JOC*Note*

Generation of Nitrile Oxides under Nanometer Micelles Built in Neutral Aqueous Media: Synthesis of Novel Glycal-Based Chiral Synthons and Optically Pure 2,8-Dioxabicyclo[4.4.0]decene Core

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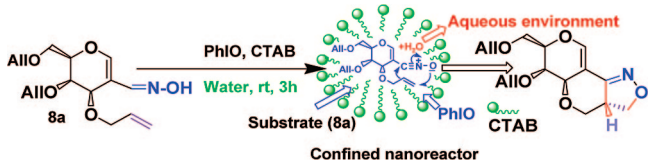

A highly efficient strategy for chemoselective oxidation of aldoximes to nitrile oxides by iodosobenzene in neutral aqueous media is reported. Their in situ intermolecular 1,3-dipolar cycloaddition (1,3-DC) with olefins in nanometer aqueous micelles occurs with improved stereoselectivity and acceleration of reaction rate toward synthesis of new chiral synthons, 3-(2′-*C*-3′,4′,6′-tri-*O*-benzylglycal)-Δ^2-isoxazolines and others. Construction of optically pure 2,8-dioxabicyclo[4.4.0]decene skeleta is performed by this green approach, and the stereochemistry of the new chiral center is predicted by B3LYP density functional theory.

Chemical coupling, reaction control, fine-tuning of the product, use of the outcome of one reaction as substrate of a next reaction and many others are performed in nature using a well-defined reaction environment through construction of extremely complex assemblies in the cell. This fosters the expectation to enhance the efficiency of chemical conversions in such a designed self-assembled reactor of nanometer to micrometer size.[1] Aqueous organized media (AOM) is one such confined environment, and the reactor is built up from molecular assemblies of amphiphilic surfactants in water media.[2] It is sufficiently hydrophobic in nature and makes organic substrates and reagents soluble and also brings them in close proximity, which enhances the efficiency of chemical transformations. This confined chemical reactor also protects water-labile reaction intermediates from hydrolytic decomposition. It simultaneously removes generated water to the aqueous environment and makes chemical transformation faster. It also enhances the possibility of performing dehydration reactions in water. At the beginning of the new century, a shift in emphasis in chemistry using water as solvent for organic reaction is very significant. Water is not only the most abundant, cheap, and environment friendly solvent, but it also exhibits unique chemical reactivity, selectivity, and properties that are different from those of organic solvents.[3]

One of the frequently used strategies employed in synthetic organic chemistry is the 1,3-DC reaction involving nitrile oxides and alkenes to afford Δ^2-isoxazolines.[4] These heterocycles offer significant synthetic potential because they can readily be converted into a variety of highly functionalized achiral and chiral compounds.[4c−g] Nitrile oxides can be prepared either by the Mukaiyama reaction from a nitro compound and phenyl isocyanate[5] or from an aldoxime and a chlorinating agent in the presence of base[6] and others.[7] Most of these methods have limitations in terms of using a complex combination of reagents and longer reaction time.

An 1,3-DC reaction proceeds in a highly stereospecific way, so regiocontrol and stereoselection in their addition step is now the major challenging task to organic chemists in both academic and industrial settings. Two major obstacles in controlling the stereoselectivity are (i) nitrile oxides are generated in situ as they are very short-lived species[8] and (ii) the tertiary amines used in their preparation can racemize the newly generated chiral

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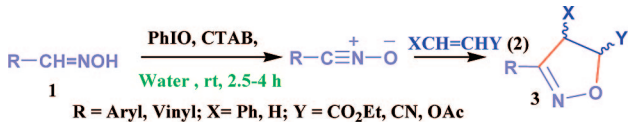
TABLE 1. Generation of Nitrile Oxide and Trapping with Olefin in AOM



product (3)	substituents R	X; Y	time (h)	yield (%)
3a	4-bromophenyl-	X = H; Y = $OCOCH_3$	3.5	81
3b	4-nitrophenyl-	X = H; Y = CO_2Et	3.0	71
3c	4-hydroxyphenyl-	X = H; Y = CO_2Et	3.0	81
3d	(*E*)-cinnamyl-	X = H; Y = CO_2Et	3.0	82
3e	4-bromophenyl-	X = H; Y = CO_2Et	2.5	81
3f	4-bromophenyl-	X = H; Y = CN	3.0	82
3g	2-furyl-	X = H; Y = CO_2Et	2.5	82
3h	(*E*)-cinnamyl-	X = Ph; Y = CO_2Et (*E*)	4.0	79

center in isoxazolines.[9a] For our ongoing project in the stereoselective synthesis of isoxazoline synthons and important skeletons for bioactive natural products, we have sought to develop a new method of preparation of nitrile oxides especially in neutral condition utilizing a commonly used oxidant. Development of this reaction in neutral aqueous media is required not only for simplification in preparation but also for improving regio- and stereoselectivities, large-scale industrial applications, and many other advantages.[3] However, the 1,3-DC reaction is studied in aqueous media in the synthesis of a variety of five-membered heterocycles including isoxazolines.[10]

