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Selective Synthesis of Eight-Membered Cyclic Ureas by the [6 + 2] Cycloaddition Reaction of 2-Vinylazetidines and Electron-Deficient Isocyanates

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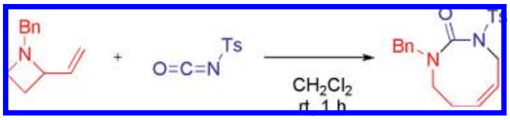
ABSTRACT



The [6 + 2] cycloaddition reaction of 2-vinylazetidines with electron-deficient isocyanates such as tosyl isocyanate proceeded smoothly in the absence of the catalyst at room temperature, and various cyclic ureas were isolated in good to high yields. Electron-deficient allenes also reacted with the 2-vinylazetidine, and the corresponding azocine derivatives were isolated.

Medium-sized *N*-heterocycles are widespread in nature and often display interesting biological properties.[1] However, the synthesis of medium-sized *N*-heterocycles is rather difficult, and the development of a new synthetic method is highly desirable.

The ring-expansion reaction of strained nitrogen heterocycles such as azetidines,[2] β-lactams,[3] and aziridines[4] is a powerful strategy for the synthesis of heterocyclic compounds, and a large number of five- or six-membered *N*-heterocycles have been synthesized. On the other hand, much fewer studies have been reported for the synthesis of the medium-sized rings by the ring-expansion reaction of these substrates.[4b,d−f,h,i]

2-Vinylazetidines are attractive substrates for the synthesis of larger nitrogen heterocycles, because unlike other azetidine derivatives, these compounds may react as a six-atom component. In the literature, however, 2-vinylazetidine reacted as a four-atom unit,[2b] and few [6 + 2] cycloaddition reactions have been reported.[5] We anticipated that 2-vinylazetidines would be suitable substrates for the synthesis of eight-membered cyclic compounds by the [6 + 2] cycloaddition reaction. In this paper we report the [6 + 2] cycloaddition reaction between 2-vinylazetidines **1** and electron-deficient isocyanates **2** (Scheme 1).

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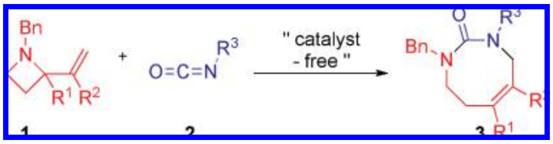
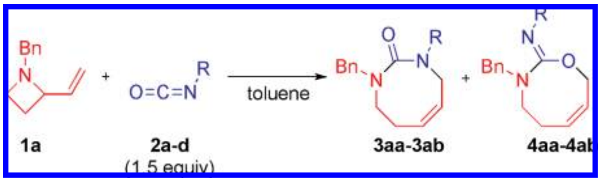
Scheme 1. [6 + 2] Cycloaddition of 2-Vinylazetidine (**1**) and Isocyanate (**2**)



The results of the reactions of 2-vinylazetidine **1a**[6] with various isocyanates **2** are summarized in Table 1. Tosyl isocyanate (**2a**) turned out to be a good substrate for this reaction, and the eight-membered cyclic urea **3aa** was isolated in 44% yield, together with an imine **4aa** (entry 1).[7]

Table 1. Reactions of **1a** with Various Isocyanates



entry	**2**	R	time (h)	temp (°C)	yield (%) **3**	yield (%) **4**
1	**2a**	Ts	1	rt	44	10
2	**2b**	Bz	17	100	19	0
3	**2c**	Ph	21	100	no reaction	
4	**2d**	4-AcC_6H_4	15	100	no reaction	

It is noteworthy that the reaction proceeded at room temperature, and no catalyst was required. On the other hand, high temperature (100 °C) was required for the reaction of **1a** and benzoyl isocyanate (**2b**), and the yield of the product was low (entry 2). Other isocyanates such as phenyl isocyanate (**2c**) or 4-acetylphenyl isocyanate (**2d**) did not react with **1a** (entries 3 and 4). These results indicate that the activation of the isocyanate group by a strong electron-withdrawing group is essential for the progress of this reaction.

