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Indium-catalyzed reductive three-component coupling reaction of aliphatic/aromatic carboxylic acids with *t*-butyl mercaptan leading to unsymmetrical dialkyl sulfides

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ABSTRACT

An InI_3–TMDS (1,1,3,3-tetramethyldisiloxane) reducing system efficiently catalyzed a sequential three-component coupling of aliphatic carboxylic acids, aromatic carboxylic acids, and *t*-butyl mercaptan (*t*-butylthiol), to produce unsymmetrical dialkyl sulfides. With this reducing system, *t*-butyl mercaptan became a new source of sulfidation via an alkyl *t*-butyl sulfide that functioned as the reaction intermediate.

Introduction

Multi-component coupling reactions are important and attractive procedures in synthetic organic chemistry. These procedures offer several advantages, such as environmentally benign system based on a reduction in the reaction process, a simultaneous formation of more than one bond on products, and a one-pot preparation of highly valuable compounds.[1] Dialkyl sulfides (thioethers) that involve two C(sp^3)–S bonds constitute the central framework of sulfur-containing natural products that function as biologically active substances and highly valuable molecules.[2] However, the development of a facile approach to the preparation of their structure has not been widely explored. As a representative approach to dialkyl sulfides, a Williamson-type synthesis that involves a substitution of alkyl halides, alcohols or their analogs with alkyl thiols (mercaptans) in the presence of a promoter, such as an acid or a base,[3] is well-known. In these methods, however, one substrate should involve a sulfur moiety, such as a thiol, in its molecular structure. Thus far, the one-pot production of unsymmetrical dialkyl sulfides has been limited to a three-component coupling reaction using two alkyl sources and one sulfur source, such as the coupling of alkyl halides, alcohols, and a thiourea derivative as a sulfur source in the presence of NaH.[4,5] Compared with inter- or intramolecular preparations of alkyl aryl sulfides using a sulfur source as a third component,[6–8] that of dialkyl sulfides has not been studied extensively. Therefore, we anticipated that there is plenty of room for development of the novel preparation of dialkyl sulfides.

In this context, we previously reported the indium-catalyzed sulfidation of aliphatic carboxylic acids with *t*-BuSH in the presence of a hydrosilane (*Si*-H) leading to alkyl sulfides (path a in Scheme 1).[9,10] During ongoing studies on sulfidation, however, we found that when aromatic carboxylic acids were reacted with the same reducing system, the corresponding dibenzyl sulfides were selectively obtained (path b in Scheme 1).[11] Therefore, we anticipated that in the first sulfidation step, alkyl carboxylic acids were treated with *t*-BuSH under an InI_3–TMDS reducing system to temporarily form an alkyl *t*-butyl sulfide, followed by the addition of an aromatic carboxylic acid to the reaction mixture, which resulted in the preparation of an unsymmetrical sulfide (path c in Scheme 1). Herein, we report the preliminary results of a sequential three-component coupling reaction of aliphatic carboxylic acids, aromatic carboxylic acids, and *t*-butyl mercaptan as a sulfur source, which led to unsymmetrical dialkyl sulfides.

Results and discussion

On the basis of our previous work, several examinations were conducted to establish the optimal conditions for the preparation of an unsymmetrical sulfide (Table 1).[12] A mixture of 3-phenylpropionic acid and *t*-BuSH was initially treated with 5 mol % of InI_3 and

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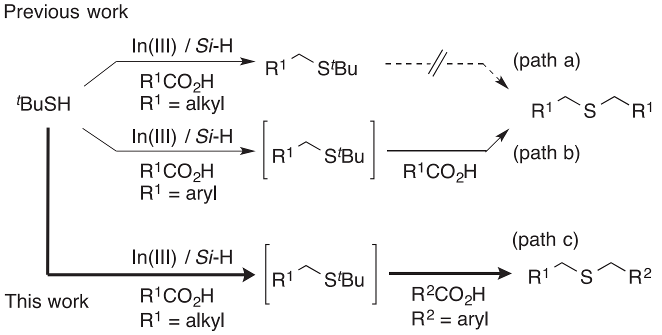


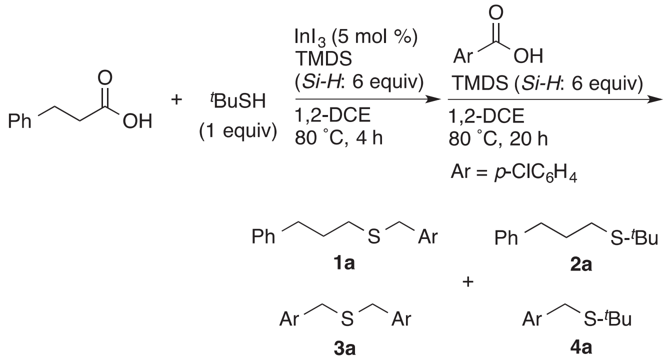
Scheme 1. Approach to unsymmetrical dialkyl sulfides.