Iodosobenzene (PhIO) serves as a source of oxygen in various metal-catalyzed oxidation reactions.[11] Interestingly other than its well-known property as oxygen donor, evolution of its oxidizing property has not been much investigated compared to the other hypervalent organoiodanes.[12c] PhIO has been used for synthesis of polyester through the formation of epoxides,[12a] oxidation of α-keto carboxylic acids and activated primary alcohols,[12d] synthesis of sugar derivatives and iminosugars[12b] and also the recently reported oxidative cleavage of olefinic double bonds to carbonyl compounds.[12e] In this paper, we wish to report another excellent oxidizing property of iodosobenzene as it has transformed aldoximes to corresponding nitrile oxides in neutral aqueous organized media at room temperature. Formation of nitrile oxide was confirmed by in situ trapping with olefins to obtain known Δ^2-isoxazolines (Table 1). The cycloaddition reaction proceeds with a large acceleration of reaction rate (2.5−4.0 h) with excellent isolated yields (71−82%). The results in Table 1 demonstrate that the reaction rate and yield were almost independent of the nature of the substrates used. We could not find any byproduct from our experiments, which is the major concern of the existing methods. As an example, in an attempt to prepare furyl isoxazoline **3g** (Table 1) by a widely employed method using NCS and DMAP, we found only the undesired 5-chlorofuryl derivative of **3g** (**3i**, Supporting Information).

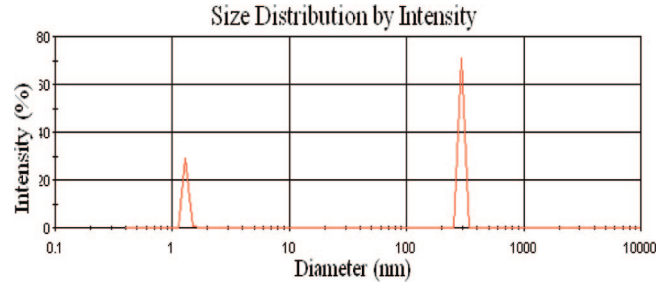
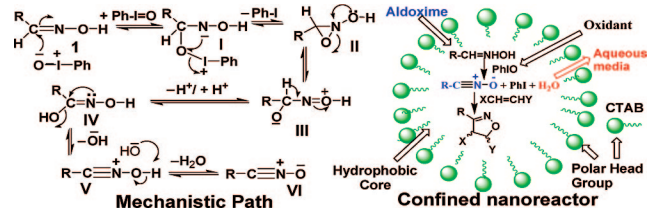


FIGURE 1. DLS data of nanoreactors formed in aqueous CTAB.

SCHEME 1. Formation of Nitrile Oxide inside the Nanoreactor



A survey was conducted with several commercially available cationic (CTAB), anionic (SDS), and neutral (Tween 40) surfactants to prepare nitrile oxides in neutral aqueous media. Best yield (**3a**, Table 1) was obtained using CTAB (~33 mol %). In the absence of CTAB the reaction did not proceed in aqueous media. We have already reported the nature of the micelles formed upon dissolution of CTAB in water by optical micrograph.[2e] Dynamic light scattering (DLS)[2d,f] measurement of the reaction mixture showed formation of a small nanoreactor of about 1 nm diameter and a larger one of 300 nm (Figure 1).

Mechanistic path of this oxidation-cum-dehydration of aldoximes to corresponding nitrile oxides under the confined nanoreactor is depicted in Scheme 1. We propose that the oxygen atom transfer to imine bond is accomplished through nucleophilic attack of PhIO followed by loss of PhI. N−O bond rupture of unstable intermediate **II** leads to formation of hydroxyaldoxime (**IV**) through breaking of the C−H bond. Removal of hydroxyl anion and deprotonation in successive steps produce nitrile oxides (**VI**).

