DOI: 10.1002/ejoc.201201305

Cycloaddition of 2-Methyleneaziridines with Isocyanates Catalyzed by Tin Iodide

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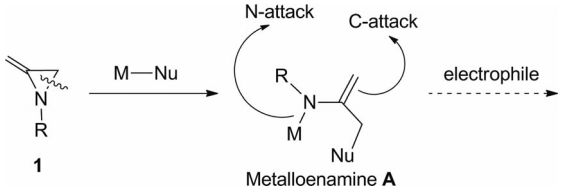
Keywords: Small-ring systems / Nitrogen heterocycles / Tin / Cycloaddition / Isocyanates

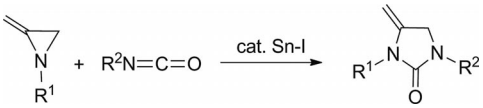
2-Methyleneaziridines proved to be good substrates for the cycloaddition with isocyanates, for which a tin iodide system, Bu_2SnI_2–LiI, was employed as an effective catalyst. Products were derived from N-attack of the ring-opened metalloenamine intermediate.

Introduction

2-Methyleneaziridines **1** are stable and easy to handle despite their highly strained structures and many preparation methods have been developed thus far.[1,2] Recently, these substrates have become versatile synthetic tools,[2,3] and multicomponent reactions based upon the strained ring system have been carried out.[3] A representative reaction involves the regioselective ring opening of 2-methyleneaziridine **1** at C-3 by using a Grignard reagent and the capture of resultant metalloenamine **A** with an electrophile by C-attack (Scheme 1). The conventional method for the conversion of **1** is based on a stoichiometric reaction with organometallic reagents. The catalytic conversion of **1** has been reported only when using transition-metal catalysts,[4,5] for which the initial addition to a C=C bond by a metal species is the key reaction.[5] From this point of view, we then focused on ring-opened intermediate **A**, which possesses two nucleophilic sites: the metal–amine and the enamine carbon atom. Thus, not only reactions resulting from C-attack but also those resulting from N-attack would occur. We present here the catalytic conversion of 2-methyleneaziridines **1** into heterocyclic compounds. The reaction proceeds through N-attack of metalloenamine **A**, for which a tin iodide system was an effective catalyst (Scheme 2).



Scheme 1. Conversion of 2-methyleneaziridine.



Scheme 2. Cycloaddition of 2-methyleneaziridine.

Results and Discussion

The catalytic preparation of heterocyclic compounds by the cycloaddition of epoxides with isocyanates was performed by using tin iodide catalysts, which can be established as the mildest conditions from among the conventional catalysts.[6] For the cycloaddition, the ring opening of an epoxide is the key step, and organotin iodides have been shown to work very well.[7] However, tin catalysts are not applicable to the reactions of simple aziridines. Because of the diminished electronegativity of nitrogen compared to that of oxygen, the ring-opening reactions of aziridines are expected to be less facile than the corresponding reactions of epoxides.[8] However, 2-methyleneaziridines **1** seem to cleave easily because of their highly strain structures. Hence, **1** are considered to be good candidates as substrates for cycloaddition reactions.

Initially, we performed the cycloaddition of **1a** with tosyl isocyanate (Table 1). Without a catalyst, no reaction proceeded at 0 °C over the course of 1 h (Table 1, entry 1). By using 0.1 equiv. of Bu_2SnI_2 as a catalyst, **2a** was obtained in 23% yield as a 1:1 adduct (Table 1, entry 2). Using LiI as a catalyst also gave **2a** in 25% yield (Table 1, entry 3). Product **2a** is derived from attack of the nitrogen atom of **1a** on the isocyanate, and the addition occurs across the C=N bond of the isocyanate. Metal bromide catalysts such as Bu_2SnBr_2 and LiBr showed no catalytic activity (Table 1, entries 4 and 5). When both Bu_2SnI_2 and LiI were added

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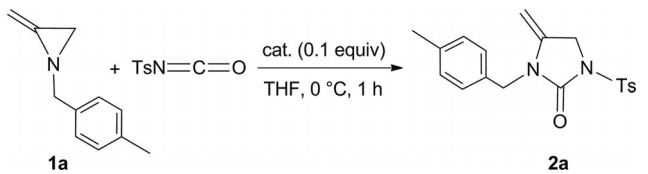
Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/ejoc.201201305.

simultaneously, however, the yield of **2a** increased to 68% (Table 1, entry 6). Higher (25 °C) and lower temperatures (–20 °C) did not improve the yield of **2a** (Table 1, entries 7 and 8).[9]

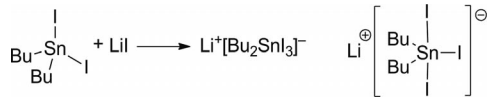
Table 1. Cycloaddition of **1a** with tosyl isocyanate.[a]



Entry	Catalyst	Temp. [°C]	Yield [%][b]
1	none	0	trace
2	Bu_2SnI_2	0	23
3	LiI	0	25
4	Bu_2SnBr_2	0	trace
5	LiBr	0	trace
6	Bu_2SnI_2–LiI	0	68
7		25	55
8		–20	27

[a] Reaction conditions: **1a** (0.8 mmol), TsN=C=O (0.5 mmol), THF (1 mL), Bu_2SnI_2 (0.05 mmol), LiI (0.05 mmol). [b] Isolated yield based on TsN=C=O.