TMDS (*Si-H*: 6 equiv) in 1,2-dichloroethane (1,2-DCE) at 80 °C for 4 h (the first sulfidation step), followed by the addition of both 4-chlorobenzoic acid and TMDS and heating for 20 h (the second sulfidation step) to produce the expected unsymmetrical sulfide **1a** in a 62% yield (entry 1).[13] Also, we observed the formations of symmetrical dibenzyl sulfide **3a** and sulfides **2a** and **4a** containing *t*-butyl mercaptan moiety. By-products **3a** and **4a** seems to be produced through coupling with the remaining *t*-butyl mercaptan in the first step. Thus, to prevent the formation of these by-products, the same reaction was then treated with a slightly excessive amount of the aliphatic carboxylic acid (1.25 equiv for ^{t}BuSH). As a result, the formation of **3a** and **4a** was undetectable (entry 2). In addition, the yield of sulfide **1a** was improved to an 80% NMR yield. An increase in the carboxylic acid to 2 equiv resulted in a decrease in the product yield (entries 3 and 4). There is no clear reason for these results at the present step. Conducting the same reaction with 10 mol% of InI$_3$ produced the best isolated yield of unsymmetrical sulfide **1a**, and the remaining of intermediate **2a** was restrained to only a 6% yield (entry 5).[14]

Next, we examined the scope and limitations of the present sulfidation of 3-phenylpropionic acid, *t*-butyl mercaptan, and a variety of aromatic carboxylic acids (Table 2). Benzoic acids with no substituent or an electron-donating group, such as a methyl group, at the para-position produced the corresponding unsymmetrical sulfides **1b** and **1c** in relatively good yields (entries 1 and 2). Also, the benzoic acid with an *o*-methyl-substituted group resulted in a decrease in the product yield (entry 3). Benzoic acids with an electron-withdrawing group, such as a halogen substituent and a trifluoromethyl group, regardless of the substituted position, afforded the expected sulfides **1e**–**1i** in modest to good yields (entries 4–8). A *p*-iodo-substituted substrate encountered a solubility problem that increased the solvent to 1 mL. On the other hand, *p*-nitrobenzoic acid did not undertake the coupling at the second step to recover the unreacted intermediate **2a**, which was formed in-situ in the first step in a high yield (entry 9). In most cases, the formation of the intermediate sulfide **2a** was detected. As described in introduction, no aliphatic carboxylic acids could be applied to the second sulfidation step.

This three-component coupling reaction could be applied to the sulfidation of several aliphatic carboxylic acids (Table 3). The cou-

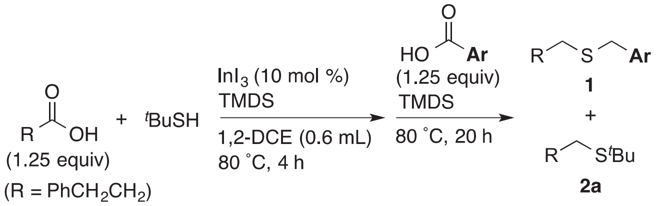
Table 1
Examinations of the reaction conditions



Entry	InI$_3$ (mol%)	PhCH$_2$CH$_2$CO$_2$H (equiv)	Yield[a] (%)			
			1a	2a	3a	4a
1	5	1.0	62	14	4	10
2	5	1.25	80	9	ND	ND
3	5	1.5	58	20	ND	ND
4	5	2.0	63	23	ND	ND
5	10	1.25	84 (78)	6	ND	ND

[a] NMR (isolated) yield.

