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$GaCl_3$- and $TiCl_4$-Catalyzed Insertion of Isocyanides into a C−S Bond of Dithioacetals

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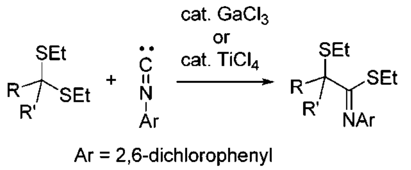
ABSTRACT

The insertion reaction of isocyanide into a C−S bond of dithioacetals is catalyzed by $GaCl_3$ or $TiCl_4$ to afford thioimidates containing an α-alkylthio group. Balanced thiophilicity of these Lewis acids is critical for efficient catalysis.

Dithioacetals, especially 1,3-dithianes, are recognized as versatile intermediates in organic synthesis.[1] The use of the lithiated dithioacetal as a masked nucleophilic acylating agent is particularly valuable, and for this purpose, the dithioacetal functionality is ultimately converted into a sulfur-free carbonyl compound.[2] Dithioacetals also serve as synthetic precursors for several organosulfur compounds in substitution reactions, in which one of the two sulfur groups is displaced by a nucleophile, such as organolithium and -magnesium reagents.[1b,c] In contrast, insertion reactions into the C−S bond of dithioacetals, which afford products bearing two sulfur-based functionalities, have not been thoroughly investigated, and successful examples are limited to intramolecular processes.[3,4] Herein, we report the intermolecular insertion of isocyanides into the C−S bond of dithioacetals catalyzed by $GaCl_3$ and $TiCl_4$ (eq 1).



(1)

As part of our research program, which is directed at the development of new reactions using isocyanides as a C1 component,[5] we recently reported the Brønsted and Lewis acid catalyzed insertion of isocyanides into the C−O bond

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(1) Selected reviews: (a) Bulman Page, P. C.; van Niel, M. B.; Prodger, J. C. *Tetrahedron* **1989**, *45*, 7643. (b) Luh, T.-Y. *Acc. Chem. Res.* **1991**, *24*, 257–263. (c) Luh, T.-Y.; Lee, C.-F. *Eur. J. Org. Chem.* **2005**, 3875. (d) Takeda, T. *Bull. Chem. Soc. Jpn.* **2005**, *78*, 195.

(2) Gröbel, B.-T.; Seebach, D. *Synthesis* **1977**, 357.

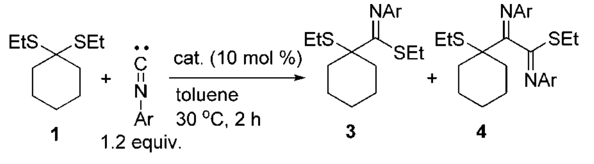
(3) (a) Nakamura, I.; Bajracharya, G. B.; Wu, H.; Oishi, K.; Mizushima, Y.; Gridnev, I. D.; Yamamoto, Y. *J. Am. Chem. Soc.* **2004**, *126*, 15423. (b) Peng, L.; Zhang, X.; Zhang, S.; Wang, J. *J. Org. Chem.* **2007**, *72*, 1192. See also (c) Nakamura, I.; Sato, T.; Yamamoto, Y. *Angew. Chem., Int. Ed.* **2006**, *45*, 4473. (d) Nakamura, I.; Sato, T.; Terada, M.; Yamamoto, Y. *Org. Lett.* **2007**, *9*, 4081. (e) Nakamura, I.; Sato, T.; Terada, M.; Yamamoto, Y. *Org. Lett.* **2008**, *10*, 2649.

(4) Intermolecular insertion of CO into the C−S bond of *N,S*-acetals has been reported: Khumtaveeporn, K.; Alper, H. *J. Org. Chem.* **1994**, *59*, 1414.

(5) (a) Chatani, N.; Oshita, M.; Tobisu, M.; Ishii, Y.; Murai, S. *J. Am. Chem. Soc.* **2003**, *125*, 7812. (b) Oshita, M.; Yamashita, K.; Tobisu, M.; Chatani, N. *J. Am. Chem. Soc.* **2005**, *127*, 761. (c) Yoshioka, S.; Oshita, M.; Tobisu, M.; Chatani, N. *Org. Lett.* **2005**, *7*, 3697. (d) Tobisu, M.; Oshita, M.; Yoshioka, S.; Kitajima, A.; Chatani, N. *Pure Appl. Chem.* **2006**, *78*, 275. (e) Tobisu, M.; Kitajima, A.; Yoshioka, S.; Hyodo, I.; Oshita, M.; Chatani, N. *J. Am. Chem. Soc.* **2007**, *129*, 11431. (f) Tobisu, M.; Yamaguchi, S.; Chatani, N. *Org. Lett.* **2007**, *9*, 3351.

