UNEXPECTED STEREOSELECTIVITY OF INTRAMOLECULAR 1,3-DIPOLAR CYCLOADDITION CAUSED BY THE PRESENCE OF FLUORINE ATOM#

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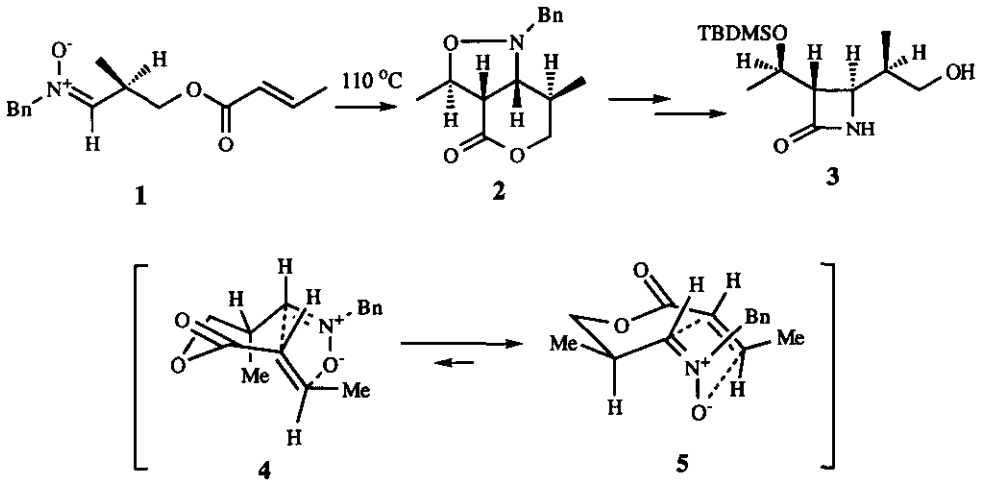
Abstract——Intramolecular 1,3-dipolar cycloaddition of nitrones (**11**; R = Me, Et, and Bn) bearing one fluorine atom at the quaternary α-position produced two diastereoisomers of bicyclic isoxazolidines (**12**) and (**13**). It was revealed that the stereochemical outcome was considerably influenced by the presence of fluorine atom.

The intramolecular 1,3-dipolar cycloaddition has become an increasingly useful methodology for the construction of natural products and biologically active substances.[1] Previously, we achieved a stereocontrolled synthesis of the key intermediate (**3**) of a 1β-methylcarbapenem antibiotic *via* the intramolecular 1,3-dipolar cycloaddition of the nitrone (**1**) forming the bicyclic isoxazolidine (**2**) (Scheme 1).[2] It was considered that the selective formation of **2** would be resulted from the preferred conformation (**5**) of the (Z)-nitrone (**1**) having the less allylic strain,



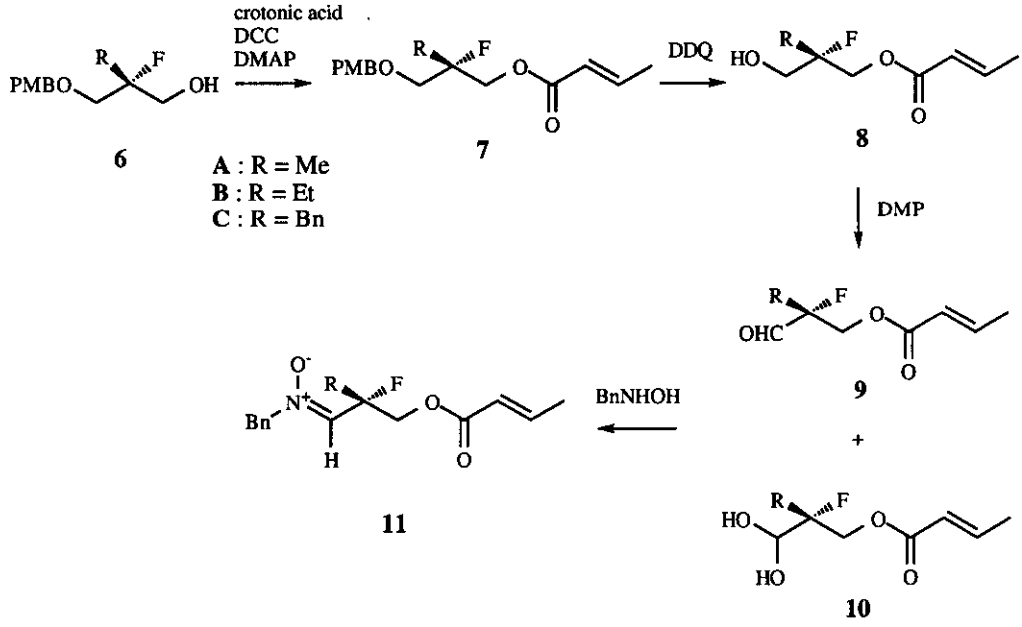
1 **2** **3** **4** **5**

Scheme 1

Dedicated to Professor R. Huisgen on the occasion of his 75th birthday.

since the steric interference of the oxygen atom of the nitrone with the methyl group would make the other conformation (**4**) unstable. Because of the enhancement of biological activity in many natural products by the selective introduction of fluorine atom(s),[3] it seems to be important to know influence of fluorine atom on stereochemistry of 1,3-dipolar cycloaddition. Therefore, the intramolecular 1,3-dipolar cycloaddition of nitrones bearing one fluorine atom at the quaternary α-position was studied.

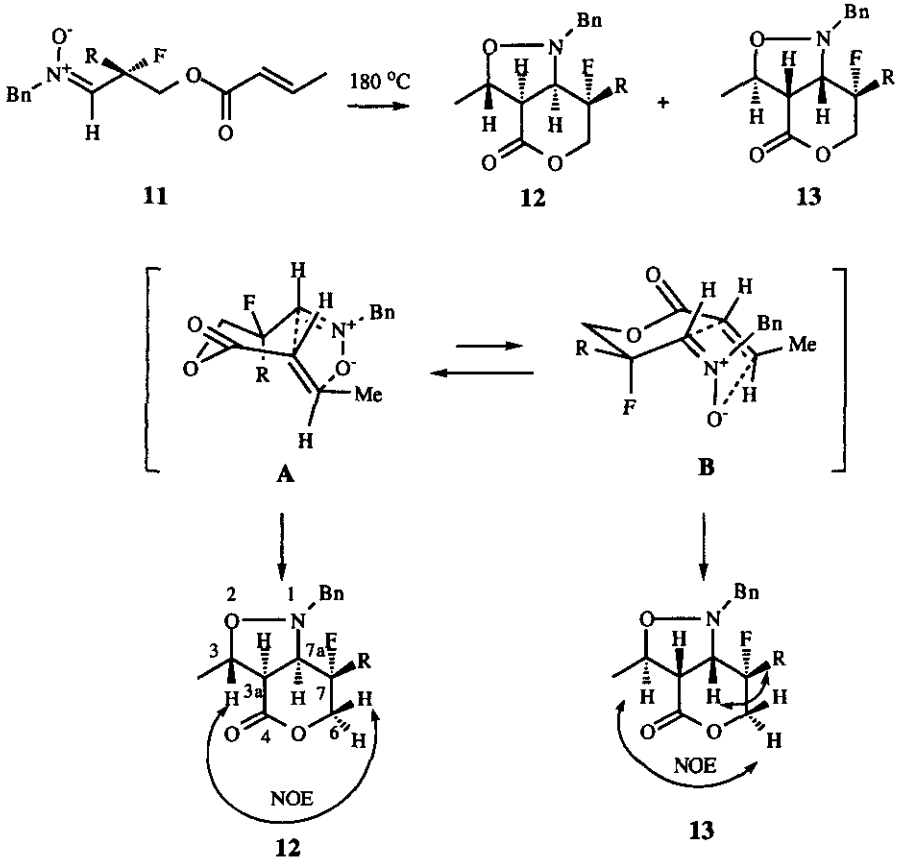
Starting with chiral propane-1,3-diols (**6**; R = Me, Et, and Bn), previously prepared by us,[4] three substrates (**11**) of the intramolecular 1,3-dipolar cycloaddition were synthesized by the route depicted in Scheme 2.



