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Single-Step Thioetherification by Indium-Catalyzed Reductive Coupling of Carboxylic Acids with Thiols

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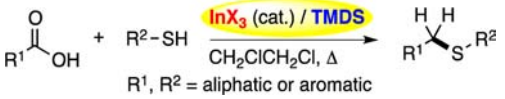
ABSTRACT



Direct thioetherification from a variety of aromatic carboxylic acids and thiols using a reducing system combined with $InBr_3$ and 1,1,3,3-teramethyldisiloxane (TMDS) in a one-pot procedure is demonstrated. It was also found that a system combined with InI_3 and TMDS underwent thioetherification of aliphatic carboxylic acids with thiols.

Thioethers (sulfides) have been utilized as an important building block for the efficient preparation of naturally occurring products and medicinal drugs.[1] The typical approach to thioethers involves the reduction of sulfoxides and sulfones (path a in Scheme 1),[2] the Williamson-type thioether synthesis from thiolate anions and alkyl halides in the presence of a base, and the condensation of thiols with benzyl/allyl alcohols in the presence of a Lewis acid (path b in Scheme 1).[3] More recently, a modified Ullmann condensation of thiols with aryl halides using a metal catalyst, such as copper,[4] palladium,[5] nickel,[6] and others,[7] has been reported (path c in Scheme 1).

Moreover, as examples using a reducing agent, such as a borane and a silane (path d in Scheme 1), Kikugawa has reported the direct reductive thioetherification of aldehydes or ketones with thiols using a pyridine–BH_3 reducing system in trifluoroacetic acid.[8] Several groups have carried out the synthesis of thioethers from aldehydes or

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(2) For example, see: (a) Hua, G.; Woollins, J. D. *Tetrahedron Lett.* **2007**, *48*, 3677. (b) Bahrami, K.; Khodaei, M. M.; Khedri, M. *Chem. Lett.* **2007**, *36*, 1324. (c) Kikuchi, S.; Konishi, H.; Hashimoto, Y. *Tetrahedron* **2005**, *61*, 3587. (d) Miller, S. J.; Collier, T. R.; Wu, W. *Tetrahedron Lett.* **2000**, *41*, 3781. (e) Shimizu, M.; Shibuya, K.; Hayakawa, R. *Synlett* **2000**, 1437. (f) Wakisaka, M.; Hatanaka, M.; Nitta, H.; Hatamura, M.; Ishimaru, T. *Synthesis* **1980**, 67. (g) Gardner, J. N.; Kaiser, S.; Krubiner, A.; Lucas, H. *Can. J. Chem.* **1973**, *51*, 1419.

(3) For example, see: (a) Han, X.; Wu, J. *Org. Lett.* **2010**, *12*, 5780. (b) Han, X.; Zhang, Y.; Wu, J. *J. Am. Chem. Soc.* **2010**, *132*, 4104. (c) Snyder, S. A.; Breazzano, S. P.; Ross, A. G.; Lin, Y.; Zografos, A. L. *J. Am. Chem. Soc.* **2009**, *131*, 1753. (d) Cozzi, P. G.; Zoli, L. *Angew. Chem., Int. Ed.* **2008**, *47*, 4162. (e) Koval, I. *Russ. J. Org. Chem.* **2007**, *43*, 319 and references cited therein. (f) Guindon, Y.; Frenette, R.; Fortin, R.; Rokach, J. *J. Org. Chem.* **1983**, *48*, 1357.

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(5) For example, see: (a) Lee, P. H.; Park, Y.; Park, S.; Lee, E.; Kim, S. *J. Org. Chem.* **2011**, *76*, 760. (b) Fernandez-Rodriguez, M. A.; Hartwig, J. F. *J. Org. Chem.* **2009**, *74*, 1663. (c) Mispelaere-Canivet, C.; Spindler, J.-F.; Perrio, S.; Beslin, P. *Tetrahedron* **2005**, *61*, 5253. (d) Murata, M.; Buchwald, S. L. *Tetrahedron* **2004**, *60*, 7397. (e) Itoh, T.; Mase, T. *Org. Lett.* **2004**, *6*, 4587. (f) Miller, K. J.; Abu-Omar, M. M. *Eur. J. Org. Chem.* **2003**, 1294. (g) Kosugi, M.; Ogata, T.; Terada, M.; Sano, H.; Migita, T. *Bull. Chem. Soc. Jpn.* **1985**, *58*, 3657.