10.1021/ol802223a CCC: $40.75

Table 1. Catalytic Insertion of Isocyanide into Dithioacetal **1**[a]



1 + **2** (1.2 equiv.) → **3** + **4**

Ar = 2,6-dichlorophenyl (**2**)

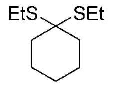
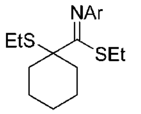
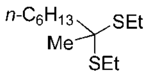
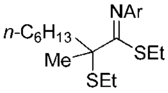
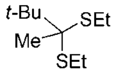
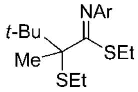
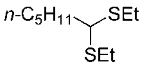
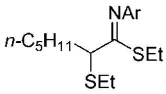
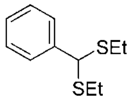
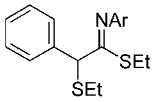
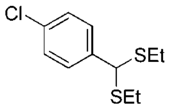
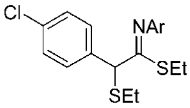
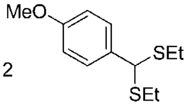
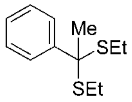
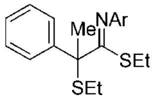
entry	catalyst	yield (%)[b] **3**	**4**
1	TfOH	0	0
2	Me_3SiOTf	0	0
3	BF_3-OEt_2	tr	0
4	$AlCl_3$	tr	0
5	$EtAlCl_2$	0	0
6	$GaCl_3$	50	20
7[c]	$GaCl_3$	80	4
8	$InCl_3$	52	14
9	$TiCl_4$	74	4

[a] Reaction conditions: dithioacetal **1** (0.5 mmol), isocyanide **2** (0.6 mmol), catalyst (0.05 mmol) in toluene (3 mL) at 30 °C, 2 h. [b] Isolated yields based on **1**. [c] Isocyanide **2** was added slowly (1 h) using $GaCl_3$ (0.1 mmol).

of acetals.[5c,d] Naturally, we were intrigued by the possibility of applying the isocyanide insertion reaction to substrates other than acetals. We envisioned that dithioacetals might be promising candidates in view of the fact that cleavage of the C−S bond in dithioacetals is promoted by the Lewis acids.[2,6] Initially, the reaction of dithioacetal **1** with isocyanide **2a**[5c,d] was examined in the presence of various acid catalysts (Table 1). TfOH (entry 1), which was the most effective catalyst for the insertion of **2** into the C−O bond of acetals, as well as boron- (entry 3) and aluminum-based (entries 4 and 5) Lewis acids failed to promote the reaction. On the other hand, the expected reaction proceeded when relatively soft Lewis acids, such as $GaCl_3$ and $InCl_3$, were used, although the products were obtained as a mixture of mono- (**3**) and double-insertion (**4**) products (entries 6 and 8).[7] Formation of the double-insertion product **4** was effectively suppressed by the slow addition of **2** (entry 7). $TiCl_4$ also proved to be an active catalyst for the selective formation of **3** that did not require the slow addition of **2**, although the yield was slightly decreased (entry 9).

After identification of suitable catalysts, the substrate scope of this transformation was explored (Table 2). In addition to dithioacetals derived from cyclic ketones (entries 1 and 2), those derived from acyclic ketones selectively afforded the mono-insertion product in the presence of $GaCl_3$ and $TiCl_4$ catalysts (entries 3−6). Introduction of a bulky *tert*-butyl group improved both yield and selectivity (entries 5 and 6).[8] These catalysts were also effective for aliphatic aldehyde-derived dithioacetals (entries 7 and 8). Next, dithioacetals prepared from aromatic aldehydes were examined. In contrast to the reactions using aliphatic derivatives, both $TiCl_4$ and $GaCl_3$ catalysts exclusively afforded mono-insertion products without the need for slow addition, even in the presence of an excess amount (2 equiv) of isocyanide 2 (entries 9−12). In a series of reactions using dithioacetals derived from *para*-substituted benzaldehydes, electron-rich systems displayed higher reactivity for the catalytic isocya-

Table 2. $TiCl_4$- and $GaCl_3$-Catalyzed Insertion of **2a** into Dithioacetals

entry	dithioacetal	method[a]	time (h)	product[b]	yield (%)[c]
1 2		A C	3 2		80 (4) 74 (4)
3[d] 4		A C	10 2		47 (5) 54 (3)
5 6		A C	3 2		88 (0) 78 (0)
7[d] 8[e]		A C	10 6		65 (7) 47 (5)
9 10[e]		B C	2 2		62 (0) 59 (0)
11		B	2		65 (0)
12		B	2		84 (0)
13[f]		B	2		21 (0)

[a] Reaction conditions: dithioacetal **1** (0.5 mmol), isocyanide **2** (0.6 mmol), catalyst in toluene (3 mL) at 30 °C. Method A: $GaCl_3$ (0.1 mmol) was used; **2** was slowly added (1 h). Method B: $GaCl_3$ (0.1 mmol) was used; **2** was added in one portion. Method C: $TiCl_4$ (0.05 mmol) was used; **2** was added in one portion. [b] Ar = 2,6-dichlorophenyl. [c] Isolated yields based on dithioacetals. Values in parentheses refer to the yields of double-insertion products. [d] Isocyanide **2** (0.75 mmol) was used. [e] Isocyanide **2** (1.0 mmol) and $TiCl_4$ (0.1 mmol) was used. [f] Carried out at 60 °C using **2** (1.0 mmol).

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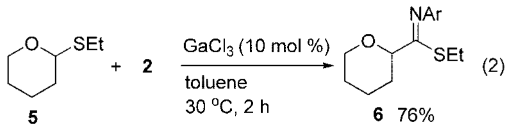
(6) For the gallium-mediated cleavage of the C−S bond in dithioacetals, see: (a) Saigo, K.; Hashimoto, Y.; Kihara, N.; Umehara, H.; Hasegawa, M. *Chem. Lett.* **1990**, *19*, 831. (b) Saigo, K.; Hashimoto, Y.; Kihara, N.; Hara, K.; Hasegawa, M. *Chem. Lett.* **1990**, *19*, 1097. (c) Ikeshita, K.; Kihara, N.; Ogawa, A. *Tetrahedron Lett.* **2005**, *46*, 8773. (d) Ikeshita, K.; Kihara, N.; Sonoda, M.; Ogawa, A. *Tetrahedron Lett.* **2007**, *48*, 3025.

(7) Notes: (a) The results when isocyanides other than **2** were used are as follows. 2,6-Dimethylphenyl isocyanide: **3** (31%), **4** (26%). 2,6-Diisopropylphenyl isocyanide: **3** (41%), **4** (18%). *tert*-Octyl isocyanide: **3** (0%), **4** (0%). (b) Diphenylthioacetals and 1,3-dithiolane did not give any insertion products.

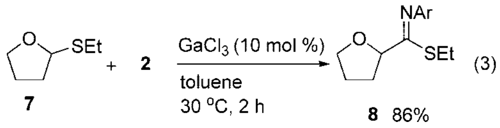
(8) Similar effect of a *tert*-butyl group was also observed in the insertion into acetals. See refs 5c and 5d.

nide insertion.[9] This observation indicates that the benzylic carbon of the substrate has some carbocation character in the transition state (vide infra). Aromatic ketone-based dithioacetals were not good substrates for the reaction (entry 13).

To further expand the scope of the catalytic insertion of isocyanide, we next examined *O*,*S*-acetals. The reaction of 2-(ethylthio)tetrahydro-2*H*-pyran (**5**) with **2** in the presence of a catalytic amount of $GaCl_3$ resulted in the selective formation of **6**, during which the insertion occurred at a C−S rather than a C−O bond (eq 2). It should be noted that, even when slow addition was not used, double-insertion did not occur. The use of the five-membered analogue **7** also furnished the corresponding product **8** in 86% yield (eq 3).[10]



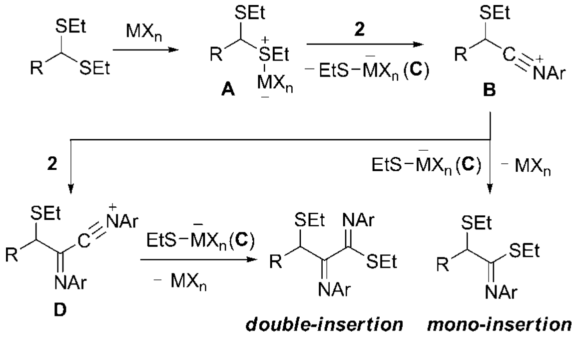
(2)



