Synthesis of Thioethers by InI₃-Catalyzed Substitution of Siloxy Group Using Thiosilanes

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Abstract: The substitution of a siloxy group using thiosilanes smoothly occurred in the presence of InI₃ catalyst to yield the corresponding thioethers. InI₃ was a specifically effective catalyst in this reaction system, while other typical Lewis acids such as BF₃·OEt₂, AlCl₃, and TiCl₄ were ineffective. Various silyl ethers such as primary alkyl, secondary alkyl, tertiary alkyl, allylic, benzylic, and propargylic types were applicable. In addition, bulky OSiBuMe₂ and OSiPr₃ groups, other than the OSiMe₃ group, were successfully substituted. The substitution reaction of enantiopure secondary benzylic silyl ether yielded the corresponding racemic thioether product, which suggested that the reaction of tertiary alkyl, secondary alkyl, benzylic, and propargylic silyl ethers would proceed via an S_N1 mechanism.

Keywords: indium; silyl ethers; thiosilanes; thioethers

1. Introduction

Organosulfur compounds are important building blocks in organic synthesis because many natural and pharmaceutical products contain sulfur [1–5]. In particular, a thioether is a popular and useful compound [1–5]. Therefore, there are various types of synthetic methods to produce thioethers such as hydrothiolation of alkenes [6–9], Chan-Lam-Evans coupling using thiols [10], and transition metal-catalyzed coupling between aryl halides and thiols [11,12]. The substitution reaction of alkyl halides with sulfur nucleophiles is one of the most typical and practical methods in the synthesis of alkyl thioethers (Scheme 1A) [13–18]. However, the use of alkyl halides has an inherent problem; that is, the potential toxicity of alkyl halides and metal halides as by-products. Recently, alcohol derivatives such as alkyl ethers, alkyl acetates, alkyl carbonates, and silyl ethers have been suggested as promising substrates that could solve the problem. In particular, silyl ethers are one of the most useful alcohol derivatives because they are often used as protected alcohols in the syntheses of complex organic compounds such as natural products, drugs, and agrichemicals [19,20]. However, there are few reports about the synthesis of thioethers via the direct use of silyl ethers, due to the very poor leaving ability of the siloxy group [21]. Although the coupling reaction between alkenyl silyl ethers and thiosilanes has been reported, a stoichiometric amount of BF₃·OEt₂ was required [22]. Electrolysis with a thiosilane using only an α-acylamino silyl ether was also reported [23]. Therefore, in general, a multi-step sequence involving deprotection and transformation of the siloxy group is required in order to transform silyl ethers to thioethers (Scheme 1B). Therefore, the establishment of a direct transformation of silyl ethers to thioethers would be ideal in terms of step-economy. Herein, we report the direct substitution of a siloxy group with thiosilanes catalyzed by InI₃ to synthesize a
variety of thioethers (Scheme 1C). A disiloxane generated as a by-product has low toxicity, is inert, and is easily removed, so the present substitution reaction is a very practical synthetic method for producing thioethers.

\[ \text{(A) typical method} \quad R^1-X + \text{Mt-SR}^2 \xrightarrow{\text{alkyl halide}} \text{R}^1\text{SR}^2 + \text{MtX} \quad \checkmark \text{potential-toxicity of metal halide} \]

\[ \text{(B) typical method} \quad R^1\text{OSi/Si-tether} \xrightarrow{\text{deprotection}} \text{R}^1-X \xrightarrow{\text{Mt-SR}^2} \text{R}^1\text{SR}^2 + \text{MtX} \]

\[ \text{(C) this work} \quad R^1\text{OSi/Si-tether} + S^2\text{-SR}^2 \xrightarrow{\text{cat. InI}} \text{R}^1\text{SR}^2 + \text{Si(OSi/Si)-tether} \quad \checkmark \text{low toxicity of Si(OSi/Si)-tether} \quad \checkmark \text{good step-economy} \]

Scheme 1. Synthetic methods for producing a thioether. (Mt = metal, R1 = alkyl, R2 = alkyl or aryl).

2. Results

First, the effect of the catalyst was investigated in the reaction of the primary alkyl silyl ether 1a with trimethyl(phenylthio)silane (2a) (Table 1). Recently, we studied the moderate Lewis acidity of indium salts in order to develop the catalytic coupling reactions of alcohols and their derivatives with various nucleophiles [24–34]. Therefore, a substitution reaction in the presence of InI3 at room temperature was carried out and produced the desired thioether 3aa with a 27% yield (Entry 1). The InI3-catalyzed reaction at 80 °C moderately proceeded to produce 3aa with a 53% yield (Entry 2). By contrast, InCl3 did not mediate this substitution reaction (Entry 3), and InBr3 gave only a 27% yield (Entry 4). Typical Lewis acids such as BF3·OEt2, AlCl3, and TiCl4 showed no catalytic activity (Entries 5–7). The use of nonpolar solvents such as toluene and hexane resulted in low yields (Entries 8 and 9). Polar tetrahydrofuran (THF) solvent was not suitable (Entry 10). Finally, the InI3-catalyzed reaction carried out in CICH2CH2Cl at 80 °C for 8 h produced the highest yield (Entry 11).