Table 2
Scope of aromatic carboxylic acids used in the second sulfidation step[a]

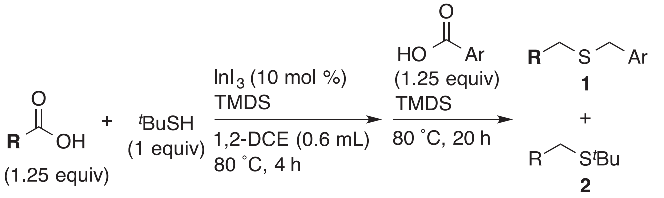


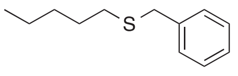
Entry	Ar	Yield (%)		
		1		2a
1	Ph	**1b**	80	12
2	*p*-MeC$_6$H$_4$	**1c**	85	6
3	*o*-MeC$_6$H$_4$	**1d**	47	8
4	*m*-ClC$_6$H$_4$	**1e**	67	3
5	*o*-ClC$_6$H$_4$	**1f**	65	6
6	*o*-BrC$_6$H$_4$	**1g**	54	Trace
7[b]	*p*-IC$_6$H$_4$	**1h**	46	Trace
8	*p*-CF$_3$C$_6$H$_4$	**1i**	67	7
9	*p*-NO$_2$C$_6$H$_4$	**1j**	nd	87

[a] Reaction conditions: 3-phenylpropionic acid (0.75 mmol), ^{t}BuSH (0.6 mmol), an aromatic carboxylic acid (0.75 mmol), TMDS (*Si-H*: 6 equiv) used in the first sulfidation step, TMDS (*Si-H*: 6 equiv) used in the second sulfidation step.

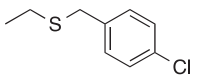
[b] 1,2-DCE (1 mL).

Table 3
Scope of the aliphatic carboxylic acids used in the first sulfidation step[a]

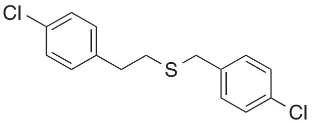




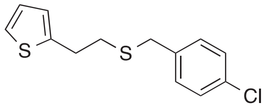
1k: 72% (**2k**: 23%)



1l: 53% (**2l**: nd)

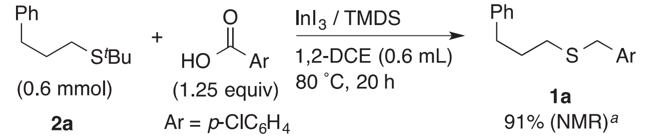


1m: 49% (**2m**: trace)



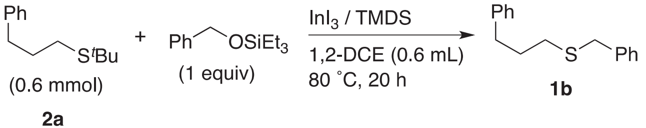
1n: 26% (**2n**: 13%)

[a] Reaction conditions: 3-phenylpropionic acid (0.75 mmol), ^{t}BuSH (0.6 mmol), an aromatic carboxylic acid (0.75 mmol), TMDS (*Si-H*: 6 equiv) used in the first sulfidation step, TMDS (*Si-H*: 6 equiv) used in the second sulfidation step.



^{a} Recovery of **2a** (5%, NMR).

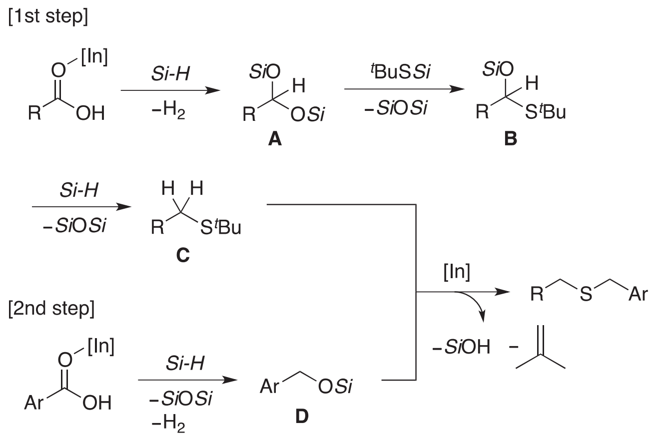
Scheme 2. Control experiment for sulfidation with the aromatic carboxylic acid.



		yield (%)^a **1b**	recovery (%)^a **2a**
InI$_3$ (10 mol %)	TMDS (*Si-H*: 1 equiv)	45	11
InI$_3$ (10 mol %)	------	46	11

^{a} NMR yield.