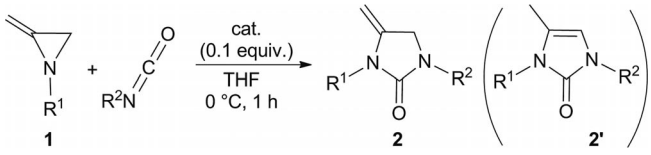
We have already studied the mixture of Bu_2SnI_2 with LiI by ^{119}Sn NMR spectroscopy.[10] Thus, as shown in Scheme 3, what is considered as the active catalytic species, a pentacoordinate tin species, $Li^+[SnBu_2I_3]^-$, was formed.[11]



Scheme 3. Tin iodide ate complex.

Table 2 shows the results of the reactions of **1** with isocyanates catalyzed by Bu_2SnI_2–LiI under the optimized conditions. The reactivity was dependent on the substituents of both substrates. The reaction of **1a** with PhN=C=O proceeded well at 0 °C over 1 h to give product **2b** (Table 2, entry 1). However, when *p*-methoxyphenyl isocyanate (PMPN=C=O) was treated under the reaction conditions, it took longer to attain a satisfactory yield of **2c** (Table 2, entries 2 and 3). Thus, the electrophilicity of the isocyanates was an important factor in the reaction. In fact, *n*BuN=C=O, which has an electron-donating alkyl substituent, was not reactive under the same conditions (Table 2, entry 4). Other alkyl-substituted 2-methyleneaziridines **1b** and **1c** were reactive to give corresponding adducts **2e** and **2f**, respectively (Table 2, entries 5 and 6). The bulky cyclohexyl substituent of **1c** prevented the reaction, even when using PhN=C=O (Table 2, entry 7). In the reactions listed in Table 2, initially formed products **2** were *exo*-methylene-type adducts that were detected in the reaction mixture by ^{1}H NMR spectroscopy. In some cases, during the isolation process, isomerization occurred to give stable, internal-alkene-type products **2′** (Table 2, see ratio in parentheses). As the ratio **2**/**2′** may not be accurate after isolation, in Table 2 we indicate the ratio based on the crude reaction mixture.

Table 2. Cycloaddition of **1** with isocyanates.[a]

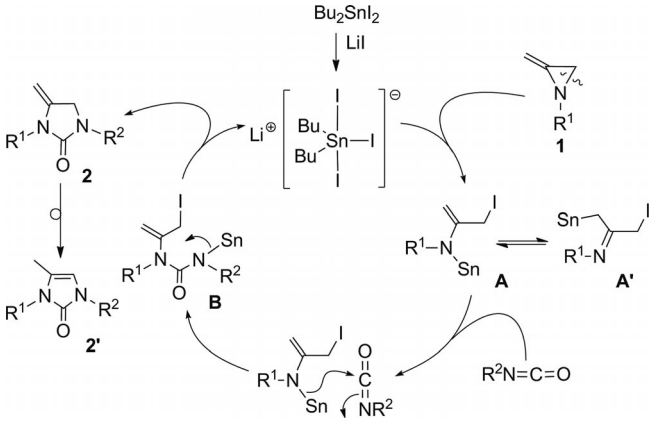


Entry	R^1	R^2	Time [h]	Product	Yield [%][b] (**2**/**2′**)[c]
1	CH_2(4-MeC_6H_4) (**1a**)	Ph	1	**2b**	89 (100:0)
2		PMP	1	**2c**	45 (84:16)
3		PMP	18	**2c**	70 (54:46)
4		*n*Bu	1	**2d**	trace
5	*n*Bu (**1b**)	Ts	1	**2e**	50 (100:0)
6	*c*-Hex (**1c**)	Ts	1	**2f**	52 (100:0)
7		Ph	1	**2g**	trace

[a] Reaction conditions: **1** (0.8 mmol), RN=C=O (0.5 mmol), THF (1 mL), Bu_2SnI_2 (0.05 mmol), LiI (0.05 mmol). [b] Isolated yield based on the isocyanate. [c] Detected by analysis of the ^{1}H NMR spectra of the reaction mixture.