We have extended this green approach for stereoselective synthesis of 3-(2′-*C*-3′,4′,6′-tri-*O*-benzyl glycal)-Δ^2-isoxazolines (**6** and **7**, Table 2), which will be used as versatile synthons for the synthesis of various chiral heterocycles. For example, reduction of the isoxazoline ring and subsequent Ferrier rearrangement[13] of the glycal double bond lead to analogues of the chiral pyranopyran motif present in natural products.[14] These sugar-based isoxazolines can also be converted into various unnatural compounds[15] for their potential application in animal

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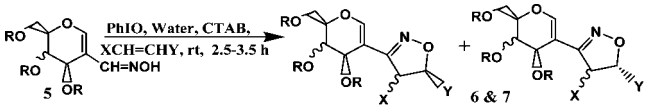
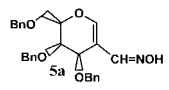
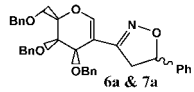
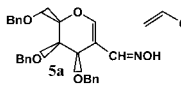
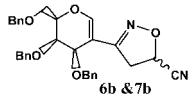
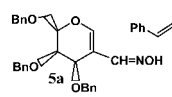
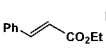
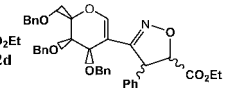
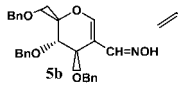
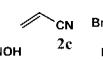
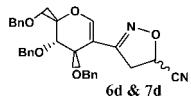
TABLE 2. Generation and 1,3-DC of Glycal Nitrile Oxides in AOM



Sugar: Glucal and Galactal; R = CH_2Ph; X = H and Ph; Y= Ph, CO_2Et and CN

Entry	Aldoxime	Alkene	Isoxazoline	Time (h)	Selectivity	Yield (%)
1.		 2c	 6a & 7a	3	72:28	58
2.		 2c	 6b &7b	3	68:32	58
3.		 2d	 6c & 7c *(anti)*	3.5	66:34	64
4.		 2c	 6d & 7d	3	65:35	57

models[16] and studies of molecular assembly properties.[17] In an attempt to make these isoxazolines using NCS and DMAP, the reactions were very slow (~3 days) and stereoselectivity was not observed in their cycloaddition (Supporting Information). By applying this environmentally benign approach to sugar aldoximes (**5**), corresponding nitrile oxides are generated in neutral media. Their in situ 1,3-DC with olefins produces the new chiral cycloadducts (**6** and **7**) in good isolated yield (57−64%). Results in Table 2 demonstrate that a large acceleration of reaction rate and improvement in stereoselectivity are observed by this robust protocol. Even though the newly generated chiral center is far away (three bond distance) from the chiral center, we found good diastereoisomeric excess, in contrary to the previous report of near absence of stereoselectivity in the 1,3-DC of common chiral nitrile oxides to achiral olefins.[9]

Intramolecular nitrile oxide cycloaddition (INOC) especially with sugar-nitrile oxides is a versatile synthetic tool for the fabrication of fully functionalized heterocycles of different ring sizes.[5d,15c,18] We are curious to determine whether this cycloaddition approach could be extended to construct a novel pyranopyran framework in one step (Table 3). Elegant routes have been devised[19c] for the synthesis of this 2,8-dioxabicyclo-[4.4.0]decane core. This is an important skeleton of biologically active natural products such as blepharocalyxin D, which is an antiproliferative agent against human fibrosarcoma HT-1080 and murine colon 26-L5 carcinoma cells.[19a,b] The results in Table 3 reveal that glycal-based aldoximes (**8a**, **8b**) are oxidized by PhIO in aqueous media to corresponding nitrile oxides and their in situ INOC constructed optically pure 2,8-dioxabicyclo-[4.4.0]decene skeleta (**9a**, **9b**) in one step. Exclusive formation

