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Intramolecular 1,3-Dipolar Cycloaddition of Nitrile *N*-Oxide Accompanied by Dearomatization

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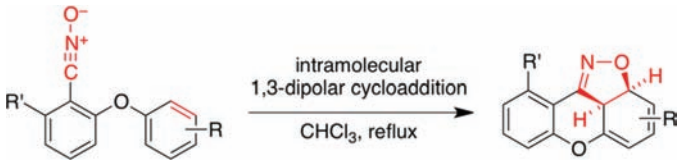
ABSTRACT



Intramolecular 1,3-dipolar cycloaddition of 2-phenoxybenzonitrile *N*-oxides to benzene rings, accompanied by dearomatization, formed the corresponding isoxazolines in high yields. The X-ray single-crystal structure analysis revealed that the reaction formed the *cis*-adduct as a single isomer. The substituents on the benzene rings markedly affected the reaction rate, yield, and structure of the final product.

Nitrile *N*-oxide is an important class of 1,3-dipoles, which facilitates catalyst-free [2 + 3] cycloaddition to various unsaturated bonds, such as alkenes, alkynes, and nitriles.[1−3] In particular, the cycloaddition of nitrile *N*-oxide is regarded as an effective tool for the synthesis of pharmaceuticals, natural products, polymeric materials, and supramolecules because it is accompanied by C−C bond formation; in addition, the resulting heterocycles serve as versatile scaffolds for a variety of reactive derivatives, such as aldol, diketone, β-aminoalcohol, and β-aminoenone.[4,5] Typically, nitrile *N*-oxide is labile and dimerizes easily to form furoxan; however, it can be made sufficiently stable by the introduction of bulky substituents, which are capable of preventing dimerization, and thus can be isolated.[6]

Recently, we developed a kinetically stabilized homoditopic nitrile *N*-oxide as a new chemical ligation tool between unsaturated bond-containing compounds, mainly directed toward both catalyst-free cross-linking reactions of common polymers, such as fibers, rubbers, and resins, and catalyst-free polycycloaddition of bisdipolarophiles.[7]

In the elaborate process of developing the homoditopic nitrile *N*-oxide, we encountered a very interesting fact: bisphenol A-skeleton-linked homoditopic nitrile *N*-oxide **1** exhibited low stability, which rapidly decomposed at room temperature, whereas the tetramethylated analogue **2** exhibited sufficient stability to be isolated without loss in the reactivity of the 1,3-dipole (Figure 1). The structural analysis of the resultant mixture from **1** revealed that

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intramolecular 1,3-dipolar cycloadditions of nitrile *N*-oxides to the neighboring bis-A benzene rings proceeded to afford the corresponding dihydrobenzoisoxazole **1′** as a diastereomixture via the dearomatization of benzene rings.

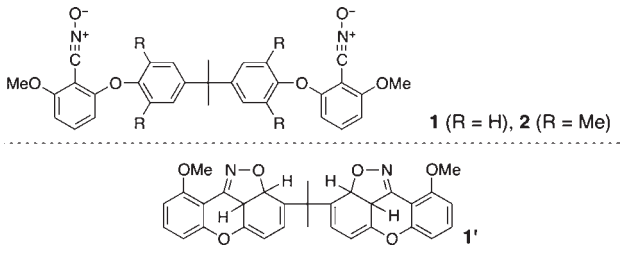


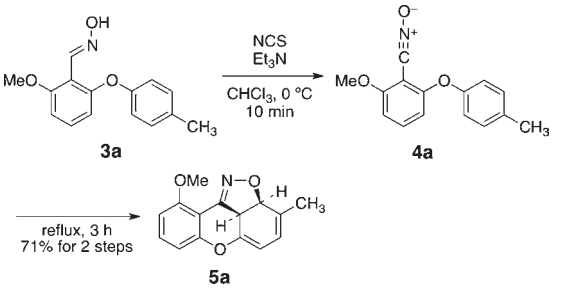
Figure 1. Homoditopic nitrile *N*-oxides (**1** and **2**) and bisdihydrobenzoisoxazole **1′**.

To the best of our knowledge, only Coustard et al. reported a study on the direct addition of nitrile *N*-oxide to a nonstrained, monocyclic phenyl ring.[8−11] They claimed that the treatment of 1-substituted-2-nitroethene derivatives with an excess amount of trifluoromethanesulfonic acid (TfOH) generated the corresponding nitrile *N*-oxides *in situ*, and successive intramolecular cycloadditions to the benzene rings afforded tricyclic isoxazolines in 41%−75% yields.