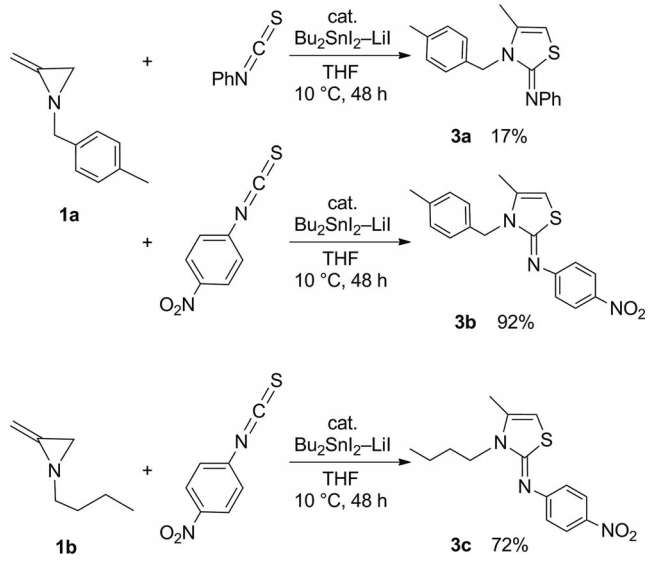
A plausible catalytic cycle is shown in Scheme 4. Initially, Sn–I attacks 2-methyleneaziridine **1** at the C-3 carbon to give enamine **A**.[12] The ring-opening step proceeds smoothly because of the strain of the 2-methyleneaziridine ring. In the subsequent reaction with an isocyanate, the tin amine moiety in **A** attacks the electrophilic carbon of an isocyanate (N-attack) to give ureidostannane **B**.[13] To make this step effective, the use of highly electrophilic isocyanates was necessary. Thus, the nucleophilicity of the Sn–N bond in **A** was insufficient by comparison with simple tin amines,[14] because of the delocalization of the enamine structure or its isomerization to an imine to form **A′**. When using a bromide salt such as Bu_2SnBr_2 or LiBr as the catalyst, no catalytic activity was observed (Table 1, entries 4 and 5). This is because the electron-withdrawing bromide substituent decreases the nucleophilicity of **A**. Next, subsequent intramolecular *N*-alkylation from resultant **B** affords 4-methylene-2-imidazolidinone **2** with regeneration of the tin iodide catalyst. During the isolation process, isomerization to a stable alkene occurred to give internal-alkene-type products **2′**. In all steps of the catalytic cycle, the Sn–I and Sn–N bonds, which occupy apical positions in the pentacoordinate trigonal bipyramidal structure of the tin atoms, worked well because of their increased length and highly nucleophilic character.[15]

We next tried to use an isothiocyanate in place of an isocyanate (Scheme 5). In the reaction of **1a** with PhN=C=S, although the yield of desired 1:1 adduct **3a** was unsatisfactory, the use of the more electrophilic *p*-nitrophenyl isothiocyanate afforded a satisfactory yield of adduct **3b**. The reaction of **1b** with *p*-nitrophenyl isothiocyanate also gave corresponding adduct **3c**. These products are derived from the addition of the isothiocyanates across the C=S bond. Namely, the resultant Sn–N bond of **A** was

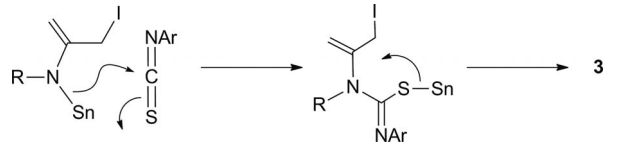


Scheme 4. Plausible catalytic cycle.

added to an isothiocyanate to form adduct **C**,[16] which included an Sn–S bond because of the high affinity of Sn for S atoms,[7] and subsequent intramolecular alkylation of the Sn–S bond afforded product **3** (Scheme 6).



Scheme 5. Reactions with isothiocyanates.



Scheme 6. Addition of **A** to isothiocyanate.

Conclusions

In conclusion, we demonstrated that 2-methyleneaziridines **1** are good substrates that can give nitrogen heterocycles through novel type of cycloaddition. The organotin iodide complex, Bu_2SnI_2–LiI was employed as an effective catalyst. We are now planning the catalytic reactions operating through C-attack of **A**.

Experimental Section

Representative Procedure: A 5-mL reaction vessel was flame-dried under reduced pressure. After filling with nitrogen, the vessel was charged successively with $n$$Bu_2SnI_2$ (0.0243 g, 0.05 mmol) and LiI (0.067 g, 0.05 mmol) in THF (1 mL). After 5 min, 2-methyleneaziridone (**1a**; 0.127 g, 0.8 mmol) and tosyl isocyanate (0.099 g, 0.5 mmol) were added with stirring. The solution was stirred at 0 °C for 1 h. Disappearance of the characteristic band of the NCO group at 2100 cm^{-1} was observed in the IR spectrum. Upon completion of the reaction, the mixture was quenched with brine (10 mL). The mixture was extracted with diethyl ether (3 × 20 mL), and the combined extract was dried with sodium sulfate and concentrated. The isolated yield of **2a** (0.1211 g, 68%) was determined based on the isocyanate (0.5 mmol). The crude product was then purified by flash column chromatography (hexane/EtOAc, 9:1 to 3:7). The desired product eluted with hexane/EtOAc = 7:3.

Supporting Information (see footnote on the first page of this article): General procedures and characterization data of new compounds.

Acknowledgments

This research was supported by a Grant-in-Aid for Scientific Research from the Ministry of Education, Science, Sports, and Culture and the Naito Foundation.

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Received: October 3, 2012
Published Online: November 13, 2012

