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DIASTEREOSELECTIVE SYNTHESIS OF 5-IODOALKENYL-2-OXAZOLINES BY ELECTROPHILIC CYCLIZATION OF ALLENYL AMIDES

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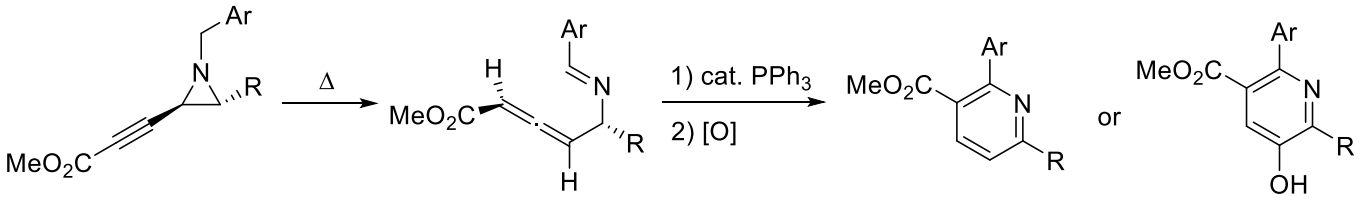
Abstract – The electrophilic cyclization of allenyl amides is described. Allenyl amides were easily prepared from the propargyl aziridines via the [1,5]-hydrogen shift followed by the conversion of the imine moiety to the amides. 5-Iodoalkenyl-2-oxazolines having a variety of substituents were diastereoselectively obtained by the reaction of the allenyl amides with iodine.

Oxazolines are an important class of heteroaromatic compounds, and these are components as a structural fragment of pharmaceutical and agricultural agents.[1,2] From this reason, constructive effort has been devoted toward developing a methodology for the synthesis of substituted oxazolines.[3-5]

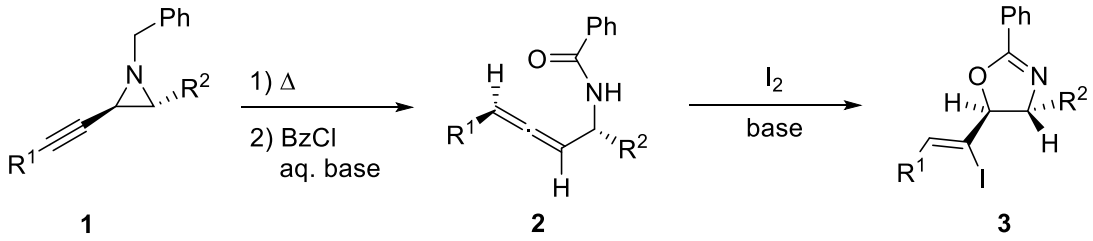
Alkynylaziridines are useful synthetic building blocks in organic chemistry, and a variety of reactions including the opening of the aziridine ring and construction of *N*-heterocyclic compounds have been reported.[6-8] Among them, we have recently reported syntheses of substituted pyridines involving sequential transformations of 3-aziridinylpropiolate esters (Scheme 1).[8] The sequence comprises a [1,5]-hydrogen shift of 3-aziridinylpropiolate esters, an intramolecular aza-Baylis-Hillman reaction of the resulting allenyl imines, and an oxidation to the pyridines. During the course of our planning for further utilization of alkynylaziridines, we found that the electrophilic cyclization of allenyl amides **2**, derived from alkynylaziridines **1**. Herein, we describe an iodine-promoted cyclization of **2**, in which the 5-iodoalkenyl-2-oxazolines **3** were produced in a diastereosective manner.

‡ This paper is dedicated to Professor Tohru Fukuyama on the occasion of his 70th birthday.

Previous work:



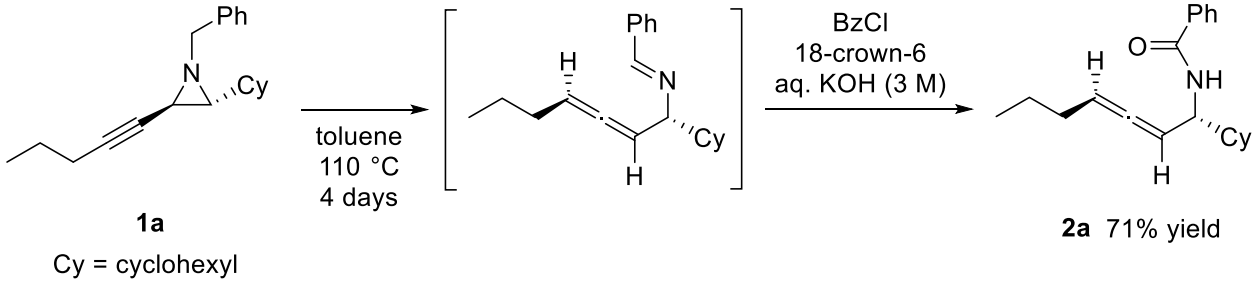
This work:



1 **2** **3**

Scheme 1

The examinations were started from a synthesis of allenyl amide **2a**, which has a cyclohexyl and a propyl group within the molecule (Scheme 2). When alkynylaziridine **1a** was heated in toluene at 110 °C, the [1,5]-hydrogen shift proceeded to produce the corresponding allenyl imine as a single diastereomer.[8] The resulting imine was further treated with benzoyl chloride and 18-crown-6 in aqueous KOH without purification to afford the allenyl amide **2a** in 71% yield in two steps.