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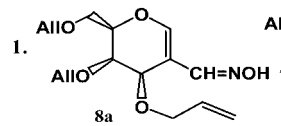
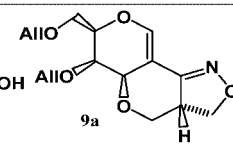
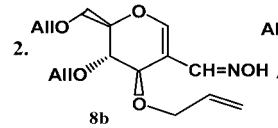
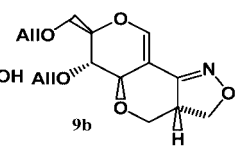
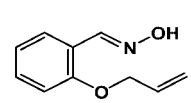
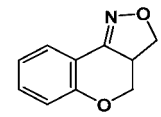
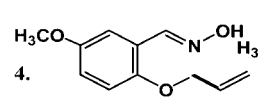
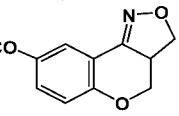
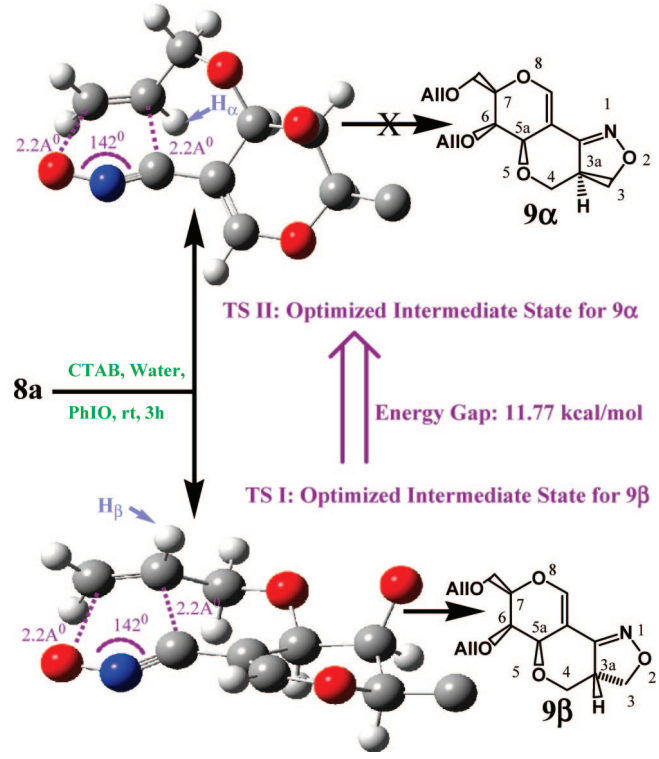
TABLE 3. Formation of Nitrile Oxide and Their INOC in AOM

Entry	Aldoxime	Isoxazoline	Time (h)	Yield (%)
1.	 8a	 9a	3.0	64
2.	 8b	 9b	2.5	63
3.	 8c	 9c	3.0	77
4.	 8d	 9d	3.0	79

SCHEME 2. DFT Energy Calculation for Favorable TS



of β-stereoisomer (+)-(3a*S*,5a*R*,6*R*,7*R*)-6-allyloxy-7-allyloxymethyl-3a,4,6,7-tetrahydro-3*H*,5a*H*-2,5,8-trioxa-1-aza-cyclopenta[*a*]naphthalene (**9a**) is in agreement with the results obtained by a geometry- and energy-optimized intermediate state (TS I, Scheme 2) computed in B3LYP density functional theory (DFT).[20] Intermediate state TS I for ***9β*** stereoisomer is stabilized by −11.77 kcal/mol compared with the alternative intermediate

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state TS II for **9α**. Calculations were made using the 6-31+G(d,p) basis set as implemented in the Gaussian 03 program.[20a] For clarity substituents at C_6 and C_7 were omitted from the optimized TSs. Easily accessible by this green approach, the chromano motif (**9c**, **9d**) is found in important bioactive natural products.[21] Glycal aldehydes[17] and PhIO[22] were prepared cheaply and conveniently by literature methods.

In conclusion, we have for the first time prepared nitrile oxides in neutral aqueous media. Reaction rate, regioselectivity, and stereoselectivity in their 1,3-DC with olefins are improved. This green approach also presents the first use of PhIO as oxidant for preparation of nitrile oxides. Generation of protected 2-*C*-glycal nitrile oxides in neutral media and their inter- and intramolecular 1,3-DC under the nanometer aqueous micelles lead to new chiral synthons and an optically pure 1,4-pyranopyran motif found in bioactive natural products. Exclusive formation of one stereoisomer in INOC is justified by DFT method. Extensions of the present strategy to other 1,3-DC reactions, conversion of chiral synthons to heterocycles, and theoretical calculation for the stereocontrolled 1,3-DC reaction are under progress.

Experimental Section

General Procedure for Intermolecular 1,3-DC Reaction. The aldoxime **5** (0.33 mmol), alkene **2** (0.66 mmol), water (10 mL), and CTAB (80 mg, 0.22 mmol) were added to a round-bottom flask, and the mixture was stirred magnetically at 0 °C for 15 min. PhIO (198 mg, 0.9 mmol) was added, and the content was allowed to attain room temperature. The reaction was complete after 3 h. The post-reaction mixture was extracted with ethyl acetate (2 × 10 mL), and the combined organic portion was washed with brine solution (2 × 10 mL), dried on anhydrous sodium sulfate, and concentrated in a rotary evaporator under reduced pressure at room temperature. The crude product was chromatographed on basic alumina (70−230 mesh) and eluted with ethyl acetate−petroleum ether. Thus, the reaction with 2-*C*-(3,4,6-tri-*O*-benzyl)galactal aldoxime (**5a**, 150 mg) and styrene (**2e**, 69 mg) afforded, after the processing, the faster moving diastereoisomer, 3-(2′-*C*-3′,4′,6′-tri-*O*-benzylgalactal)-5-phenyl-Δ^2-isoxazoline (**6a**, 29 mg, 0.05 mmol) and the slower moving diastereoisomer **7a** (77 mg, 0.14 mmol) in combined isolated yield of 58%.