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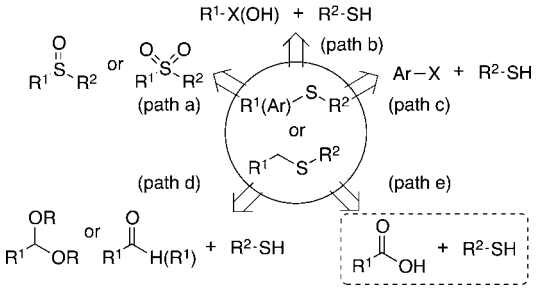
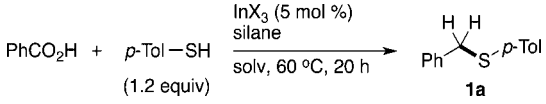
ketones and thiols using a reducing system combined with a Lewis or Brønsted acid and a hydrosilane.[9] In this context, during ongoing studies on a functional group conversion using an $InBr_3-Et_3SiH$ reducing system,[10,11] we accomplished a direct reductive thioetherification of acetals with disulfides.[12] However, the substrate employed in these contributions is generally limited to an aldehyde, a ketone, or an acetal. As far as can be ascertained, the direct conversion from carboxylic acids, which are relatively tolerant to a reducing agent, and thiols to thioethers has not been studied (path e in Scheme 1).[13] Herein, we report the first example of a single-step synthesis of thioethers by the indium-catalyzed reductive coupling of carboxylic acids with thiols.

Scheme 1. Diverse Approaches to Thioethers



Initially, to find the optimal conditions, the solvent effect and amount of a reducing reagent, a hydrosilane, were examined using a model reaction of benzoic acid with *p*-toluenethiol in the presence of 5 mol % of indium trihalide (Table 1). Use of the best hydrosilane, Et_3SiH, in our previous work was ineffective for the reductive conversion (entries 1—3). Thus, in cases using $InBr_3$, when Et_3SiH was changed to another hydrosilane, $PhSiH_3$, and a siloxane, TMDS, the yield of thioether **1a** was remarkably increased (entries 4 and 5).[14] After further adjustment, the reaction conditions that consisted of 5 mol % of $InBr_3$ or InI_3 and 6 equiv (*Si*−*H*) of TMDS in 1,2-dichloroethane at 80 °C were determined to be the best for this thioetherification (entries 6 and 7).

Table 1. Examinations of the Optimal Conditions for Thioetherification from Benzoic Acid and *p*-Toluenethiol



entry	InX_3	silane (*Si*−*H* equiv)	solvent	temp (°C)	yield (%)[a]
1	$InBr_3$	Et_3SiH (4)	$CHCl_3$	60	4
2	$InCl_3$	Et_3SiH (4)	$CHCl_3$	60	7
3	$In(OTf)_3$	Et_3SiH (4)	$CHCl_3$	60	11
4	$InBr_3$	$PhSiH_3$ (12)	$CHCl_3$	60	59
5	$InBr_3$	TMDS[b] (8)	$CHCl_3$	60	69
6	$InBr_3$	TMDS[b] (6)	CH_2ClCH_2Cl	80	(91)
7[c]	InI_3	TMDS[b] (6)	CH_2ClCH_2Cl	80	(94)

[a] GC (isolated) yield. [b] TMDS = tetramethyldisiloxane. [c] Reaction time: 4 h.

With the optimal conditions that mainly used economical $InBr_3$, the scope and limitations of the thioetherification of benzoic acids were examined with a variety of thiols (Scheme 2). When the reaction was run with benzenethiols having an electron-donating or -withdrawing group, the corresponding thioethers **2a**−**5a** were produced in good to excellent yields. When the reaction with an aliphatic thiol, such as thiobenzyl alcohol and 1-octanethiol, was also carried out, the corresponding thioether derivatives **6a** and **7a** were obtained in good yields. When the reaction was performed with 1,2-ethanedithiol, the cyclic thioacetal derivatives **8a** and **9a** were obtained in good yields.[15] Also the electronic effect of a substituent on the benzoic acid did not affect the reaction yield to afford the expected thiols **10a**−**17a**. However, for the substrate with an iodo substituent, when the reaction was carried out with InI_3, only the expected thioether **16a** was obtained in a yield of 82%. When using $InBr_3$, the formation of a trace amount of the deiodinated product **1a** was detected by GC. This result implied that some part of the reaction series might involve