The molecular structure of an eight-membered cyclic urea (**3aa**) was confirmed by an X-ray analysis (Figure 1).[8,9] The observed result is in sharp contrast to the studies reported by Alper:[2b] the formation of a six-membered cyclic urea (tetrahydropyrimidin-2-one) was observed in the reaction of 2-vinylazetidines and isocyanates in the presence of a Pd catalyst.

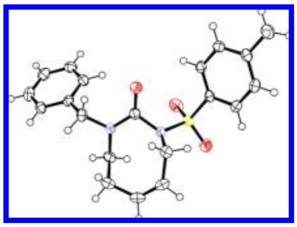
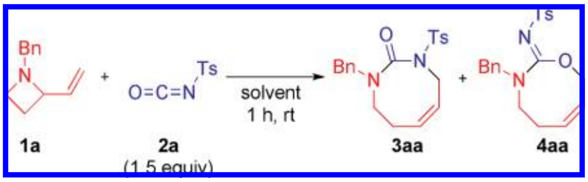


Figure 1. X-ray structure of **3aa**.

We also studied the solvent effect on this reaction (Table 2). Polar solvents turned out to be suitable for this reaction.

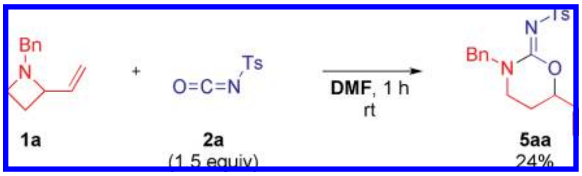
Table 2. Solvent Effect on the Cycloaddition Reaction



entry	solvent	yield (%) **3aa**	yield (%) **4aa**
1	toluene	44	10
2	THF	60	12
3	CH_3CN	56	23
4	CH_2Cl_2	71	19

Thus, when THF was selected as the solvent, compound **3aa** was isolated in 60% yield, together with a small amount of **4aa** (entry 2). Though the yields of the products did not significantly improve by switching the solvent to acetonitrile (entry 3), the yield of **3aa** reached to 71% when the reaction was carried out in CH_2Cl_2 (entry 4). It is noteworthy that a six-membered cycloadduct **5aa** was isolated in 24% yield when the reaction was carried out in DMF; no eight-membered heterocycle was isolated (Scheme 2).[10]

Scheme 2. Reaction of **1a** with **2a** in DMF



The generality of the cycloaddition was examined by carrying out the reaction of 2-vinylazetidines with various

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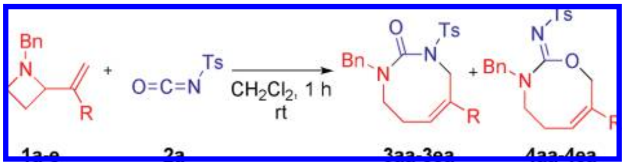
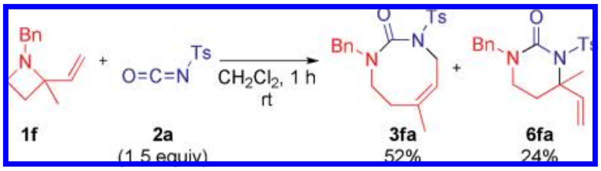
substituents. The results are summarized in Table 3. Cycloaddition of **1b** ($R^1 = CH_3$) with **2a** proceeded smoothly, and **3ba**, together with a small amount of **4ba**, was isolated in good yield (entry 2). The reaction proceeded selectively when the phenyl group was introduced, and the reaction of **1c** with **2a** gave the corresponding cyclic urea **3ca** in 77% yield (entry 3). The electronic effect on the reaction was examined by introducing substituted phenyl groups to the olefin moiety. The yield of the product decreased when a 4-methoxyphenyl group was introduced as a substituent (entry 4). On the other hand, the yield of **3ea** increased to 89% when a 2-vinylazetidine substituted with a 4-(trifluoromethyl)phenyl group was used as the substrate (entry 5). The formation of the eight-membered cyclic urea **3fa** was observed even when the 2-vinylazetidine (**1f**) reacted with **2a** (Scheme 3). In this reaction, however, the formation of a significant amount of the six-membered cyclic urea **6fa** was observed.