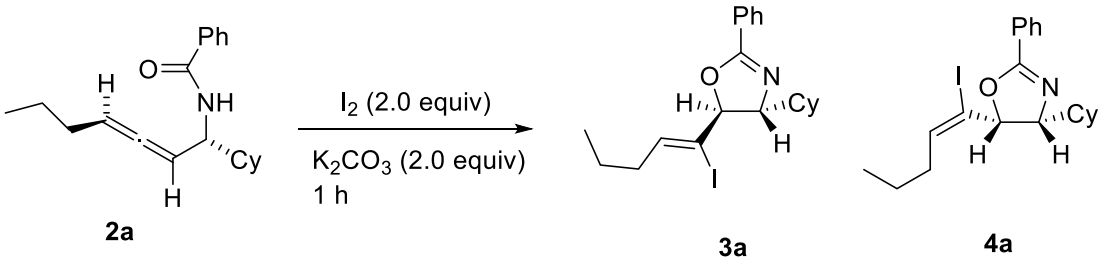
1a
Cy = cyclohexyl

2a 71% yield

Scheme 2

We next investigated the iodine-promoted electrophilic cyclization of allenyl amide **2a** (Table 1). When **2a** was subjected to the reaction with 2 equiv iodine and 2 equiv K_2CO_3 in THF at 20 °C for 1 h, the expected 5-iodoalkenyl-2-oxazoline **3a** and the stereoisomer **4a** were produced in a 7.8 : 1 ratio and 90% yield (entry 1).[9] The yield was decreased to 79% in case the reaction was carried out at 0 ºC (entry 2). The experiments using toluene and DMF as the solvent (entries 3 and 4) revealed that **3a** was exclusively obtained in the case of toluene in 93% yield (entry 3).

Table 1. Initial attempts using **2a**



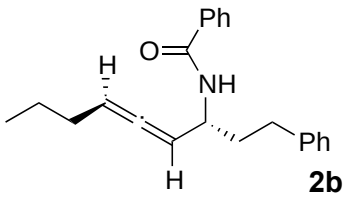
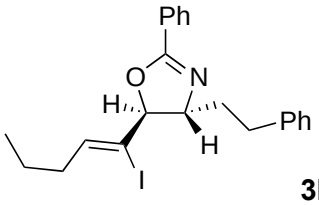
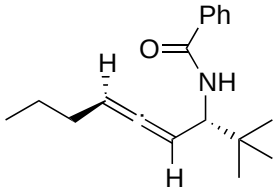
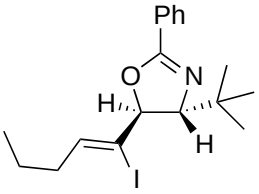
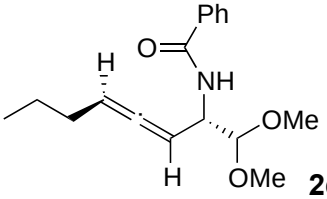
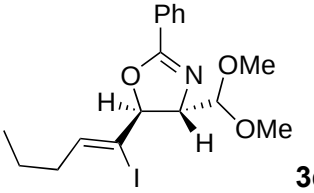
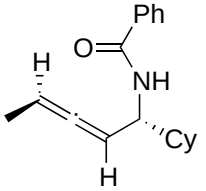
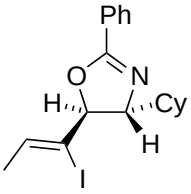
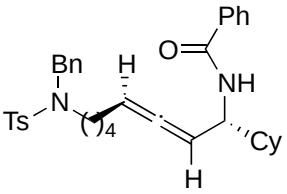
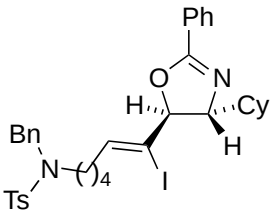
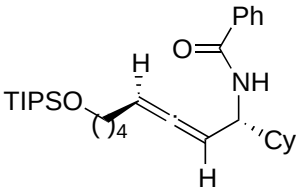
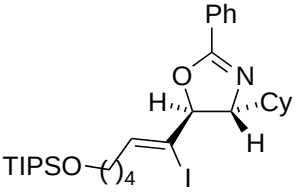
2a **3a** **4a**