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(10) (a) Sakai, N.; Usui, Y.; Ikeda, R.; Konakahara, T. *Adv. Synth. Catal.* **2011**, *353*, 3397. (b) Sakai, N.; Nagasawa, K.; Ikeda, R.; Nakaike, Y.; Konakahara, T. *Tetrahedron Lett.* **2011**, *52*, 3133. (c) Sakai, N.; Kawana, K.; Ikeda, R.; Nakaike, Y.; Konakahara, T. *Eur. J. Org. Chem.* **2011**, 3178. (d) Sakai, N.; Fujii, K.; Nabeshima, S.; Ikeda, R.; Konakahara, T. *Chem. Commun.* **2010**, *46*, 3173. (e) Sakai, N.; Moritaka, K.; Konakahara, T. *Eur. J. Org. Chem.* **2009**, 4123. (f) Sakai, N.; Moriya, T.; Fujii, K.; Konakahara, T. *Synthesis* **2008**, 3533. (g) Sakai, N.; Fujii, K.; Konakahara, T. *Tetrahedron Lett.* **2008**, *49*, 6873. (h) Sakai, N.; Moriya, T.; Konakahara, T. *J. Org. Chem.* **2007**, *72*, 5920. (i) Sakai, N.; Hirasawa, M.; Konakahara, T. *Tetrahedron Lett.* **2005**, *46*, 6407.

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(12) For selected papers of preparation of thioethers using *O,O*- or *O,S*-acetals, see: (a) Mukaiyama, T.; Ohno, T.; Nishimura, T.; Han, J. S.; Kobayashi, S. *Bull. Chem. Soc. Jpn.* **1991**, *64*, 2524. (b) Mukaiyama, T.; Ohno, T.; Nishimura, T.; Han, J. S.; Kobayashi, S. *Chem. Lett.* **1990**, *19*, 2239. (c) Kim, S.; Ho Park, J.; Lee, S. *Tetrahedron Lett.* **1989**, *30*, 6697.

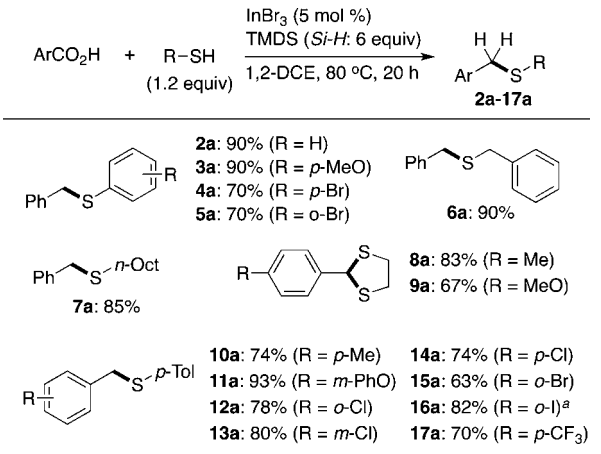
(13) (a) Reductive conversion from carboxylic acids to *S,S*-acetals was reported; see: Kim, S.; Kim, S. S. *Tetrahedron Lett.* **1987**, *28*, 1913. (b) For reduction of thioesters to sulfides with $LiAlH_4-AlCl_3$, see: Bublitz, D. E. *J. Org. Chem.* **1967**, *32*, 1630.

(14) To avoid a drastic decrease in the yield by polymerization of a silane, the amount of the silane was adjusted in each case. Also an $In(OTf)_3$−TMDS reducing system did not produce the corresponding thioether.

(15) Kim, S.; Kim, S. S.; Lim, S. T.; Shim, S. C. *J. Org. Chem.* **1987**, *52*, 2114.

a radical path. Unfortunately, the reductive thioetherification of the aromatic carboxylic acids having the nitro group, the nitrile group, and alkenes did not occur.

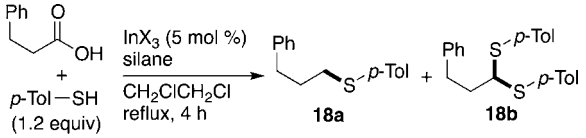
Scheme 2. Synthesis of Thioethers from Aromatic Carboxylic Acids and Thiols



[a] InI_3 was used.