Compound 6a. Yellow color viscous liquid; $[\alpha]^{20}_D$ −83.7° (*c* 1.16, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.99 (1H, dd, J = 8.4, 15.9 Hz), 3.40 (1H, dd, J = 10.5, 15.9 Hz), 3.95−4.07 (3H, m), 4.44−4.91 (8H, m), 5.58 (1H, dd, J = 8.4, 10.5 Hz), 6.58 (1H, s), 7.25−7.38 (20H, m). ^{13}C NMR (75 MHz, $CDCl_3$): δ 42.5, 68.3, 68.3, 71.7, 73.4, 73.9, 75.0, 76.6, 81.8, 107.5, 125.8, 127.3, 127.5, 127.6, 127.9, 127.9, 128.1, 128.1, 128.3, 128.5, 128.7, 137.6, 138.1, 138.9, 140.9, 147.1, 154.1. EI-MS (*m*/*z*): 561 (M^+), 337, 278, 253, 224, 223. IR (neat, cm^{-1}): 898, 1098, 1187, 1402, 1452, 1633, 1733, 2926, 2867. Anal. Calcd for $C_{36}H_{35}NO_5$: C 76.98, H 6.28, N 2.49. Found: C 76.89, H 6.26, N 2.50.

Compound 7a. Yellow color viscous liquid; $[\alpha]^{20}_D$ −8.2° (*c* 1.0, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.95 (1H, dd, J = 8.1, 15.9 Hz), 3.42 (1H, dd, J = 10.5, 15.9 Hz), 3.94−4.06 (3H, m), 4.43−4.91 (8H, m), 5.55 (1H, dd, J = 8.1, 10.5 Hz), 6.58 (1H, s), 7.24−7.36 (20H, m). ^{13}C NMR (75 MHz, $CDCl_3$): δ 42.5, 68.2, 68.2, 71.6, 73.3, 73.9, 74.9, 76.6, 81.9, 107.5, 125.8, 126.9, 127.3, 127.5, 127.8, 127.9, 128.1, 128.3, 128.5, 128.7, 137.6, 138.1, 139.1, 140.8, 146.9, 154.2. EI-MS (*m*/*z*): 561 (M^+), 300, 278, 253, 224, 212, 206. IR (neat, cm^{-1}): 699, 744, 899, 1098, 1187, 1402, 1452, 1633, 1733, 2866, 2926. Anal. Calcd for $C_{36}H_{35}NO_5$: C 76.98, H 6.28, N 2.49. Found: C 76.92, H 6.29, N 2.48.

General Procedure for Intramolecular 1,3-DC Reaction. The aldoxime **8** (0.5 mmol), water (12 mL), and CTAB (100 mg, 0.27 mmol) were added to a round-bottom flask (25 mL,) and the mixture was stirred at 0 °C for 15 min to prepare the aqueous micelles. PhIO (275 mg, 1.25 mmol) was added, and the reaction mixture was allowed to attain room temperature. The reaction was complete after 3 h. The post reaction mixture was extracted with ethyl acetate (3 × 5 mL), and the combined organic portion was washed with brine solution (2 × 10 mL), dried on activated sodium sulfate, and concentrated in a rotary evaporator under reduced pressure at room temperature. The crude product was chromatographed on basic alumina (70−230 mesh) and eluted with ethyl acetate−petroleum ether. Thus, the reaction with 2-*C*-(3,4,6-tri-*O*-allyl)-galactal aldoxime (**8a**, 155 mg) afforded (+)-(3a*S*,5a*R*,6*R*,7*R*)-6-allyloxy-7-allyloxymethyl-3a,4,6,7-tetrahydro-3*H*,5a*H*-2,5,8-trioxa-1-aza-cyclopenta[*a*]naphthalene (**9a**) after processing in an isolated yield of 64% (98 mg, 0.32 mmol). Elucidation of structure and the stereochemistry were confirmed by 2D NMR (Supporting Information). