A Direct Conversion of Alkenes to Isocyanides

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Abstract: Treatment of alkenes with silver salts ($AgClO_4$, $AgBF_4$, or AgOTf) and trimethylsilyl cyanide (TMSCN) in dichloromethane followed by hydrolysis affords the corresponding isocyanides directly in high yields. The addition of the isocyano function is carried out in accordance with Markovnikov's rule.

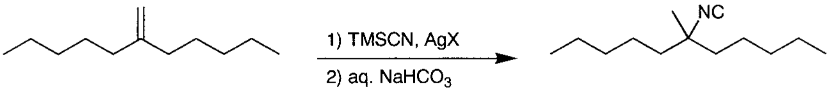
Key words: addition reactions, alkenes, isocyanides

Tertiary isocyanide is a versatile compound because biologically active isocyanoterpenes from which marine organisms have been isolated have tertiary isocyanide as a main component.[1] Isocyanides are commonly prepared by dehydration of formamides.[2] However, the preparation of tertiary isocyanides presents some difficulties. Harsh conditions are generally required in order to prepare tertiary alkyl amines as precursors of formamides. In addition, product yield is low throughout the process. Recently, we reported a new method for preparing tertiary isocyanides from tertiary alcohols directly.[3] This method was accomplished by performing the Ritter-type reaction[4] under anhydrous conditions with TMSCN as a cyano source. TMSCN is often utilized as a useful reagent for the preparation of tertiary isocyanides.[3, 5] However, to the best of our knowledge, no published research indicates how to prepare tertiary isocyanides directly from alkenes. For this reason, we developed a milder, direct conversion method to prepare tertiary isocyanides from alkenes. We thought the desired conversion might be achieved by activating alkenes with an appropriate Lewis acid followed by nucleophilic attack with TMSCN. After some examination, the desired conversion was achieved by using silver salts. We describe herein a direct conversion method of alkenes to isocyanides by using TMSCN and silver salts.

The reactions were carried out with 3.0 equivalents of TMSCN and 2.0 equivalents of silver salts (AgX), respectively.[6] Results for the reaction of 6-methyleneundecane **1** are summarized in Table 1. These results showed that 6-isocyano-6-methylundecane **2** was obtained with $AgClO_4$, $AgBF_4$, or AgOTf as a Lewis acid. The addition of the isocyano function was carried out in accordance with Markovnikov's rule. In all cases, **2** was obtained with no significant byproducts, but the reaction proceeded more rapidly with $AgClO_4$ than with $AgBF_4$ or AgOTf. Nitrile was not observed under these conditions.[7] However, it turned out that other silver salts such as AgF, AgCl, AgBr, AgI, AgO_2CCF_3, $AgNO_3$, and $AgIO_3$ were either unreactive or caused partial decomposition.

Reactions of other alkenes with TMSCN and $AgClO_4$ are summarized in Table 2. It can be seen that 1,1-di-substituted, tri-substituted, and tetra-substituted alkene afforded the corresponding tertiary isocyanides in high yields (entries 1, 2, and 3). In entries 4-7, the substrates which possess substituents at the 4-position were examined. In all cases, the stereochemistry of the major isomer was the isocyano substituent axially oriented. Moreover, 1,1-di-substituted and tri-substituted alkenes, which afforded the same product, revealed that stereoisomers were obtained at approximately the same ratio. The addition of the iscyano function was particularly observed in high stereoselectivity (entries 4, 5, and 6). The ester group was not affected under these conditions (entries 6 and 7). In entry 8, intramolecular chemoselectivity was examined with the substrate which possesses two different types of substituted olefinic bonds. The addition of isocyano only occurred at the 1,1-di-substituted olefinic bond with complete chemoselectivity. As regards our other results, cyclohexene, 1-tetradecene, and 2-tetradecene, which afforded a

Table 1



1 **2**

Entry	Reagent	Time (h)	Yield[a]
1	$AgClO_4$	12	94
2	$AgBF_4$	18	92
3	AgOTf	60	90

[a] Determined by GLC analysis.