Scheme 3. Control experiments for sulfidation with the benzyl silyl ether.



Scheme 4. Plausible reaction mechanism for sulfidation.

pling of linear aliphatic carboxylic acids, such as propionic acid, acetic acid, and 4-chlorophenylacetic acid, with *t*-butyl mercaptan and benzoic acids proceeded in practical yields, and produced the corresponding sulfides **1k**–**1m**. Gratifyingly, although the product yield was relatively low, the reducing system could be applied to the sulfidation of an aliphatic carboxylic acid with a thiophene ring to produce sulfide **1n**.

To further understand the reaction pathway series, several control experiments were examined using the reaction intermediate, sulfide **2a**, and the results are summarized in Schemes 2 and 3. Initially, when the coupling of the prepared intermediate **2a** with 4-chlorobenzoic acid was treated under the optimal conditions composed of InI$_3$ and TMDS, the final sulfide **1a** was obtained in a high yield (91%) with the recovery of **2a** (5%). Consequently, these results show that a combination of both reagents is essential to effectively promote the second-step of sulfidation. Also, when a similar reaction of **2a** with a benzyl silyl ether derivative derived from an aromatic carboxylic acid and a hydrosilane was examined with the catalytic system involving both InI$_3$ and TMDS, sulfide **1b** was obtained in a moderate yield. In a similar manner, only the indium catalyst also produced **1b** in the same yield.

On the basis of the results of the control experiments,[15] a plausible pathway for the three-component coupling reaction is shown in Scheme 4. In the first sulfidation step, the reaction of a carboxylic acid with a hydrosilane occurred twice to produce silyl acetal **A**.[16] Then, the silyl acetal was reacted with a thiosilane, which was derived from *t*-butyl mercaptan and a hydrosilane,[17] to form *O*,*S*-acetal **B**. The acetal **B** was nucleophilically reduced with a hydrosilane to afford the sulfide intermediate **C**. In the second sulfidation step, an aromatic carboxylic acid was reduced to produce the corresponding silyl ether **D**. The silyl ether **D** was coupled with the previous sulfide intermediate **C**, finally leading to the unsymmetrical sulfide with the release of isobutene and a silanol.

Conclusions

We demonstrated that an indium(III)-hydrosilane reducing system effectively catalyzed a three-component coupling reaction of aliphatic carboxylic acids, aromatic carboxylic acids, and *t*-butyl mercaptan, which led to a one-pot preparation of unsymmetrical dialkyl sulfides. We also found that *t*-butyl mercaptan successfully functioned as one sulfur source in the sulfide skeleton, and disclosed that an alkyl *t*-butyl sulfide was a key intermediate in this sulfidation series.

Acknowledgments

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Supplementary data

Supplementary data (copies of the ^{1}H and ^{13}C NMR spectra of sulfides **1** that were produced by this procedure were supplied) associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2016.06.001.

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12. General procedure for the preparation of dialkyl sulfides: To a freshly distilled 1,2-dichloroethane solution (0.6 mL) in a screw-capped tube under a N_2 atmosphere were successively added a magnetic stirrer bar, an aliphatic carboxylic acid (0.75 mmol), ^{t}BuSH (0.60 mmol, 54 mg), InI_3 (0.060 mmol, 30 mg), and TMDS (1.8 mmol, 3.2×10^2 μL). The reaction tube was heated at 80 °C for 4 h. After cooling to room temperature, an aromatic carboxylic acid (0.75 mmol) and TMDS (1.8 mmol, 3.2×10^2 μL) were then added to the reaction vial. The mixture was heated at 80 °C for 20 h again. After the reaction, the reaction resultant mixture was quenched by a saturated $NaHCO_3$ aqueous solution (3 mL). The aqueous layer was extracted with chloroform (3 mL × 3). The combined organic phase was dried over anhydrous Na_2SO_4, filtered, and then evaporated under reduced pressure. The crude material was purified by column chromatography (silica gel, 99/1 = hexane/EtOAc) to give the corresponding dialkyl sulfide. The ratio of the remaining intermediate was determined by NMR using 1,1,2,2-tetrachloroethane as an internal standard.
13. Although the use of other hydrosilanes, such as Et_3SiH, $PhSiH_3$, and $MePh_2SiH$, was ineffective, Me_2PhSiH shows a relatively good effect for the similar sulfidation to give the corresponding unsymmetrical sulfide in an 80% yield.
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