When the optimal conditions using $InBr_3$ and TMDS in CH_2ClCH_2Cl were applied to the reaction of an aliphatic carboxylic acid with a thiol, contrary to our expectations, there was a decrease in the yield of the thioether **18a** and the formation of *S,S*-acetal **18b** as a major product (entry 1 in Table 2). Thus, when InI_3 was used, the yield of thioether **18a** was drastically improved to 60% (entry 2). Moreover, when the amount of siloxane increased to 4 equiv, the quantitative formation of thioether **18a** was observed without the production of thioacetal **18b** (entry 3).

Table 2. Re-examination of the Reaction Conditions

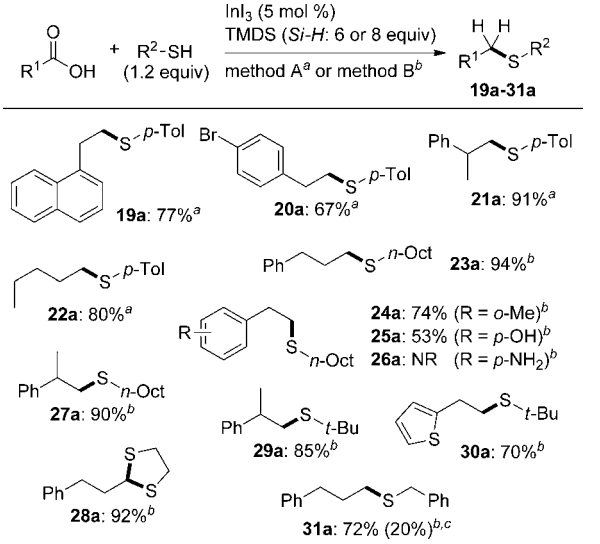


			yield (%)[a]	
entry	InX_3	silane (*Si–H* equiv)	**18a**	**18b**
1	$InBr_3$	TMDS (8)	33	58
2	InI_3	TMDS (6)	60	35
3	InI_3	TMDS (8)	(97)	ND

[a] GC (Isolated) yield.

With the optimal conditions, when the reactions of aliphatic carboxylic acids having a naphthylmethyl substituent, a benzyl substituent, a branched carbon chain, or a linear carbon chain with *p*-toluenethiol were conducted, the corresponding thioethers **19a**–**22a** were obtained in good to excellent yields (Scheme 3). When the subsequent reaction of an aliphatic carboxylic acid with an aliphatic thiol, 1-octanethiol, was carried out, formation of the expected thioether derivatives **23a**–**25a** and **27a** was observed in moderate to good yields. The reducing system did not affect a halogen substituent or a hydroxy group to any great extent. However, a primary amino group strongly coordinated to the indium catalyst, retarding the expected thioetherification. Use of 1,2-ethanedithiol gave the cyclic thioacetal **28a** as well as the case using an aromatic carboxylic acid. Although the unreacted siloxane remained in this case, further reduction to a linear thioether did not occur (see Table 2 and Scheme 5). When the reaction of a carboxylic acid with a more hindered aliphatic thiol, 2-methyl-2-butanethiol, was run, the thioetherification proceeded smoothly to produce the corresponding thioether derivative **29a** in good yield. Moreover, the reaction of the carboxylic acid having thiophene with the bulky thiol as a heterocycle gave the desired thioether **30a** in good yield. Only when using thiobenzyl alcohol was the formation of the *S,S*-acetal **31b** observed with the thioether **31a**.

Scheme 3. Direct Synthesis of Thioethers from Aliphatic Carboxylic Acids and Thiols



[a] Method A: InI_3 (5 mol %), TMDS (8 equiv), CH_2ClCH_2Cl, 80 °C, 4 h. [b] Method B: InI_3 (5 mol %), TMDS (6 equiv), $CHCl_3$, 60 °C, 4 h. [c] Yield of *S,S*-acetal **31b** was in parentheses.

It was noteworthy that although a conventional Williamson-type thioether synthesis using a bulky thiol gave the expected thioether **32a** in low yield, our method produced the same thioether in a good yield (Scheme 4).

To understand the reaction pathway for thioetherification, several control experiments were then conducted.

(16) A reductive C–S bond cleavage of an *S,S*-acetal by a metal hydride complex was reported; see: Ikeshita, K.-i.; Kihara, N.; Sonoda, M.; Ogawa, A. *Tetrahedron Lett.* **2007**, *48*, 3025.

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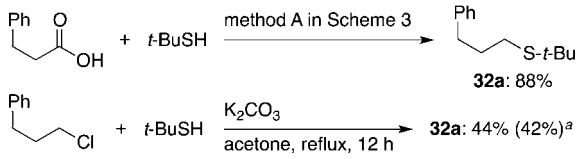
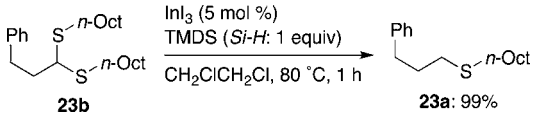
Scheme 4. Comparison of the Present Method with a Williamson-Type Thioether Synthesis



[a] Recovery of the alkyl chloride.

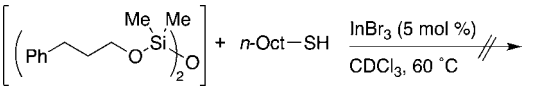
When the isolated thioacetal **23b** was treated with 5 mol % of InI_3 and 1 equiv (Si−H) of TMDS in CH_2ClCH_2Cl at 80 °C, the *S,S*-acetal was smoothly consumed within 1 h to produce the corresponding thioether **23a** in a nearly quantitative yield (Scheme 5). Additionally, when the reaction of the silyl ether, which was in situ derived from 3-phenylpropionic acid and TMDS in $CDCl_3$, with 1-octanethiol was monitored in the presence of 5 mol % of InI_3 by ^{13}C NMR, no formation of thioether **23a** was observed (Scheme 6). Therefore, in this reaction system, nucleophilic substitution of the corresponding silyl ether with a thiol did not occur. Also these results showed that the *S,S*-acetal was an intermediate in the thioetherification series (see Table 2).[16]

Scheme 5. Reductive Conversion of *S,S*-Acetal **23b** to Thioether **23a**

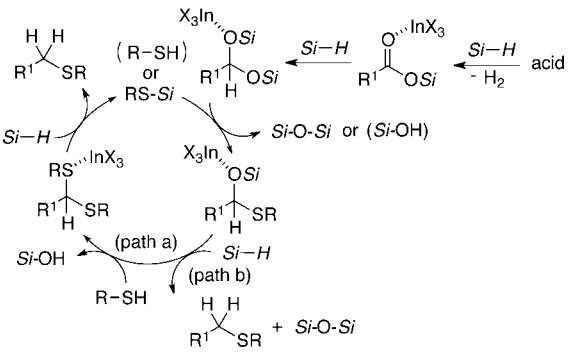


On the basis of these results, we present a plausible mechanism for the thioetherification as shown in Scheme 7. A carboxylic acid was reduced to the corresponding silyl acetal by a siloxane with the liberation of H_2. The formed silyl acetal was subsequnetly reacted with two molecules of a thiol to produce the expected *S,S*-acetal (path a). The

Scheme 6. Substitution of an in Situ Generated Silyl Ether with 1-Octanethiol



Scheme 7. Plausible Reaction Path of the Thioetherification



S,S-acetal was finally reduced by a siloxane to produce the thioether with the formation of a thiosilane. The thiosilane, which functions as an effective thiolate nucleophile,[17] probably drove the catalytic cycle. As an alternative path, there may be direct reduction from the *O,S*-acetal to the thioether (path b).[18−20]

We have demonstrated direct thioetherification from a variety of aliphatic or aromatic carboxylic acids and thiols using a reducing system combined with either $InBr_3$ or InI_3 and an economical disiloxane in a one-pot procedure. This simple catalytic system enabled the reductive introduction of a nucleophile onto the carbonyl carbon in a carboxylic acid under gentle conditions.

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Supporting Information Available. Copies of the NMR spectra of the new compounds are supplied. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.

(18) An *O,S*-acetal, which was prepared in situ by an aldehyde and a thiosilane, was readily reduced to produce the corresponding thioether; see: Glass, R. S. *Synth. Commun.* **1976**, *6*, 47. See also ref 9d.

(19) No formation of thioesters was observed under our optimal conditions (entries 6 and 7 in Table 1) through the reaction series. Also, the indium catalyst did not catalyze a formation of thioesters from the corresponding carboxylic acids and thiols with condensation. See details in Supporting Information.

(20) When a thioester was treated with the optimal conditions, the corresponding thioether was obtained in good yield; however, it required a quite long time (>48 h) to complete the reaction. See details in Supporting Information.