

## A DIRECT CONVERSION OF ALCOHOLS TO ISOCYANIDES

Yoshikazu Kitano, Kazuhiro Chiba, and Masahiro Tada\*

Laboratory of Bio-organic Chemistry, Tokyo University of Agriculture and Technology,  
3-5-8 Saiwai-cho, Fuchu, Tokyo 183, Japan

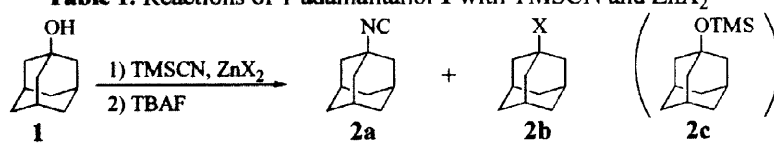
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**Abstract:** A new method for the preparation of the isocyanide group is described. Treatment of alcohols with zinc reagents ( $\text{ZnI}_2$ ,  $\text{ZnBr}_2$ , or  $\text{ZnCl}_2$ ) and trimethylsilyl cyanide (TMSCN) in dichloromethane followed by desilylation with tetrabutylammonium fluoride (TBAF) affords the corresponding isocyanides directly in good yields. © 1998 Elsevier Science Ltd. All rights reserved.

In recent years, various biologically active terpenes with an isocyanide functionality have been isolated from marine organisms.<sup>1,2,3</sup> Antifouling active isocyanoterpenes were isolated from nudibranchs,<sup>1,2</sup> and they have mainly a tertiary isocyanide. In order to synthesize these natural compounds, the key step has been introduction of an isocyano group to the tertiary carbon center. It can be prepared from a tertiary alcohol by such procedures as chlorination or trifluoroacetylation of alcohol followed by treatment with TMSCN in the presence of titanium tetrachloride ( $\text{TiCl}_4$ ),<sup>4,5</sup> or treatment with TMSCN and conc.  $\text{H}_2\text{SO}_4$  (modified Ritter reaction)<sup>6</sup> followed by dehydration of the corresponding formamide. These methods, however, need harsh conditions and take two steps. In order to solve these problems, we tried to develop a milder, direct conversion method of tertiary alcohols to isocyanides. In the modified Ritter reaction described above,<sup>6</sup> alcohols were converted to the corresponding formamides by hydrolysis of the intermediate. We thus thought the desired conversion might be obtained by preventing hydrolysis. After some examination, this was achieved by using zinc reagents instead of conc.  $\text{H}_2\text{SO}_4$ .<sup>7</sup> We describe herein a milder, direct conversion method of tertiary alcohols to isocyanides by using TMSCN and zinc reagents.

The reactions were carried out with 3.0 equivalents each of TMSCN, zinc reagents ( $\text{ZnX}_2$ ), and TBAF respectively.<sup>8</sup> Results for the reaction of 1-adamantanol **1** are summarized in Table 1. These results showed that 1-isocyanoadamantane **2a** was obtained with  $\text{ZnI}_2$ ,  $\text{ZnBr}_2$ , or  $\text{ZnCl}_2$  as a Lewis acid. In particular,  $\text{ZnI}_2$  and  $\text{ZnBr}_2$  gave **2a** in high yield. One byproduct was 1-haloadamantane **2b**, and nitrile was not observed under these conditions<sup>9</sup> (entry 1, 2, and 3), while using  $\text{ZnF}_2$  gave the silylated product<sup>10</sup> **2c** instead of **2a** (entry 4).

**Table 1.** Reactions of 1-adamantanol **1** with TMSCN and  $\text{ZnX}_2$

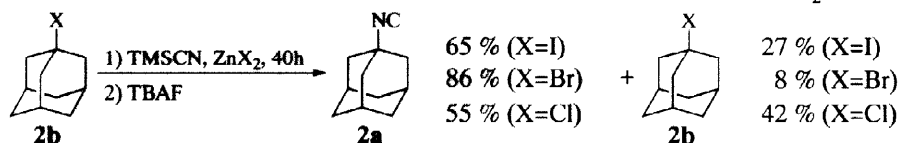
				
Entry	Reagent	Time (h)	Products (% Yield <sup>a</sup> )	
1	$\text{ZnI}_2$	18	<b>2a</b> (95)	<b>2b</b> (2)
2	$\text{ZnBr}_2$	18	<b>2a</b> (94)	<b>2b</b> (2)
3	$\text{ZnCl}_2$	18	<b>2a</b> (68)	<b>2b</b> (25)
4 <sup>b</sup>	$\text{ZnF}_2$	18	<b>2c</b> (99)	

<sup>a</sup>Determined by GLC analysis. <sup>b</sup>TBAF was not added.

1-Haloadamantanes **2b** were then examined instead of **1** under the same condition. Results are summarized in Scheme 1. Contrary to our expectation, **2a** was obtained from **2b** in each case, but reaction time was longer and yields were lower than in the case with **1**. We speculate from these results that isocyanide is mainly obtained from alcohol, and alkyl halide as a byproduct should be converted to isocyanide by slow

degrees.

**Scheme 1.** Reactions of 1-haloadamantane **2b** with TMSCN and  $\text{ZnX}_2$



Yields were determined by GLC analysis.

Reactions of other tertiary alcohols with TMSCN and  $\text{ZnI}_2$  or  $\text{ZnBr}_2$  are summarized in Table 2. Each example afforded the corresponding isocyanide in good yield, and the main byproduct was the corresponding alkene by dehydration of alcohol or dehydrohalogenation of the corresponding alkyl halide. The study of stereoisomeric alcohol gave the same product in about the same ratio (entry 2, 3). Therefore, we think this reaction obviously proceeds through on  $\text{S}_{\text{N}}1$  mechanism.

**Table 2.** Reactions of alcohols with TMSCN and  $\text{ZnBr}_2$  or  $\text{ZnI}_2$

Entry	Reactant	Product	% Yield <sup>a</sup>	
			$\text{ZnBr}_2$	$\text{ZnI}_2$
1			90	76
2			74	60
3			73	70
4			82	78

<sup>a</sup>Determined by GLC analysis. <sup>b</sup>The ratio which was determined by  $^1\text{H-NMR}$  was about 10:1 in each case.

In summary, we have developed a new method which directly converts tertiary alcohols to the corresponding isocyanides. We believe this method provides a convenient and useful way to synthesize natural compounds, biologically active compounds, and others. Further study of other trimethylsilyl reagents with alcohols and total synthesis of isocyanoterpenes is underway.

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