Herein, we report the intramolecular cycloaddition reactions of the nitrile *N*-oxide moiety to the neighboring benzene ring using kinetically stabilized 2-phenoxybenzonitrile *N*-oxide derivatives. The reaction was accompanied by dearomatization, leading to the formation of dihydrobenzoisoxazoles (isoxazolines) in excellent yield and high regioselectivity. The X-ray crystal-structure analysis of the product revealed the formation of the *cis*-adduct as a single isomer. By investigating the scope of various substrates, we observed that the substituents on the benzene ring markedly affected the reaction rate, yield, and structure of the final product.

First, we investigated the use of 6-methoxy-2-(*p*-tolyoxy)-benzonitrile *N*-oxide (**4a**) (Scheme 1), which was prepared from 2-fluoro-6-methoxybenzaldehyde via the aromatic nucleophilic substitution of *p*-cresol, oxime formation, and oxidation.

Scheme 1. Intramolecular Cycloaddition of Nitrile *N*-Oxide **4a**



According to Huisgen's procedure,[2] the treatment of **3a** with *N*-chlorosuccinimide (NCS) in the presence of Et_3N in $CHCl_3$ (5 mM) at 0 °C immediately afforded the corresponding nitrile *N*-oxide **4a** in 91% yield (NMR yield). Although **4a** was isolable, it gradually isomerized to isoxazoline **5a** at rt. Therefore, after confirming the generation of **4a** by TLC analysis, the reaction mixture of **3a** was refluxed for 3 h to afford **5a**, without the isolation of **4a**, in 71% yield as a single regioisomer.

The evidence for dearomatization was confirmed unambiguously by ^{1}H NMR spectroscopy (Figure 2). During the reaction, the aromatic signals originating from the tolyl group of **4a** disappeared as the peaks at 5.76, 5.54, 5.37, and 4.31 ppm increased. The former two peaks (J_{HH} = 6.4 Hz) were assigned to the conjugated diene signals, while the latter two (J_{HH} = 15.6 Hz) were assigned to the isoxazoline methine protons. Finally, the structure of **5a** was determined by X-ray crystallographic analysis.

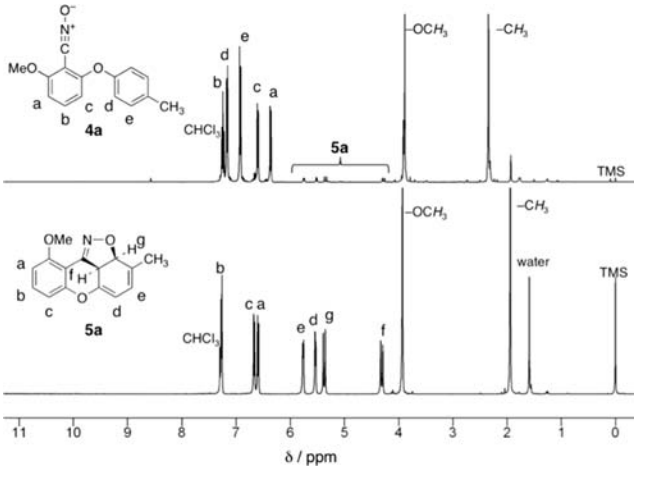


Figure 2. ^{1}H NMR spectra of nitrile *N*-oxide **4a** and isoxazoline **5a** (400 MHz, $CDCl_3$, 298 K).

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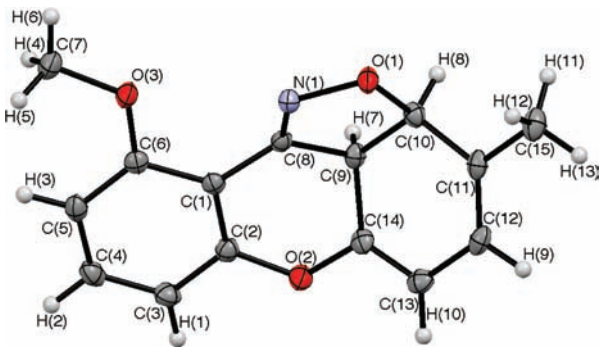


Figure 3. ORTEP structure of isoxazoline **5a**. Thermal ellipsoids are drawn at 50% probability.

