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Stereoselective intramolecular 1,3-dipolar nitrile oxide cycloaddition reaction of *N*-formyl-β-nitroamides

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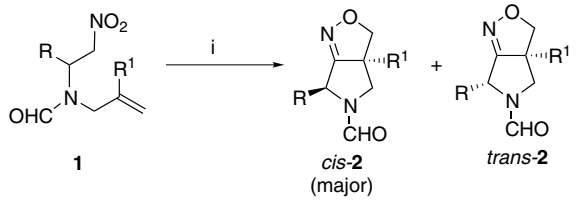
Abstract—The stereoselective intramolecular nitrile oxide cycloaddition (INOC) reaction was achieved from *N*-formyl-β-nitroamides, which were prepared through the Michael addition of allylic formamides to nitroalkenes, and *cis*-pyrroroisoxazoles and *trans*-piperidinoisoxazoles were obtained in a stereoselective manner.

1,3-Dipolar cycloaddition of nitrile oxide is regarded one of a useful synthetic method in organic synthesis.[1] The cycloaddition occurs in a stereospecific way to provide 4,5-dihydroisoxazoles, which undergoes reductive cleavage of the N–O bond on treatment with reducing agents to give γ-amino alcohols or β-hydroxy ketones in a stereoselective manner.[2] Nitrile oxides are readily generated through various methods such as dehydration of primary nitro compounds[3] or oxidative treatment of oximes.[4] Intramolecular nitrile oxide cycloaddition (INOC) reaction offers a powerful strategy to construct carbo- or heterocyclic compounds and many reports on the stereoselective INOC reaction have been published in recent years.[5] Nitroalkenes have been known as a good Michael acceptor and widely used in organic synthesis.[6] Conjugate addition to nitroalkene and subsequent generation of nitrile oxide is frequently applied to achieve successful INOC reaction.[7] Carbon, oxygen, and sulfur nucleophiles are usually employed for this reaction, while nitrogen nucleophiles were rarely used because of less stability of β-aminonitro compounds.[8] Recently we have reported formamides serve as a good nitrogen-centered nucleophile for the Michael addition to nitroalkenes.[9,10] In this Letter, we describe the Michael adducts of formamides to nitroalkenes act as useful precursors for stereoselective INOC reaction and pyrroloisoxazoles or piperdinoisoxazoles, potentially useful building block for aza-heterocyclic synthesis, are readily prepared in two steps from nitroalkenes and formamides. It is remarkable that the observed stereoselectivity is completely opposite to a similar INOC reaction starting from β-nitro ethers and β-nitro sulfides.

The precursors of the INOC reaction **1** were prepared by the method reported previously.[9] For example, precursor **1a** was obtained in 90% yield from the reaction between 3-methyl-1-nitro-1-butene and *N*-allylformamide. Generation of nitrile oxides was carried out by treatment of **1** with phenyl isocyanate in the presence of catalytic amounts of base (Scheme 1).[3] The results are summarized in Table 1.

The cycloaddition of compound **1** took place smoothly. For example, compound **1a** underwent smooth generation of nitrile oxide on treatment of phenyl isocyanate and desired pyrroloisoxazole **2a** in 90% yield (entry 1). The NMR spectrum for **2a** was somewhat complicated



1 *cis*-**2** (major)

Scheme 1. Reagents and conditions: (i) PhNCO, Et_3N, dry ether, rt–45 °C, 2–4 h.

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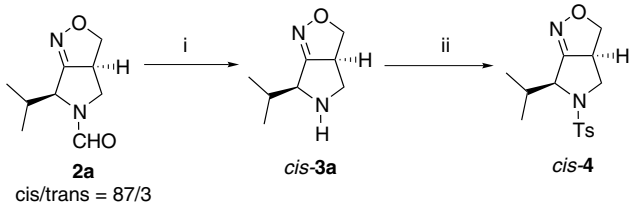
Table 1. INOC reaction for Michael adducts of formamides **1**

Entry	R	R^1	**2**	Yield[a] (%)	cis/trans[b]
1	*i*-Pr	H	**2a**	90	87/13
2	Pr	H	**2b**	82	82/18
3	Ph	H	**2c**	91	65/35
4	*i*-Pr	Me	**2d**	86	98/2

[a] Isolated yield.
[b] Determined by HPLC analyses after removal of *N*-formyl group.

due to the existence of rotational isomers of formamide unit. Fortunately exposure of **2a** to excess amounts of methylmagnesium bromide in THF resulted in the smooth removal of the formyl group and N-free pyrroloisoxazole **3a** was isolated in 65% yield (Scheme 2). Compound **3a** contained two of diastereomers and HPLC analysis showed the ratio was 87:13. The major stereoisomer was purified and N-tosylation of major

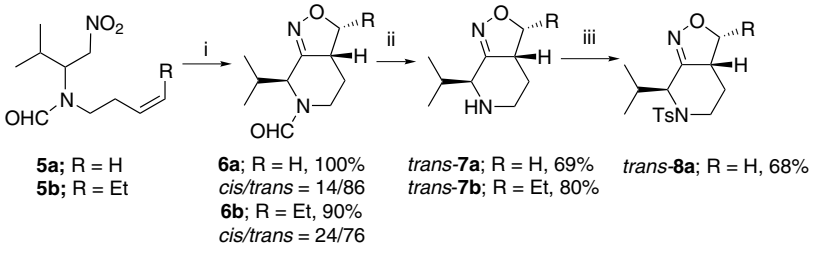


Scheme 2. Reagents and conditions: (i) MeMgBr (4 equiv), THF, −50 °C, 65%, then purification of major isomer; (ii) TsCl, Et_3N, DMAP, CH_2Cl_2, rt (99%).

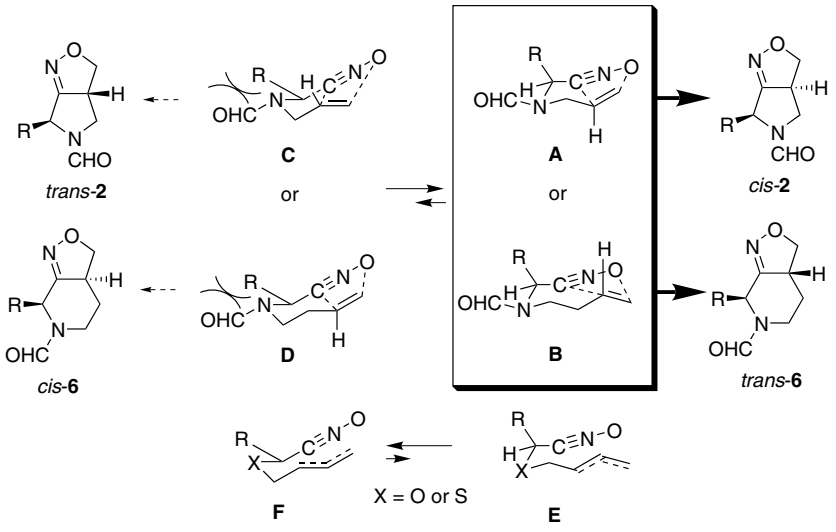
3a gave **4** as a good crystal for X-ray analysis which clearly showed the configuration between C3a and C6 was cis.[11] Other precursors **1** also gave cycloadducts **2** in similar yields. The stereoselectivity ranged more than 82:18 except for compounds **2c**, which might have epimerized during the removal of the formyl group due to the phenyl group at C6 position.

We next examined INOC reaction with homoallylamide analogue **5** (Scheme 3). Treatment of **5a** under Mukaiyama conditions again generated nitrile oxide that immediately attacked the terminal vinyl group to give piperidinoisoxazole **6a** in quantitative yield. The formyl group was readily removed by basic treatment to give N-free compound **7**. Diastereomeric ratio of **7a** was determined to be 14:86 by HPLC analysis. To elucidate the stereochemistry of the adduct, major isomer of **7a** was converted tosylamide **8a**, which fortunately crystallized to give a suitable sample for X-ray crystallographic analysis that unambiguously indicated trans configuration between C3a and C7.[12] Hence, the stereochemical outcome during the formation of the present 5,6-fused ring system was opposite to that of 5,5-fused ring system.

The present cis- and trans-selectivity of the INOC reaction is explained by the following way: there are two pairs of possible conformation **A**, **B** and **C**, **D** for the cycloaddition process, which are depicted in Scheme 4.



Scheme 3. Reagents and conditions: (i) PhNCO, Et_3N, dry ether, rt–45 °C, 3 h; (ii) NaOH, MeOH, reflux, then purified the major isomer; (iii) TsCl, Et_3N, CH_2Cl_2, DMAP.



Scheme 4.

Due to the presence of *N*-formyl group that gives rise a steric interaction between R group, much favorable conformation should be **A** and **B**, in which R group occupies the axial position to avoid gauche interaction coming from the *N*-formyl group.[13] As a result nitrile oxide prefers to attack the terminal double bond selectively through conformation **A** that gives *cis*-**2** or through conformation **B** that gives *trans*-**6**. It should be remarked that the present stereoselectivity in the cycloaddition is totally reversal to the INOC reaction from β-nitro ether or β-nitro sulfides reported by Kurth and co-workers,[7a] who showed C3a–C6 trans-selectivity was observed for the formation of furanoisoxazoles and C3a–C7 cis-selectivity was observed for the formation of pyranoisoxazoles. In their cases, there are no substituent on the oxygen or sulfur atom so that R group enjoys to occupy the pseudo-equatorial position (see transition state **E** and **F**). On the other hand, there is a nitrogen atom at X position in our case, and it attaches a substituent which offers a crucial steric bias to change of stereochemical course of the reaction (Scheme 4).

In conclusion, we have succeeded to provide a new two-step stereoselective synthesis of bicyclic 4,5-dihydroisoxazole system starting from readily available nitroalkenes and formamides. The adducts of the present method are regarded as a good precursor for piperidines and pyrrolidines which are seen widely among natural products. Thus, the present method provides a useful access to a variety of aza-heterocyclic compounds in a stereoselective manner. Further synthetic application of the present method is now underway in our laboratory.

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11. Crystallographic data (excluding structure factors) for the structures *cis*-**4** have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication numbers CCDC629252. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [fax: +44 (0)1223-336033 or e-mail: deposit@ccdc.cam.ac.uk].
12. Crystallographic data (excluding structure factors) for the structures *trans*-**8a** have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication numbers CCDC629253. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [fax: +44 (0)1223-336033 or e-mail: deposit@ccdc.cam.ac.uk].
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