

(6) Sakai, N.; Moritaka, K.; Konakahara, T. *Eur. J. Org. Chem*. **2009**, 4123.

(7) Eccles, K. S.; Elcoate, C. J.; Lawrence, S. E.; Maguire, A. R. *ARKIVOC* **2010**, 216.

(8) Enthaler, S. *ChemCatChem* **2011**, *3*, 666.

(9) Park, Y. W.; Na, Y.; Baek, D.-J. *Bull. Korean Chem. Soc*. **2006**, *27*, 2023.

(10) Benjamin, S. L.; Karagiannidis, L.; Levason, W.; Reid, G.; Roger, M. *Organometallics* **2011**, *30*, 895.

(11) Overberger, C. G.; Gadea, R. A.; Smith, J. A. Kogon, I. C. *J. Am. Chem. Soc*. **1953**, *75*, 2075.

Chapter 4.
Conclusion

The author found the reductive sulfidation from carboxylic acids, esters and aldehydes using a catalytic amount of $InBr_3$ or InI_3 and 6 or 8 equiv of TMDS or $PhSiH_3$.

In *Chapter 1*, the sulfidation from carboxylic acids or esters and thiols was described. This the author found that the reaction could proceed with the reaction system combined with InX_3 (X = Br, I) and TMDS ($PhSiH_3$). This methodology could be applied to not only aromatic substrates but also aliphatic substrates. Consequently, 41 examples of sulfides could be prepared. Compared with $AlCl_3$, ZnI_2, strong acids as catalysts, the sulfidation used a catalytic amount of a Lewis acid. Furthermore, this methodology used commercially available thiols and hydrosilanes in comparison with Zn-promoted reductive sulfidation from esters. As application, a gram-scale synthesis of a sulfide was performed.

In *Chapter 2*, elemental sulfur as a sulfur source was applied to the indium-catalyzed reducing system. When a benzoic acid or a benzaldehyde was treated with elemental sulfur in the presence of an InI_3 catalyst and TMDS, 12 example of dibenzyl sulfide was obtained up to 99%. By combination of an InI_3 catalyst and Et_3SiH, the author succeeded in conversion of benzyl alcohols into dibenzyl sulfide. The developed sulfidation used milder hydrosilanes to activate elemental sulfur in comparison with Na, $LiEt_3BH$, SmI_2.

In conclusion, the author thinks that these methodologies would be versatile to prepare sulfides efficiently and safely.

List of Publication

1. Single-Step Thioetherification by Indium-Catalyzed Reductive Coupling of Carboxylic Acids with Thiols
   Norio Sakai, Takahiro Miyazaki, Tomohiro Sakamoto, Takuma Yatsuda, Toshimitsu Moriya, Reiko Ikeda, Takeo Konakahara
   Org. Lett. **2012**, *14*, 4366-4369.
2. Indium-Catalyzed Reductive Sulfidation of Aromatic Carboxylic Acids and Aldehydes with Elemental Sulfur to Prepare Symmetrical Benzyl Sulfides
   Takahiro Miyazaki, Kota Nishino, Shunsuke Yoshimoto, Yohei Ogiwara, Norio Sakai
   Eur. J. Org. Chem. **2015**, 1991-1994.
3. Indium(III)-Catalyzed Reductive One-Pot Synthesis of Thioethers from Aromatic Aldehydes and Elemental Sulfur
   Takahiro Miyazaki, Kouta Nishino, Takeo Konakahara, Norio Sakai
   Phosphorus, Sulfur, Silicon Relat. Elem. **2015**, *190*, 1378-1379.
4. Indium-Catalyzed Reductive Sulfidation of Esters by Using Thiols: An Approach to the Diverse Synthesis of Sulfides
   Takahiro Miyazaki, Shinsei Kasai, Yohei Ogiwara, Norio Sakai
   Eur. J. Org. Chem. **2016**, in press.
5. Indium-Catalyzed Direct Preparation of Dibenzyl Sulfides from Benzyl Alcohols and Elemental sulfur with a Hydrosilane and Its Application to the Preparation of Dibenzyl Selenide.
   Takahiro Miyazaki, Masahiro Katayama, Shunsuke Yoshimoto, Yohei Ogiwara, Norio Sakai
   Tetrahedron Lett. **2016**, 676-679.

Acknowledgement

The author with to express his sincerest gratitude to Associate Professor Dr. Norio Sakai, Department of Pure and Applied Chemistry, Faculty of Science and Technology, Tokyo University of Science (RIKADAI) for his continuous guidance, many invaluable suggestions, and his sincere encouragement throughout this work.

The author is indebted to Professor Dr. Takahiro Gunji, Professor Dr Hideki Sakai, Professor Dr. Hayato Ohwada, Professor Dr. Shin Aoki, and Professor Dr. Hiromi Uchiro for their advices. The author is indebted to Professor Dr. Takeo Konakahara for his encouragement and advice during the course of this work. The author also would like to express Dr. Yohei Ogiwara, Dr. Reiko Ikeda and Dr. Yumi Nakaike for their advice.

The author is much obliged to Mr. Tomohiro Sakamoto, Mr. Takuma Yatsuda, Mr. Shinsei Kasai, Mr. Kouta Nishino, Mr. Shunsuke Yoshimoto, Mr. Masahiro Katayama, Mr. Minetada Kiho and Mr. Kohji Fujii for their assistance and support in the course of this work. The author is thankful to members of Associate Professor Sakai's research group for their active collaborations.

The author deeply thank Shin-Etsu Chemical Co., Ltd., for the gift of hydrosilanes.

Finally, the author is deeply frateful to his parents, Mr. Hiroo Miyazaki and Mrs. Chizuko Miyazaki, and his sisters, Ms. Honami Miyazaki and Ms. Kaho Miyazaki, for their constant assistance and encouragement.