Scheme 2

Reactions of the alcohols (**6**) with crotonic acid in the presence of dicyclohexylcarbodiimide (DCC) and 4-dimethylaminopyridine (DMAP) afforded the esters (**7A**) (94% yield), (**7B**) (89% yield), and (**7C**) (96% yield). On the deprotection of the *p*-methoxybenzyl group of **7** using 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ),[5] **8A**, **B**, and **C** were gained in 87%, 90%, and 84% yield, respectively. Oxidation of the alcohol (**8A**) with Dess-Martin periodinane (DMP)[6] provided a 1 : 2.5 mixture of the aldehyde (**9A**) and the hydrate (**10A**) in 71% yield, while the same reaction of **8B** gave only the aldehyde (**9B**) in 91% yield. A 3 : 1 mixture of **9C** and **10C** was obtained in 65% yield by the oxidation of **8C**. These products (**9** and **10**) were transformed to the nitrones (**11A**, 53% yield), (**11B**, 71% yield), and (**11C**, 34% yield) by the treatments with *N*-benzylhydroxylamine[7] in the presence of anhydrous $MgSO_4$ in CH_2Cl_2. The (*Z*)-structures of **11** were determined by the ^{1}H-nmr signals due to the hydrogen on the nitrone, observed at 6.81 ppm as doublet (J = 12.1 Hz) for **11A**, 6.77 ppm as doublet (J = 12.1 Hz) for **11B**, and 6.52 ppm as doublet (J = 12.1 Hz) for **11C**, respectively.[8]

A higher temperature was required for the 1,3-dipolar cycloaddition of the nitrones (**11**) in comparison with the case of the previous nitrone (**1**) bearing a hydrogen atom instead of the fluorine atom, carried out at 110 °C. This fact would indicate that the HOMO of the nitrone interacts with the LUMO of the dipolarophile on the above 1,3-dipolar cycloaddition reactions, since it is expected that fluorine atom lowers energies both frontier orbitals of the nitrone moiety.[9]



11 **12** **13** **A** **B** **12** **13**

Scheme 3

Heating the nitrone (**11A**) in toluene at 180 °C for 12 h in a sealed tube provided two diastereoisomers of isoxazolidines (**12A**) and (**13A**) in 37% and 13% yield, respectively (Scheme 3). Their stereochemistries were assigned on the basis of the nuclear Overhauser effect (NOE) in their ^{1}H-nmr spectra. The NOE between the hydrogen at the 3 position and the β-hydrogen at the 6 position was observed in **12A**, but no NOE between the hydrogen at the 7a position and the methyl group at the 7 position was detected. On the other hand, there were NOEs between the hydrogen at the 3 position and the α-hydrogen at the 6 position and between the hydrogen at the 7a position and the methyl group at the 7 position in **13A**. It was remarkable that **12A** was the major product and the stereochemistries, newly introduced at the 3, 3a, and 7a positions of **12A**, were reverse when the outcome was compared with that of the conversion of **1** to **2**. The fact suggests that the conformation **B** (R =

Me) becomes unstable because of the electronic effects between the fluorine atom and the oxygen of the nitrone as well as between the fluorine atom and the lone-pair electron of the oxygen of the ester group in the conformation **B** (R = Me). Thus, the electronic effects in the conformation **B** (R = Me) overcome the steric repulsion between the oxygen of the nitrone and the methyl group in the conformation **A** (R = Me) during the 1,3-dipolar cycloaddition of the methyl compound (**11A**).

The 1,3-dipolar cycloaddition of the ethyl compound (**11B**), performed at 180 °C for 28 h, produced two bicyclic compounds (**12B**) and (**13B**) in 47% and 29% yield, respectively. The stereostructures of the products were also determined by the NOE experiment. Moreover, a 1 : 1 mixture of two separable isoxazolidines (**12C**) and (**13C**) was obtained in 76% yield by the 1,3-dipolar cycloaddition of the benzyl compound (**11C**), carried out at 180 °C for 24 h. Thus, it was made clear that the ratio of two diasereoisomers (**12**) and (**13**) depended upon the bulkiness of the alkyl group at the quaternary α-position. The result firmly supports the above discussion on the mechanism.

Further research on the effect of fluorine atom to the intra- and intermolecular 1,3-dipolar cycloadditions would be a very fascinating one and the results will be published in due course.

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