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$AlCl_3$-catalyzed insertion of isocyanides into nitrogen–sulfur bonds of sulfenamides

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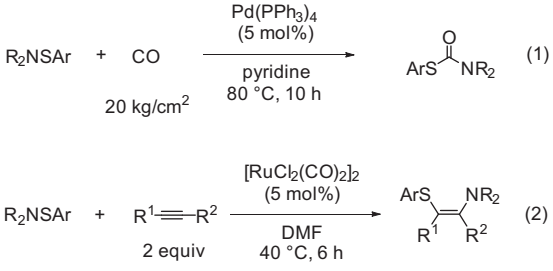
ABSTRACT

Lewis acid-catalyzed insertion of isocyanides **2** into nitrogen–sulfur bonds of sulfenamides **1** was developed. This method provided a convenient method for the synthesis of isothioureas **3**. Among Lewis acids examined, $AlCl_3$ brought about the best result. Acetic acid assisted one-pot preparation of unsymmetrical ureas was also described.

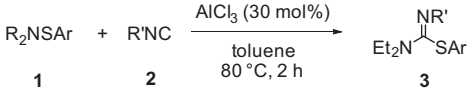
Introduction

Sulfenamides, R_2NSR', are synthetically interesting and important compounds due to their wide availability[1,2] and the unique reactivity of the N–S bond.[1] Sulfenamides have been utilized as aminating reagents[3] and sulfenyating reagents[4] in addition to as aminyl radical precursors[5] and catalysts for the oxidation of alcohols.[6] Furthermore, unsaturated molecules such as carbon monoxide and alkynes can be inserted into the N–S bond of sulfenamides. For example, Kurosawa and co-workers revealed for the first time in 1999 that the reaction of sulfenamides with carbon monoxide was catalyzed by $Pd(PPh_3)_4$ in pyridine to provide thiocarbamates in high yields (Scheme 1, Eq. 1).[7,8] Mitsudo and co-workers disclosed that the reaction of sulfenamides with alkynes was catalyzed by $[RuCl_2(CO)_2]_2$ in DMF to provide the corresponding adducts with high regio- and stereoselectivity (Scheme 1, Eq. 2).[9–13]

Here we wish to report that $AlCl_3$ catalyzes insertion of isocyanides **2** into N–S bonds of sulfenamides **1** giving rise to the formation of isothioureas **3** (Scheme 2).



Scheme 1. Insertion of CO and alkynes into sulfenamides.



Scheme 2. $AlCl_3$-catalyzed syntheses of isothioureas from isocyanides and sulfenamides.

Results and discussions

It was reported that thiophthalimides reacted with isocyanides without a catalyst in refluxing acetonitrile to give insertion products.[14] However, when we heated a mixture of *S*-phenyl-*N*,*N*-diethylsulfenamide **1a** and 2,6-xylyl isocyanide **2a** in acetonitrile

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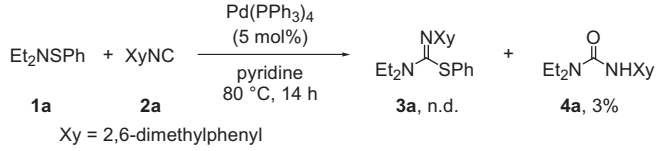
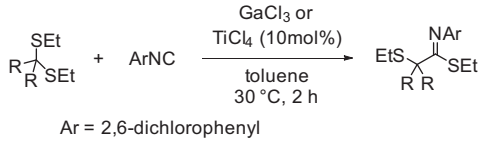
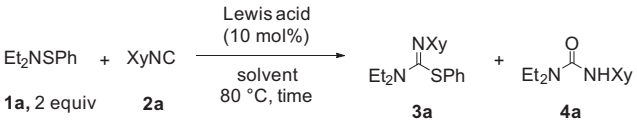


Scheme 3. Reaction of a sulfenamide with an isocyanide in the presence of $Pd(PPh_3)_4$.



Scheme 4. Lewis acid-catalyzed insertion of isocyanides to a C–S bond of dithioacetals.

Table 1
Screening of Lewis acids

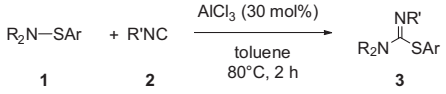


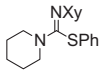
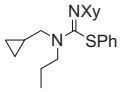
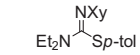
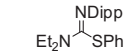
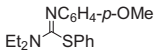
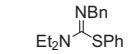
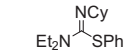
run	Lewis acid	solvent	time	yield **3a**, %[a,b]	yield **4a**, %[a,b]
1	$GaCl_3$	DMF	24 h	72	8
2	$TiCl_4$	DMF	24 h	32	50
3	$InCl_4$	DMF	24 h	72	9
4	$AlCl_3$	DMF	24 h	72	2
5	$ZrCl_4$	DMF	24 h	70	14
6	BBu_3	DMF	24 h	58	9
7	BPh_3	DMF	24 h	72	4
8	$B(C_6F_5)_3$	DMF	24 h	66	14
9	$BF_3{\cdot}OEt_2$	DMF	24 h	72	10
10[c]	CH_3COOH	DMF	30 h	6	79 (78)
11[d]	$AlCl_3$	DMF	24 h	75	3
12[d]	$AlCl_3$	toluene	24 h	81	n.d.
13[d,e]	$AlCl_3$	toluene	2 h	80 (77)	n.d.

Conditions: **2a** (0.4 mmol), **1a** (2 equiv), Lewis acid (1 equiv), solvent (0.4 mL). [a] NMR yields. [b] Isolated yield in parentheses. [c] CH_3COOH (1 equiv). [d] $AlCl_3$ (30 mol%). [e] **1a** (1 equiv).

under similar conditions, insertion reaction did not proceed at all. Then we examined the palladium catalyzed system developed for azathiolation of carbon monoxide shown in Scheme 1. When a pyridine (0.4 mL) solution of sulfenamide **1a** (0.4 mmol), isocyanide **2a** (0.4 mmol), and $Pd(PPh_3)_4$ (5 mol %) was heated at 80 °C for

Table 2
$AlCl_3$-catalyzed reaction of isocyanides with sulfenamides leading to isothioureas



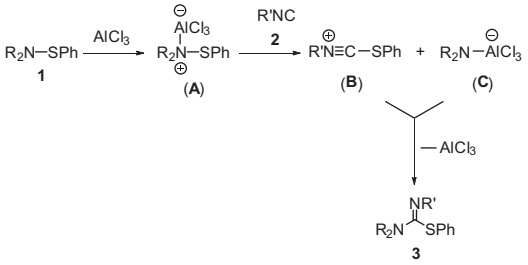
run	sulfenamide	isocyanide	isothiourea	yield[a]
1	 **1b**	XyNC **2a**	 **3b**	79%
2	 **1c**	**2a**	 **3c**	69%
3	Et_2NSp-tol **1d**	**2a**	 **3d**	70%
4[b]	Et_2NSPh **1a**	DippNC **2b**	 **3e**	78%
5[c]	**1a**	p-$MeOC_6H_4NC$ **2c**	 **3f**	47%
6	**1a**	BnNC **2d**	 **3g**	93%
7	**1a**	CyNC **2e**	 **3h**	35%

Conditions: sulfenamide **1** (0.4 mmol), isocyanide **2** (0.4 mmol), $AlCl_3$ (30 mol%), toluene (0.4 mL), 80 °C, 2 h. [a] Isolated yield. [b] DippNC = 2,6-diisopropylphenylisocyanide. [c] p-$MeOC_6H_4NC$ (2 equiv), 5 h.

14 h, desired isothiourea **3a** was not formed and the corresponding urea **4a**, a hydrolyzed product of **3a**, was obtained in 3% yield (Scheme 3). Even after several trials by the use of other metal catalysts such as $Rh(PPh_3)_3Cl$ the yields of **3a** and **4a** were not improved so much.

Recently, Chatani and co-workers disclosed that isocyanides reacted with dithioacetals to give insertion products in the presence of Lewis acids such as $GaCl_3$ and $TiCl_4$ (Scheme 4).[15]

Then we conducted the reaction of sulfenamide **1a** with isocyanide **2a** in the presence of Lewis acids and the results are given in Table 1. When 2,6-xylyl isocyanide **2a** (0.4 mmol) was allowed to react with sulfenamide **1a** (2 equiv) in the presence of $GaCl_3$ (10 mol %) in DMF at 80 °C for 24 h, isothiourea **3a** was formed in 72% yield (run 1). In this reaction, 8% of urea **4a** was also obtained; however, multiple insertion products incorporating more than one isocyanide molecules were not detected. In the case of $TiCl_4$, urea **4a** became the major product (run 2). $InCl_3$, $ZrCl_4$, and BPh_3 exhibited similar activities as $GaCl_3$, and the use of $AlCl_3$ gave the best selectivity (runs 3–9). Interestingly, when 1 equiv of acetic acid was employed as an additive, urea **4a** was formed in 79% yield (run 10). Since 13% of isocyanide **2a** remained unreacted in run 4, we used 30 mol % of $AlCl_3$ but the yield of **3a** was improved only

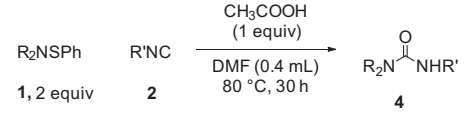


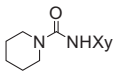
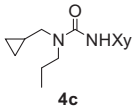
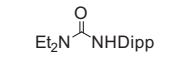
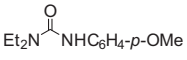
Scheme 5. A possible reaction pathway.

slightly (runs 4 and 11). Use of toluene as the solvent retarded the formation of urea **4a** (run 12). Isothiourea **3a** was obtained in good yields when the amount of sulfenamide **1a** was reduced to 1 equiv and the reaction time was shortened to 2 h (run 13).[16,17]

Table 2 summarizes the results obtained using several sulfenamides **1** and isocyanides **2** under the optimized reaction conditions (run 13 in Table 1). 2,6-Xylyl isocyanide **2a** was also inserted into sulfenamides **1b**, **1c**, and **1d** affording the corresponding isothioureas **3b**, **3c**, and **3d** in 79%, 69%, and 70% yields, respectively (runs 1–3). The reaction of sterically hindered 2,6-diisopropylphenyl isocyanide **2b** gave isothiourea **3e** in 78% yield (run 4). Insertion of *p*-methoxyphenyl isocyanide **2c** was inefficient and **3f** was formed in 47% yield even when the reaction was run using 2 equiv of **2c** for prolonged reaction time (5 h) (run 5). Aliphatic isocyanides could also be employed as suitable reagents. For example, the reaction of benzyl isocyanide **2d** with sulfenamide **1a** afforded the corresponding product **3g** in 93% yield (run 6). However, the desired product **3h** was obtained in a low yield (35%) when cyclohexyl isocyanide **2e** was employed (run 7). These isothioureas **3g** and **3h**, obtained from aliphatic isocyanides, were labile and easily hydrolyzed to ureas during purification by preparative TLC. So the isolation was performed by recycling preparative HPLC.

Table 3
Acetic acid-assisted preparation of unsymmetrical ureas from isocyanides and sulfenamides



run	sulfenamide	isocyanide	urea	yield[a]
1	 **1b**	XyNC **2a**	 **4b**	77%
2	 **1c**	**2a**	 **4c**	81%
3	Et_2NSPh **1a**	DippNC **2b**	 **4d**	72%
4	**1a**	*p*-$MeOC_6H_4NC$ **2c**	 **4e**	50%

Conditions: sulfenamide **1** (0.8 mmol), isocyanide **2** (0.4 mmol), CH_3COOH (0.4 mmol), DMF (0.4 mL), 80 °C, 30 h. [a] Isolated yield.
[b] DippNC = 2,6-diisopropylphenylisocyanide.

The reaction pathway for the present $AlCl_3$-catalyzed insertion of isocyanides into sulfenamides is not clear yet but a possible pathway was depicted in Scheme 5. The N–S bond in sulfenamide **1** is activated by the coordination of $AlCl_3$ to the nitrogen atom generating **A**. Then isocyanide **2** attacks the sulfur atom of the intermediate **A** to generate an ion pair **B** and **C** which then react with each other to afford isothiourea **3**.

Isothioureas are useful and interesting compounds as inhibitors of nitric oxide synthases (NOS)[18] and Lewis base organocatalysts.[19] As for the synthesis of isothioureas, they have been usually prepared by the alkylation of isolated or in situ generated thioureas.[20] Our method described here is synthetically useful since various isothioureas are obtained by a convenient one-pot procedure from easily available substrates.

Finally, we undertook a one-pot synthesis of unsymmetrical ureas **4** under the reaction conditions employed in run 10 in Table 2,[21] and the results are summarized in Table 3. In all runs unsymmetrical ureas **4** were obtained in moderate to high yields.[22]

Conclusions

We have developed a simple and convenient reaction for the synthesis of isothioureas by Lewis acid-catalyzed insertion of isocyanides into the N–S bond of sulfenamides. Since only a few classical preparative methods of isothioureas are available, the present new approach would attract considerable attention as a practical supplemental method for isothiourea synthesis.

Acknowledgment

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Supplementary data

Supplementary data (characterization data of new compounds) associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2015.01.096.

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15. Tobisu, M.; Ito, S.; Kitajima, A.; Chatani, N. *Org. Lett.* **2008**, *10*, 5223.
16. Typical procedure: Into a 5-mL flask equipped with a reflux condenser were placed 2,6-xylyl isocyanide **2a** (0.4 mmol), sulfenamide **1a** (0.4 mmol), toluene (0.4 mL), and $AlCl_3$ (0.12 mmol) at room temperature under N_2. The mixture was heated at 80 °C for 2 h, then filtered through the celite pad with AcOEt, and volatiles were removed in vacuo. After the yield was determined by ^1H NMR (80%), the crude product was purified by preparative TLC (silica gel, hexane/Et_2O = 10:1, R_f = 0.60) to obtain phenyl *N*′-(2,6-dimethylphenyl)-*N*,*N*-diethylcarbamimidothioate **3a** in 77% yield as a colorless oil.
17. According to a reviewer's suggestion, the reaction of 2 equiv of sulfenamide **1a** with isocyanide **2a** was carried out in toluene in the presence of 10 mol % of $AlCl_3$ at 80 °C for 24 h, a similar result as in runs 12 and 13 was also obtained.
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21. Typical procedure: Into a 5-mL flask equipped with a reflux condenser were placed 2,6-xylyl isocyanide **2a** (0.4 mmol), sulfenamide **1a** (0.8 mmol), DMF (0.4 mL), and acetic acid (0.4 mmol) at room temperature under N_2. The mixture was heated at 80 °C for 30 h, then filtered through the celite pad with AcOEt, and volatiles were removed in vacuo. After the yield was determined by ^1H NMR (79%), the crude product was purified by preparative TLC (silica gel, hexane/Et_2O = 10:1, R_f = 0.10) to obtain 3-(2,6-dimethylphenyl)-1,1-diethylurea **4a** in 78% yield as a white needle.
22. Since the formation of unsymmetrical ureas was confirmed in the reaction mixture before purification, the oxygen source would be water contaminated in DMF.