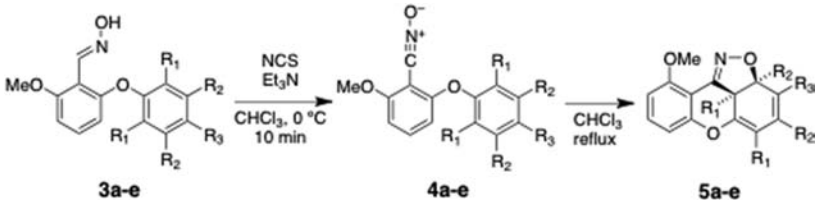
Figure 3 shows an ORTEP drawing of **5a**. It revealed that the nitrile *N*-oxide moiety was added to the benzene ring in a *cis*-manner. The four rings are not periplanar because two carbons, C9 and C10, adopt sp^3 hybrid orbitals. Notably, the dihedral angle N1−C8−C9−H7 is 117.15°, which can result in the decreased acidity of H7 by the stereoelectronic effect, thereby efficiently preventing the rearomatization of the cyclohexadiene ring via the E1cB reaction of the O1 atom. The distortion of the dihedral angle appears to be mainly attributed to the steric repulsion between the methoxy group at the peri position and the C=N bond of the isoxazoline moiety.

To clarify the effects of steric hindrance and electron demand of the benzene ring on the reaction, the reactions of 2-phenoxy-6-methoxybenzonitrile *N*-oxides with various substituents were examined, as shown in Table 1. Initially, we investigated the effects of the substituted position of the methyl group (entries 1−3). Interestingly, **4b** resulted in the corresponding cycloadduct **5b** in 81% yield (entry 2) in the same manner as entry 1, whereas the expected product **5c** was hardly observed, and the nitrile *N*-oxide **4c** was almost recovered (entry 3). It is suggested that the introduction of substituents at the R_1 positions would effectively suppress the cycloaddition reaction to the benzene ring, probably because the substituents would kinetically prevent the approach of the benzene ring to the nitrile *N*-oxide moiety. This is consistent with the successful synthesis of the stable homoditopic nitrile *N*-oxide **2**. Meanwhile, it is very interesing that the methyl groups at the R_2 positions negligibly affected the [2 + 3] cycloaddition.

The electron demand of the benzene ring also influenced the cycloaddition reaction. The reaction of **4d**, which has no substituents on the benzene ring, required a slightly long time, probably because of the electron density of the benzene ring. The yield of **5d** was lower than that of **5a** (entry 4), because an additional reaction occurred between the other nitrile *N*-oxide and the disubstituted olefin of cyclohexadiene. On the other hand, *p*-methoxy substituted **4e** was sufficiently reactive to form the cycloadduct **5e** in high yield (93%, entry 5).

In the case of **4f**, which has an electron-withdrawing group, an unexpected result was obtained (entry 6, Scheme 2). During the reflux of the **4f** solution, we noticed that the reaction was considerably slow, and a few spots appeared on the TLC after several hours. After 3 days, the reaction was quenched and purified by silica-gel column chromatography because the spots mainly converged at one spot. As a result, the main product was not the expected isoxazoline **5f** but iminophenol **6f** (75% yield) via the intramolecular redox reaction of isoxazoline[12] and cyclohexadiene rings. The structure of **6f** was determined from the following reasons: In the ^{1}H NMR spectrum, two new singlet peaks were observed in the downfield region (imine and phenol protons); the integral ratios of the five peaks in the aromatic region were equal, indicating disubstitution and

Table 1. Intramolecular Cycloaddition of 2-Phenoxynitrile *N*-Oxides **4a**−**e**