Table 3. Reactions of Various 2-Vinylazetidines with Tosyl Isocyanate (**2a**)



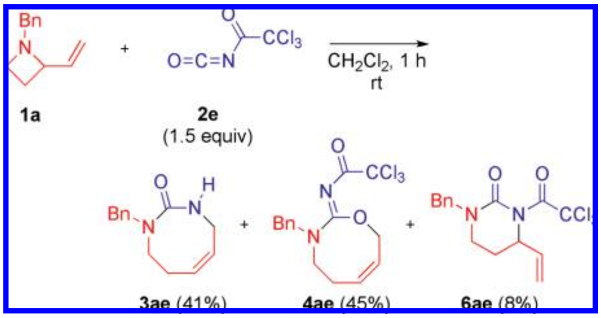
entry	1	R	yield (%) 3	4
1	**1a**	H	71	19
2	**1b**	CH_3	65	18
3	**1c**	Ph	77	trace
4	**1d**	4-$MeOC_6H_4$	67	6
5	**1e**	4-$CF_3C_6H_4$	89	3

Scheme 3. Reaction of **1f** and **2a**



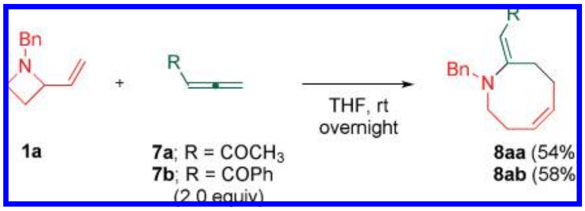
When the reaction of **1a** with trichloroacetyl isocyanate (**2e**) was examined, the eight-membered cyclic imine (**4ae**) was isolated as the major product, along with the N-deacylated cyclic urea (**3ae**). A small amount of a six-membered cyclic urea (**6ae**) was also isolated (Scheme 4).

Scheme 4. Reaction of **1a** with Trichloroacetyl Isocyanate (**2e**)



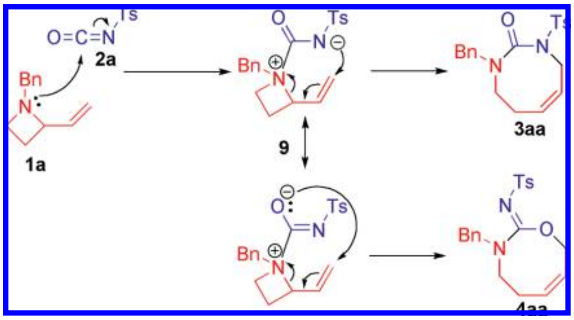
Finally, we found that the [6 + 2] cycloaddition reaction proceeded with other electron-deficient cumulenes. Thus, the reaction of **1a** with acetylallene (**7a**) as well as benzoylallene (**7b**) proceeded smoothly, and the corresponding azocine derivatives were isolated in moderate yields (Scheme 5).

Scheme 5. Reaction of **1a** with Allenes **7a,b**



A plausible mechanism for the formation of the eight-membered compound is shown in Scheme 6. The reaction would be initiated by the nucleophilic attack of the nitrogen atom of the 2-vinylazetidine to the carbon atom of the isocyanate group. The electron-withdrawing group bound to the isocyanate moiety would facilitate this process. The initially formed zwitterionic intermediate (**9**) would be converted to the eight-membered ring by the intramolecular S_N2' reaction. The formation of **3aa** would proceed when the nitrogen atom attacked the electrophilic allylic moiety,

Scheme 6. Proposed Mechanism for the Formation of Eight-Membered Cyclic Compounds



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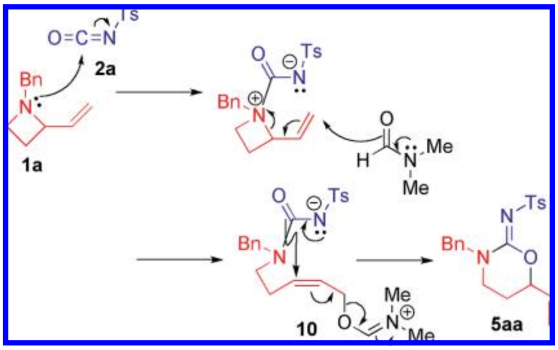
and the imine **4aa** would be generated by the attack of the oxygen atom. The selective formation of eight-membered cyclic urea (not the imine) in many reactions could be reasonably explained in terms of the higher nucleophilicity of the nitrogen atom compared to the oxygen atom.