| Entry | Catalyst (10 mol %) | Solvent | Conditions | Yield (%) b |
|-------|---------------------|---------|------------|------------|
| 1     | InI3               | CH2Cl2  | RT c, 2 h  | 27         |
| 2     | InI3               | CICH2CH2Cl | 80 °C, 2 h | 53         |
| 3     | InCl3             | CICH2CH2Cl | 80 °C, 2 h | 0          |
| 4     | InBr3             | CICH2CH2Cl | 80 °C, 2 h | 27         |
| 5     | BF3·OEt2          | CICH2CH2Cl | 80 °C, 2 h | 0          |
| 6     | AlCl3             | CICH2CH2Cl | 80 °C, 2 h | 0          |
| 7     | TiCl4             | CICH2CH2Cl | 80 °C, 2 h | 0          |
| 8     | InI3             | Toluene  | 80 °C, 2 h | 30         |
| 9     | InI3             | Hexane   | 68 °C, 2 h | 17         |
| 10    | InI3             | THF d    | 66 °C, 2 h | 0          |
| 11    | InI3             | CICH2CH2Cl | 80 °C, 8 h | 67         |

a 1a (1.2 equiv.), 2a (1 equiv.), catalyst (0.1 equiv.), solvent (1 M); b Yields were determined by 1H-NMR; c RT = room temperature; d THF = Tetrahydrofuran.

The scope of the silyl ethers is listed in Table 2. The reaction of secondary alkyl silyl ether 1b resulted in only a 32% yield of thioether 3ba (Entry 1). On the other hand, tertiary alkyl and secondary benzyl silyl ethers (1c and 1d) gave very high yields even at room temperature (Entries 2 and 3). Primary benzyllic substrates were also suitable for this system, and both electron-rich and electron-poor benzyl silyl ethers produced the corresponding thioethers 3ea, 3fa, and 3ga in high yields (Entries 4–6).
The substitution reaction of propargylic silyl ether \(1h\) smoothly occurred at room temperature without an allenic thioether product being generated in a rearrangement reaction (Entry 7). Additionally, the primary alkyl silyl ether \(1i\), which bears an olefin moiety, was applicable to this reaction (Entry 8).

**Table 2.** Scope of the silyl ethers \(1b\)–\(i\) in the \(\text{InI}_3\)-catalyzed substitution reaction using thiosilane \(2a\) \(^a\).

| Entry | \(\text{R}^1\text{OSiMe}_3\) | Conditions | Product | Yield (%) \(^b\) |
|-------|----------------|------------|---------|-----------------|
| 1     | \(\text{Ph-OSiMe}_3\) | 80 °C, 8 h  | \(3\text{ba}\) | 32              |
| 2     | \(\text{Ph-OSiMe}_3\) | RT, 2 h    | \(3\text{ca}\) | 99 (95) \(^c\) |
| 3     | \(\text{Ph-OSiMe}_3\) | RT, 2 h    | \(3\text{da}\) | 98              |
| 4     | \(\text{Ph-OSiMe}_3\) | 80 °C, 2 h  | \(3\text{ea}\) | 85              |
| 5     | \(\text{MeO-OSiMe}_3\) | RT, 2 h    | \(3\text{fa}\) | 88              |
| 6     | \(\text{Cl-OSiMe}_3\) | 80 °C, 2 h  | \(3\text{ga}\) | 83              |
| 7     | \(\text{Ph-SiMe}_3\)  | RT, 2 h    | \(3\text{ha}\) | 67              |
| 8     | \(\text{Ph-SiMe}_3\)  | 80 °C, 2 h  | \(3\text{ia}\) | 36              |

\(^a\) \(1,2\text{ equiv.}\), \(2a\) (1 equiv.), \(\text{InI}_3\) (0.1 equiv.), solvent (1 M); \(^b\) Yields were determined by \(^1\text{H}-\text{NMR};\) \(^c\) Isolated yield.

Various types of thiosilanes were examined in this reaction system (Scheme 2). Arylthiosilanes bearing electron-withdrawing and electron-donating groups produced the desired products \(3\text{eb}\) and \(3\text{ec}\) in high yields, respectively. An alkyl thiosilane, other than an aryl type, was also applicable to the present substitution reaction. The reaction of benzyl silyl ether \(1e\) with trimethyl(dodecylthio)silane (2d) smoothly occurred to produce the corresponding dialkyl thioether \(3\text{ed}\) with 92% yield.

**Scheme 2.** Substitution reaction using different types of thiosilanes.
Bulky silyl groups are generally more useful and robust protecting groups compared with the trimethylsilyl group in organic synthesis. We examined OSiBuMe₂, OSiPrMe₂, and OSiPr₃ groups for the substitution reaction (Scheme 3). Despite the large steric hindrance, the bulky silyl ethers 1j, 1k, and 1l reacted with thiosilane 2a to produce the corresponding thioether 3aa in high yields.