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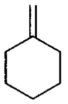
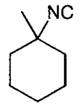
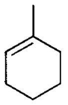
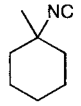
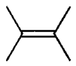
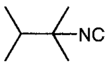
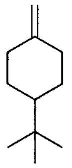
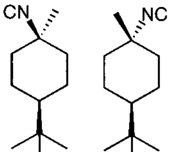
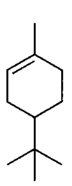
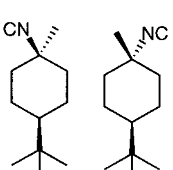
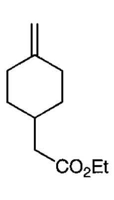
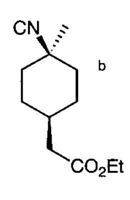
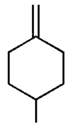
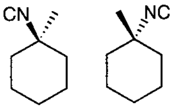
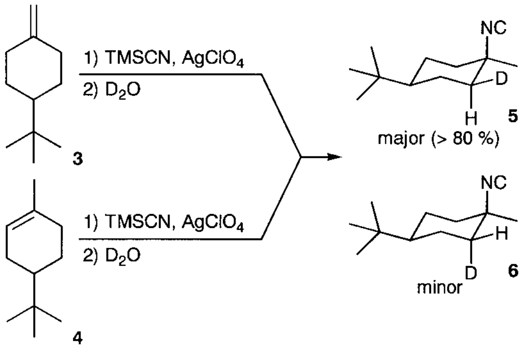
secondary isocyanide, were inert under these conditions. Therefore, we consider that this reaction proceeds selectively with the alkenes which afforded tertiary isocyanide.

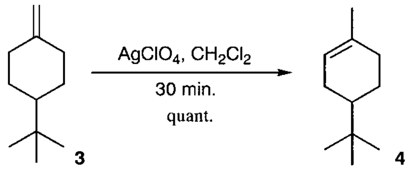
Table 2

Entry	Substrate	Product	Time (h)	% Yield
1			12	90[a]
2			12	80[a]
3			24	91[a]
4		 97 : 3[a]	12	88[a]
5		 97 : 3[a]	12	81[a]
6		 [b]	18	83[c]
7[d]		 75 : 25	48	60[c]
8			12	91[c]

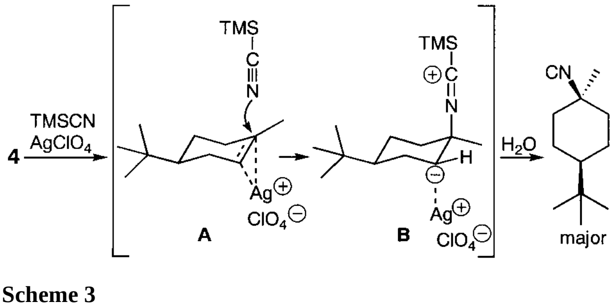
[a] Determined by GLC. [b] Stereoisomer was almost not detected. [c] Isolated yield. [d] 4.0 eq. of TBAF and 3.0 eq. of $AgClO_4$ were used.



Scheme 1



Scheme 2



Scheme 3

Similar reactions with **3** and **4** by hydrolysis with D_2O are summarized in Scheme 1. These results showed that obtaining deuterium introduced products was possible, but obtaining products with deuterium being introduced into their methyl group was hardly likely with **3**. The reaction of **3** with $AgClO_4$ in the absence of TMSCN is summarized in Scheme 2. This result showed that 1,1-di-substiuted alkene **3** was rearranged to internal trisubstituted alkene **4** rapidly. It was suggested that isocyano addition occurred after 1,1-di-substituted alkene had been transformed to tri-substituted alkene.

The reaction mechanism is proposed in Scheme 3. It is considered that this reaction involves the anti-parallel electrophilic addition of $AgClO_4$ and TMSCN to the olefinic bond (intermediate A). The initial attack by $AgClO_4$ occurs from a less hindered site through a conformation where the substituent of the 4-position is equatorially oriented. A complex of silver salt and carbanion (intermediate B) is then hydrolyzed to isocyanide. From the above proposed reaction mechanism, the high steroselectivity of this method is clearly understood.

In summary, we have developed a new method which directly converts alkenes into the corresponding isocyanides. We believe this method provides a convenient and useful way to synthesize tertiary isocyanides.

References and Notes

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(6) *General Procedure*: TMSCN (1.5 mmol) and silver salt (1.0 mmol) under argon were added to a solution of alkene (0.5 mmol) in 2 ml of dry dichloromethane. The reaction mixture was adequately stirred at ambient temperature, and then saturated aq. $NaHCO_3$ (2 ml) was added. After stirring for an additional 10 min, the mixture was then analyzed by GLC or poured into saturated aq. $NaHCO_3$ and extracted with diethyl ether. The combined organic extracts were washed with water and brine and dried over $MgSO_4$. The crude product was purified by silica gel column chromatography.

(7) Tertiary isocyanides are rearranged to the corresponding nitriles in the presence of tin tetrachloride ($SnCl_4$). Reetz, M. T.; Chatziiosifidis, I.; Künzer, H.; Müller-Starke, H. *Tetrahedron* **1983**, *39*, 961.