The formation of a six-membered cyclic imine in DMF would also proceed via an acyclic zwitterionic intermediate. Thus, DMF is a strong nucleophile compared to other solvents, and it may induce the ring-opening reaction to give **10**.[11] This intermediate would cyclize to give a six-membered cyclic imine (Scheme 7).[12]

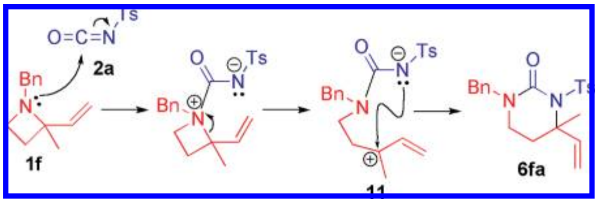
Scheme 7. Proposed Mechanism for the Formation of Cyclic Imine **5aa**



The formation of six-membered urea in the reaction of **1f** with **2a** would not proceed via S_N2' pathway, and the S_N1 reaction would proceed instead. In this reaction, the ring opening of the zwitterionic intermediate would give a linear intermediate (**11**), which would undergo cyclization (Scheme 8).

In summary, we developed a new, simple, and practical method for the synthesis of eight-membered cyclic ureas by the [6 + 2] cycloaddition reaction of 2-vinylazetidines with electron-deficient isocyanates. The reaction proceeded by mixing the substrates in CH_2Cl_2 at room temperature, and no catalyst was required. Further extension of this reaction to the synthesis of other medium-sized heterocycles is ongoing.

Scheme 8. Proposed Mechanism for the Formation of Cyclic Urea **6fa**



Supporting Information Available: Experimental procedures, characterization data, and copies of NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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(7) The structual determination of **4** was based on the analysis of the ^{1}H NMR spectra: the ^{1}H NMR data of structurally similar iminooxazolidines (five-membered cyclic ureas) and imidazolidinones (five-membered cyclic imines) were utilized to confirm the formation of **4**. See ref 4e.

(8) Crystallographic data were collected on a CCD detector with graphite monocromated Mo Kα (λ = 0.71073 Å), ϕ and ω scans. The crystal structure was solved by direct methods SHELXS-97 and refined by full-matrix least-squares SHELXL-97.[8] All non-hydrogen atoms were refined anisotropically. All hydrogen atoms were included as their calculated positions. Crystallographic data for **3aa**: $C_{20}H_{22}N_2O_3S$, $M_r = 370.46$, 0.50 × 0.40 × 0.30 mm, orthorhombic, $P2_12_12_1$, $a = 10.0224(6)$, $b = 10.6131(6)$, $c = 17.094(1)$ Å, $V = 1818.3(2)$ Å^3, $Z = 4$, $\rho_{calcd} = 1.353$ Mg m^{-3}, $2\theta_{max} = 54.44°$, $T = 150$ K, 8937 reflections measured, 3696 unique ($R_{int} = 0.0171$). $\mu = 0.201$ mm^{-1}, The final R_1 and $wR(F2)$ was 0.03043 and 0.0658 (all data) The residual electron densities (peak and hole) were 0.229 and −0.263 e Å^{-3}. Flack parameter is 0.02(6). CCDC-739891 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

(9) A short history of SHELX: Sheldrick, G. M. *Acta Crystallogr.* **2008**, *A64*, 112–122.

(10) The reason for the observed low yield of **5aa** is not clear at present. Products derived from tosyl isocyanate were also recovered.

(11) Alternatively, the solvent (DMF) may stabilize the allyl cation and the S_N1 reaction might proceed.

(12) It is noteworthy that the imine, not the urea, was formed in this reaction. We assume that the nucleophilicity of the nitrogen atom was reduced by solvation.