Entry	Temp (°C)	Solvent	**3a** : **4a**	Yields (%)
1	20	THF	7.8 : 1	90
2	0	THF	6.8 : 1	79
3	20	toluene	**3a** only	93
4	20	DMF	5.5 : 1	71

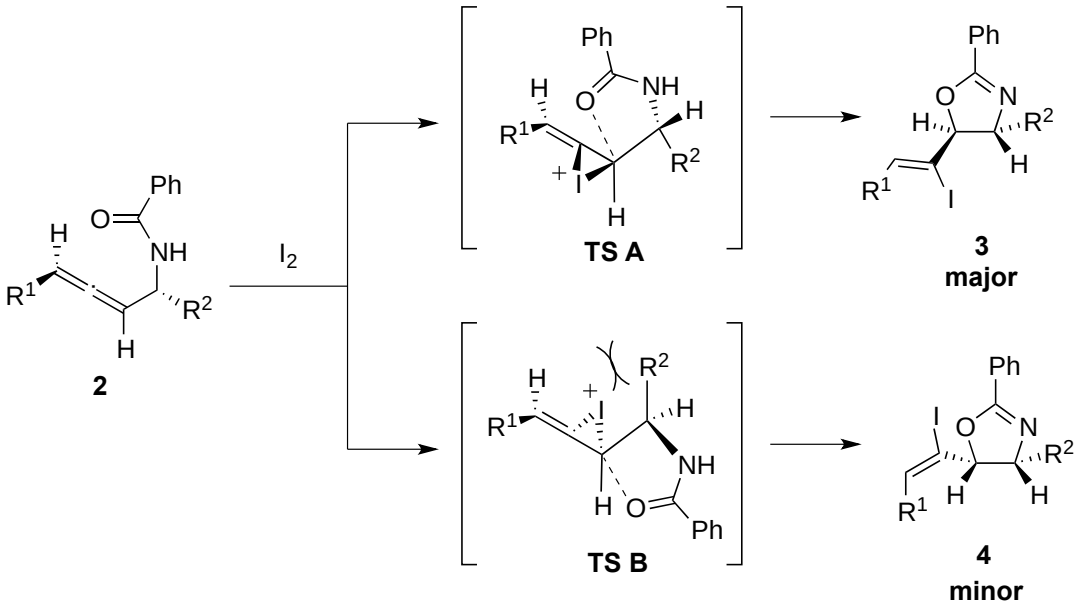
Having identified a useful set of reaction conditions, we carried out a study using various substituted allenyl amides **2b–2g** (Table 2). When a phenetyl-substituted substrate **2b** was exposed to the optimal conditions, the 5-iodoalkenyl-2-oxazolines **3b** and **4b** were obtained in a 4 : 1 ratio and 83% yield (entry 1). Substrates **2c** and **2d** having a *tert*-butyl and a dimethyl acetal group reacted without problems to afford the corresponding products **3c** and **3d** as the sole products, respectively (entries 2 and 3). The reaction of **2e** which contains a methyl group at the allenyl position proceeded to give the cyclized product **3e** in 95% yield (entry 4). Similarly, substrates **2f** and **2g** having a tosylamide and a siloxy moiety successfully converted to the corresponding products **3f** and **3g** with high diastereoselctivity (entries 5 and 6).

A plausible mechanism for the diastereoselective production of **3** is shown in Scheme 3. The observed diastereoselectivity would be the result of steric factors in the cyclization step. It was expected that the transition state **TS A**, leading to the major product **3**, would have lower energy because of the absence of steric repulsion that is present in **TS B**, which would furnish the minor product **4**.[10]

Table 2. Reactions using various allenyl amides **2b–2g**[a]

Entry	Substrate	Major product	**3** : **4**	Yields (%)
1	 **2b**	 **3b**	**3b** : **4b** = 4 : 1	83
2	 **2c**	 **3c**	**3c** only	96
3	 **2d**	 **3d**	**3d** only	74
4	 **2e**	 **3e**	**3e** only	95
5	 **2f**	 **3f**	**3f** only	85
6	 **2g**	 **3g**	**3g** : **4g** = 15 : 1	91

[a]Reactions were carried out in the presence of I_2 (2 equiv) and K_2CO_3 (2 equiv) in toluene at 20 °C.



Scheme 3

In conclusion, the studies described above have resulted in the synthesis of functionalized 5-iodoalkenyl-2-oxazolines by the iodine-promoted electrophilic cyclization of allenyl amides. Allenyl amides were easily prepared from the propargyl aziridines, and the electrophilic cyclization proceeded in a diastereosective manner. Since many biologically active molecules containing an oxazoline component have been reported, our methodology could provide a new protocol for the syntheses of these compounds.

ACKNOWLEDGEMENT

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9. The stereochemistry of the resulting products **3a** and **4a** were determined by NOESY correlation (see supporting information).
10. The reason for the solvent effect that nonpolar solvent such as toluene gave better result is not clear.