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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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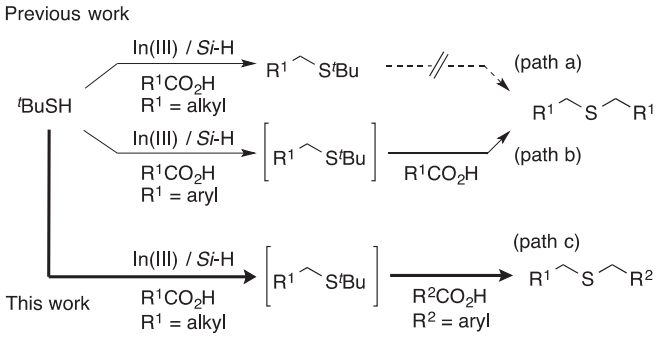


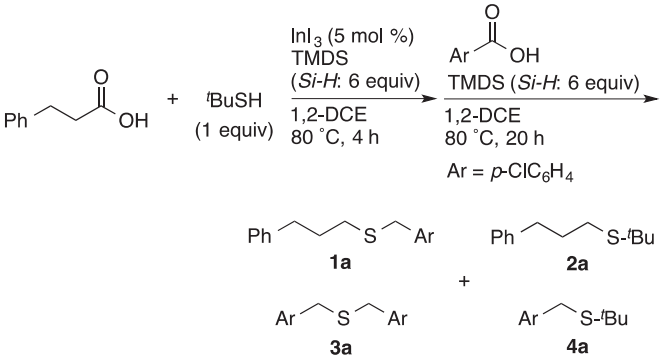
Scheme 1. Approach to unsymmetrical dialkyl sulfides.

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-

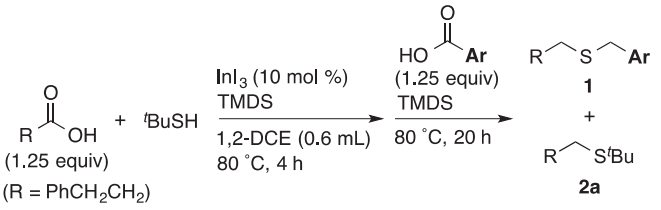
Table 1
Examinations of the reaction conditions



Entry	InI_3 (mol%)	$PhCH_2CH_2CO_2H$ (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.

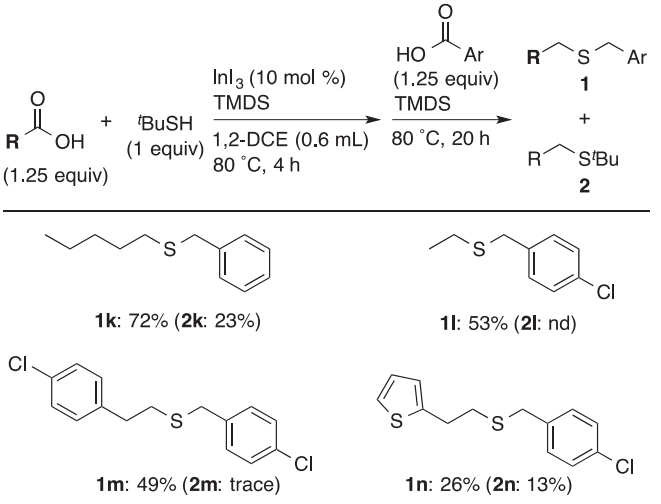
Table 2
Scope of aromatic carboxylic acids used in the second sulfidation step[a]



Entry	Ar	1	Yield (%) 1	2a
1	Ph	**1b**	80	12
2	*p*-MeC_6H_4	**1c**	85	6
3	*o*-MeC_6H_4	**1d**	47	8
4	*m*-ClC_6H_4	**1e**	67	3
5	*o*-ClC_6H_4	**1f**	65	6
6	*o*-BrC_6H_4	**1g**	54	Trace
7[b]	*p*-IC_6H_4	**1h**	46	Trace
8	*p*-$CF_3C_6H_4$	**1i**	67	7
9	*p*-$NO_2C_6H_4$	**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]



[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.