![Scheme 3. Substitution of bulky silyloxy groups. RT: room temperature.](image_url)

The excellent results given by the reaction using tertiary alkyl and benzylic thioethers suggested that the substitution reaction using these thioethers occurred via the S_N1 mechanism involving a carbocation intermediate. Actually, the reaction of the enantiopure benzyl silyl ether (R)-1d catalyzed by InI₃ produced a racemic mixture of 3aa (Scheme 4, upper line) [35]. The reaction using the allyl silyl ether 1m exclusively yielded thioether 3mb-1 without producing the thioether 3mb-2 through allylic rearrangement (S_N2' mechanism) (Scheme 4, lower line). This result showed that the reaction of a primary allylic silyl ether involves a S_N2 mechanism.

![Scheme 4. Mechanistic study.](image_url)

Plausible reaction mechanisms are illustrated in Scheme 5. From the result of Equation 1, the substitution reactions of tertiary alkyl, secondary alkyl, benzylic, and propargylic silyl ethers would proceed via the S_N1 mechanism (Scheme 5A). A silyloxy group coordinates to InI₃ (4), and then the cleavage of the C–O bond generates a carbocation intermediate. The nucleophilic attack of the thiosilane 2 to the carbocation intermediate gives thioether 3 and Me₃SiOSiMe₃, and InI₃ regenerates. On the other hand, the reaction of a primary alkyl silyl ether would proceed via a S_N2-type mechanism (Scheme 5B), because a primary alkyl cation is not easily generated. First, the coordination of a silyloxy group to InI₃ enhances polarization of the C–O bond. Then, an S_N2 reaction of the InI₃-activated silyl ether 4 with thiosilane 2 occurs. The reaction of a primary alkyl silyl ether also involves this type of mechanism (Scheme 4, lower line). Generally, transmetalation between a metal salt (MtXₙ) and thiosilane (R²S-SiMe₃) may occur to generate a metal thiolate (MtXₙ−SR²). Actually, AlCl₃ and BF₃·OEt₂ transmetalate with thiosilane 2a to form thioaluminum and thioborane, respectively [36]. On the other hand, the transmetalation between InI₃ and thiosilane 2a does not occur, which allows InI₃ to work as a Lewis acid catalyst in the present substitution reaction [36]. A disiloxane by-product has low toxicity and is easily removed by column chromatography on silica gel, which enhances the utility of this reaction system in organic synthesis.
3. Experimental Section

Typical Procedure: Silyl ether 1c (0.135 g, 0.6 mmol) was added to a suspended solution of thiosilane 2a (0.089 g, 0.5 mmol) and InI$_3$ (0.026 g, 0.05 mmol) in dichloromethane (0.5 mL). The reaction mixture was stirred at room temperature for 2 h and was then quenched by a saturated aqueous solution of NaHCO$_3$. The crude product was extracted with dichloromethane. The combined organic layer was dried over MgSO$_4$ and concentrated under reduced pressure. The NMR yield was determined by $^1$H-NMR ($^1$H-NMR spectra were recorded on a JMTC-400/54/SS instrument at 400 MHz (JEOL Ltd., Tokyo, Japan), using 1,1,2,2-tetrachloroethane as an internal standard. The crude product was purified by flash chromatography (Hexane/EtOAc = 95:5, spherical silica gel 60 $\mu$m, 30 g, diameter 2.7 cm, Shoko Scientific Co., Ltd., Kanagawa, Japan) to afford the corresponding thioether 3ca (0.119 g, 95%).

4. Conclusions

We have developed an InI$_3$-catalyzed coupling reaction of silyl ethers with thiosilanes. A variety of silyl ethers and thiosilanes are applicable to the present coupling reaction. In particular, the scope of silyl ethers is significantly broad, and primary alkyl, secondary alkyl, tertiary alkyl, benzylic, and propargylic silyl ethers are feasible substrates. In addition, the substitution of OSiMe$_3$ as well as OSiBuMe$_2$ and OSiPr$_3$ groups smoothly occurred. InI$_3$ specifically achieved this catalytic substitution reaction unlike other typical Lewis acids. This was possible because the transmetalation between InI$_3$ and thiosilane does not occur, and InI$_3$ sufficiently activates silyl ether due to its moderate Lewis acidity.

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Author Contributions: Yoshihiro Nishimoto, Akio Baba, and Makoto Yasuda conceived and designed the experiments and wrote the paper. Yoshihiro Nishimoto and Aya Okita performed the experiments.

Conflicts of Interest: The authors declare no conflict of interest.

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35. Enantiopure silyl ether ($R$)-1d was synthesized by the silylation of ($R$)-1-phenylethanol (97% enantiomeric excess, purchased from Wako Pure Chemical Industries, Ltd., Osaka, Japan) using trimethylsilyl chloride and Et$_3$N.

36. NMR studies showed that AlCl$_3$ and BF$_3$·OEt$_2$ transmetalated with thiosilane 2a to generate Me$_3$SiCl and Me$_3$SiF, respectively. In contrast, when an equivalent amount of InI$_3$ and thiosilane 2a was mixed, no transmetalation was observed by $^{13}$C-NMR. See reference 24.

**Sample Availability:** Not available.

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