

Communication

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 OSi^tBuMe₂ and OSi^tPr₃ 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 a 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

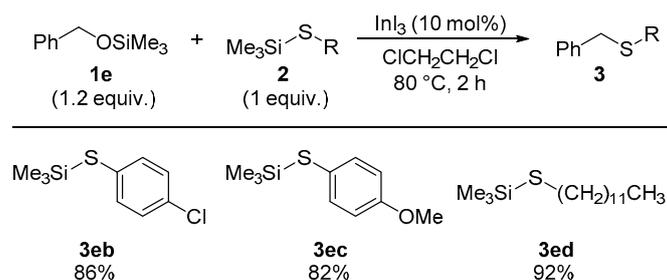
The substitution reaction of propargylic silyl ether **1h** smoothly occurred at room temperature without an allenylic thioether product being generated in a rearrangement reaction (Entry 7). Additionally, the primary alkyl silyl ether **1i**, which bears an olefin moiety, was applicable to this reaction (Entry 8).

Table 2. Scope of the silyl ethers **1b–i** in the InI_3 -catalyzed substitution reaction using thiosilane **2a** ^a.

$\text{R}^1\text{-OSiMe}_3 + \text{Me}_3\text{Si-SPh} \xrightarrow[\text{Conditions}]{\text{cat. InI}_3} \text{R}^1\text{-S-Ph}$				
Entry	R^1OSiMe_3	Conditions	Product	Yield (%) ^b
1		$\text{ClCH}_2\text{CH}_2\text{Cl}$ 80 °C, 8 h		32
2		CH_2Cl_2 RT, 2 h		99 (95) ^c
3		CH_2Cl_2 RT, 2 h		98
4		$\text{ClCH}_2\text{CH}_2\text{Cl}$ 80 °C, 2 h		85
5		CH_2Cl_2 RT, 2 h		88
6		$\text{ClCH}_2\text{CH}_2\text{Cl}$ 80 °C, 2 h		83
7		CH_2Cl_2 RT, 2 h		67
8		$\text{ClCH}_2\text{CH}_2\text{Cl}$ 80 °C, 2 h		36

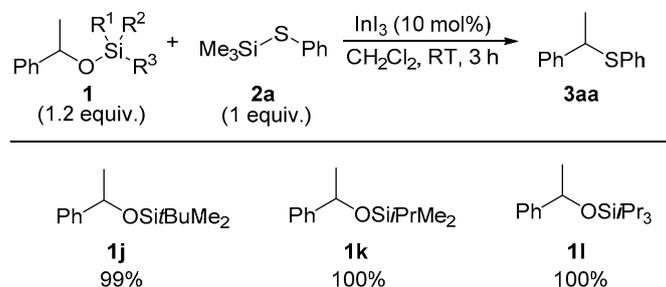
^a **1** (1.2 equiv.), **2a** (1 equiv.), InI_3 (0.1 equiv.), solvent (1 M); ^b Yields were determined by $^1\text{H-NMR}$; ^c Isolated yield.

Various types of thiosilanes were examined in this reaction system (Scheme 2). Arylthiosilanes bearing electron-withdrawing and electron-donating groups produced the desired products **3eb** and **3ec** 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 **3ed** with 92% yield.



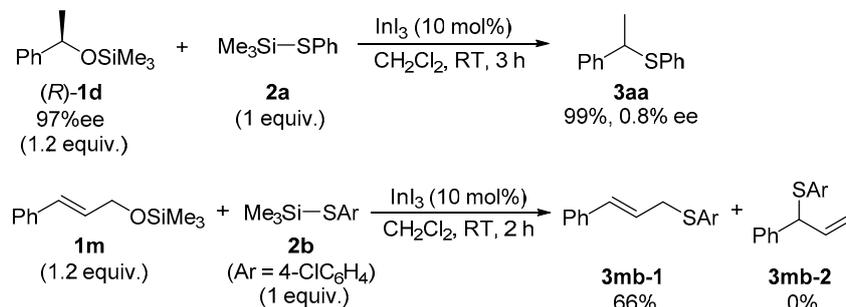
Scheme 2. Substitution reaction using different types of thiosilanes.

Bulky silyl groups are generally more useful and robust protecting groups compared with the trimethylsilyl group in organic synthesis. We examined OSi*t*BuMe₂, OSi*i*PrMe₂, and OSi*i*Pr₃ 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.



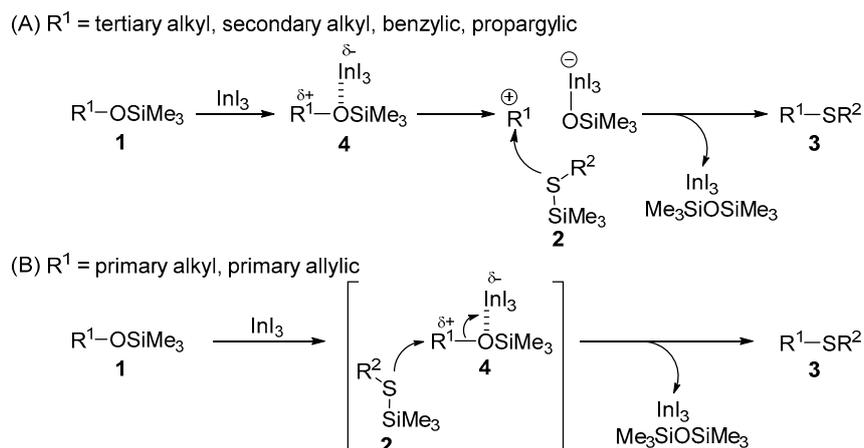
Scheme 3. Substitution of bulky siloxy groups. RT: room temperature.

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.

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 siloxy 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 siloxy 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 allyl silyl ether also involves this type of mechanism (Scheme 4, lower line). Generally, transmetalation between a metal salt (MtX_n) and thiosilane (R²S–SiMe₃) may occur to generate a metal thiolate (MtX_{n-y}(SR²)_y). 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.



Scheme 5. Plausible reaction mechanisms.

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 InI₃ (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 NaHCO₃. The crude product was extracted with dichloromethane. The combined organic layer was dried over MgSO₄, and concentrated under reduced pressure. The NMR yield was determined by ¹H-NMR (¹H-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 μm, 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 InI₃-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 OSiMe₃ as well as OSi*t*BuMe₂ and OSiPr₃ groups smoothly occurred. InI₃ specifically achieved this catalytic substitution reaction unlike other typical Lewis acids. This was possible because the transmetalation between InI₃ and thiosilane does not occur, and InI₃ 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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36. NMR studies showed that AlCl_3 and $\text{BF}_3 \cdot \text{OEt}_2$ transmetalated with thiosilane **2a** to generate Me_3SiCl and Me_3SiF , 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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