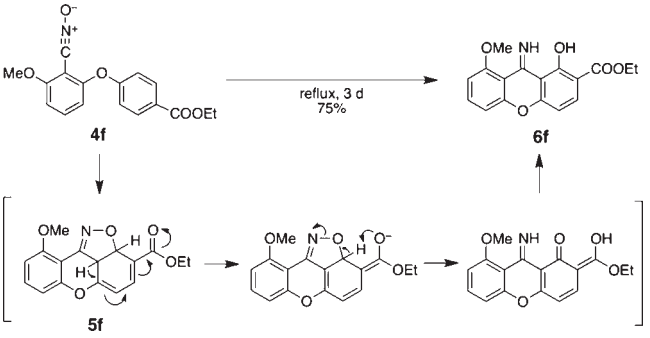
entry[a]	**3**	R_1	R_2	R_3	**4**	yield[b]/%	time/h	**5**	yield[c]/%
1	**3a**	H	H	Me	**4a**	91	3	**5a**	71
2	**3b**	H	Me	H	**4b**	92	3	**5b**	81
3	**3c**	Me	H	H	**4c**	quant	3	**5c**	trace
4	**3d**	H	H	H	**4d**	92	4.5	**5d**	52
5	**3e**	H	H	OMe	**4e**	91	3	**5e**	93
6	**3f**	H	H	CO_2Et	**4f**	94	3 d	**5f**	–[d]

[a] Reaction was carried out by using **3**, NCS (1.5 equiv), and Et_3N (1.5 equiv) in $CHCl_3$. The mixture was stirred at 0 °C for 10 min and then refluxed for 3−4.5 h. [b] NMR yield. [c] Isolated yield. [d] Not isolated.

desymmetrization of the *p*-ester benzene moiety; and the signals from olefinic protons were not observed from 4.6 to 6.6 ppm. Moreover, ^{13}C NMR, IR spectra, and elemental analysis of **6f** were consistent with the structure of **6f**.[13]

As a plausible reaction mechanism, isoxazoline **5f** would probably be formed as an intermediate, following the redox pathway (Scheme 2). Namely, the reaction of **4f** initiated the [2 + 3] cycloaddition of nitrile *N*-oxide to the benzene ring, as well as other examples, although the reaction rate was very slow because of the electron deficiency of the ester-substituted benzene ring. With the help of the ester carbonyl group, the resulting cyclohexadiene ring was aromatized to obtain **6f**.

Scheme 2. Reaction of **4f** and Plausible Reaction Pathway to **6f**



Finally, the reaction of 2-phenoxybenzonitrile *N*-oxide **4g**, the most simplified substrate, was utilized to evaluate the effect of the methoxy group at the C6 position on the cycloaddition reaction (Scheme 3). The reaction of hydroxamoyl chloride **3g** with Et_3N in $CHCl_3$ was carried out to generate 2-phenoxybenzonitrile *N*-oxide **4g** *in situ*, which could not be isolated because of the lack of the substituent at the C6 position. After refluxing for 1 h, xanthone oxime **6g** was obtained in 76% yield.[13,14]

A plausible reason for the formation of a different skeleton is the absence of steric repulsion from the peri position of the isoxazoline moiety, providing relatively small amount of torsion to enable the E1cB reaction of **5g**.

(13) See Supporting Information.

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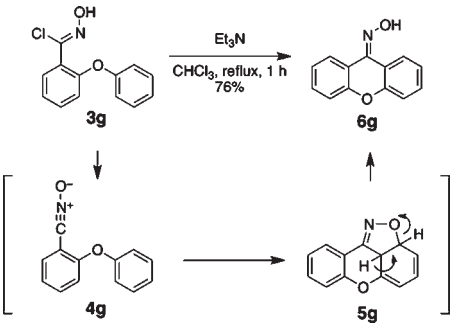
Scheme 3. Reaction of **3g** and Plausible Reaction Pathway of **6g**



In conclusion, we investigated the intramolecular 1,3-dipolar cycloaddition of nitrile *N*-oxides to the neighboring benzene ring and clarified the scope and limitation of the reaction. The reaction simply proceeded by refluxing the solutions of isolatable nitrile *N*-oxide for several hours to afford the corresponding isoxazolines in high yields. The X-ray single-crystal structure analysis of the resulting isoxazoline not only revealed that the reaction formed the *cis*-adduct as a single isomer but also indicated the chemical stability of the dearomatized structure. The present study features the development of not only the strong acid-free cycloaddition reaction to the non-strained, monocyclic phenyl ring but also the easy synthetic method of partially dearomatized dihydrobenzoisoxazole frameworks, which could provide a promising synthetic method for benzopyrano-fused natural products such as flavonoids.

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Supporting Information Available. Detailed experimental procedures and spectroscopic data for all new compounds and X-ray crystal data of **5a**. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.