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

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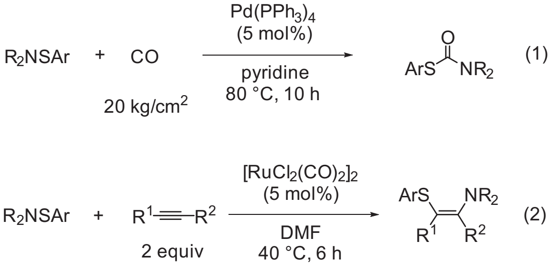
ABSTRACT

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.

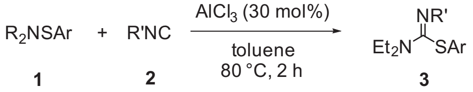
Introduction

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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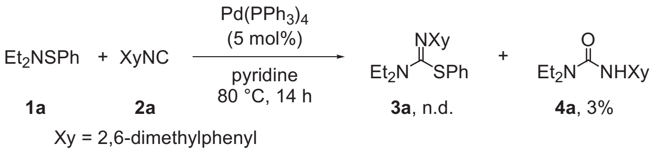
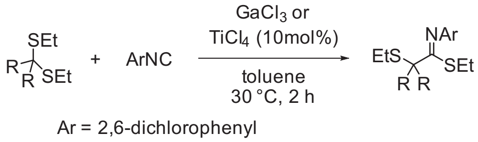
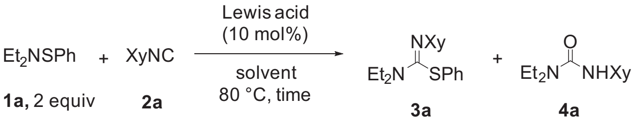


Scheme 3. Reaction of a sulfenamide with an isocyanide in the presence of Pd(PPh$_3$)$_4$.



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

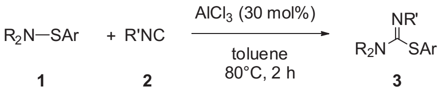
Table 1
Screening of Lewis acids

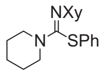
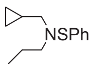
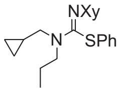
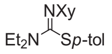
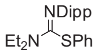
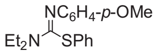
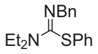
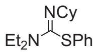


run	Lewis acid	solvent	time	yield	
				3a, %[a,b]	**4a**, %[a,b]
1	GaCl$_3$	DMF	24 h	72	8
2	TiCl$_4$	DMF	24 h	32	50
3	InCl$_4$	DMF	24 h	72	9
4	AlCl$_3$	DMF	24 h	72	2
5	ZrCl$_4$	DMF	24 h	70	14
6	BBu$_3$	DMF	24 h	58	9
7	BPh$_3$	DMF	24 h	72	4
8	B(C$_6$F$_5$)$_3$	DMF	24 h	66	14
9	BF$_3$•OEt$_2$	DMF	24 h	72	10
10[c]	CH$_3$COOH	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$_3$COOH (1 equiv). [d] AlCl$_3$ (30 mol%). [e] **1a** (1 equiv).

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$_2$NS*p*-tol **1d**	**2a**	 **3d**	70%
4[b]	Et$_2$NSPh **1a**	DippNC **2b**	 **3e**	78%
5[c]	**1a**	*p*-MeOC$_6$H$_4$NC **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$_6$H$_4$NC (2 equiv), 5 h.

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 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$_3$)$_3$Cl 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