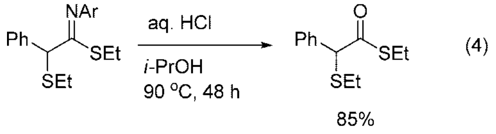
(3)

A plausible mechanism for the Lewis acid catalyzed insertion of isocyanides into dithioacetals is illustrated in Scheme 1. Activation of the C−S bond in dithioacetals by Lewis acid via **A**,[2,6] and the subsequent reaction with isocyanide **2** affords a nitrinium cation **B**. Interception of the cation **B** by the metal−thiolate **C** leads to the formation of a mono-insertion product. On the other hand, a double-insertion product is obtained if another molecule of **2** reacts with **B** prior to the attack by **C**.[11] Because the Lewis acid employed in the present reaction acts as a thiolate shuttle, balanced thiophilicity is required for efficient catalysis; a high affinity for sulfur accelerates the C−S bond activation step and retards the thiolate transfer from **C** to **B**.

Scheme 1. Plausible Mechanism



The resultant thioimidates can be converted into the corresponding thioesters under acidic conditions (eq 4). Considering the synthetic utility of the thioester functionality,[12,13] a series of hydrolyzed compounds obtained from our isocyanide insertion reaction should serve as useful building blocks for the synthesis of a range of organosulfur compounds.



(4)

In summary, we have described $TiCl_4$- and $GaCl_3$-catalyzed insertion reactions of isocyanides into C−S bonds in dithioacetals. We believe that balanced thiophilicity of these Lewis acids is critical for successful catalysis. In contrast to use of the dithioacetal functionality as a protecting group and as an electrophile in substitution reactions, the present reaction opens up a new atom-economical pathway for the transformation of this functionality. Additional studies that aim to develop new reactions using isocyanides as the C1 component are ongoing.

Acknowledgment. This work has been carried out, in part, by the Program of Promotion of Environmental Improvement to Enhance Young Researchers' Independence, the Special Coordination Funds for Promoting Science and Technology, Ministry of Education, Culture, Sports, Science and Technology (MEXT), Japan. We also thank the Instrumental Analysis Center, Faculty of Engineering, Osaka University, for assistance with the MS, HRMS, and elemental analyses.

Supporting Information Available: Detailed experimental procedures and characterization of products. This material is available free of charge via the Internet at http://pubs.acs.org.

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[9] Competition experiments between dithioacetals derived from substituted benzaldehydes using a $GaCl_3$ catalyst determined the relative reactivity as follows: 4-MeO-$C_6H_4CH(SEt)_2$:$C_6H_5CH(SEt)_2$:4-Cl-$C_6H_4CH(SEt)_2$ = 6.9:1:0.4.

[10] $TiCl_4$ were ineffective for the reactions of **5** (12%) and **7** (9%), probably due to high oxophilicity of $TiCl_4$.

[11] Notes: (a) A mono-insertion product did not give a double-insertion product upon exposure to $GaCl_3$ (or $TiCl_4$) and **2**. (b) Treatment of a mixture of $PhCH(SPr)_2$ and 4-Cl-$C_6H_4CH(SEt)_2$ with $GaCl_3$ resulted in a complete scrambling of the alkylthio groups between the starting meterials. This observation indicates the involvement of free metal−thiolate species, as in **C**, rather than involving an intimate ion pair.

[12] For reviews, see: (a) Ogawa, A.; Sonoda, N. In *Comprehensive Organic Functional Group Transformations*; Katritzky, A. R., Meth-Cohn, O., Rees, C. W., Eds.; Pergamon: Oxford, 1995; Vol. 5 (Moody, C. J., Ed.), p 233. (b) Fujiwara, S.; Kambe, N. *Top. Curr. Chem.* **2005**, *251*, 87.

[13] For recent reports on catalytic transformation of thioesters, see: (a) Villalobos, J. M.; Srogl, J.; Liebeskind, L. S. *J. Am. Chem. Soc.* **2007**, *129*, 15734. (b) Yang, H.; Li, H.; Wittenberg, R.; Egi, M.; Huang, W.; Liebeskind, L. S. *J. Am. Chem. Soc.* **2007**, *129*, 1132. (c) Yamashita, F.; Kuniyasu, H.; Terao, J.; Kambe, N. *Org. Lett.* **2008**, *10*, 101. (d) Li, H.; Yang, H.; Liebeskind, L. S. *Org. Lett.* **2008**, *10*, 4375.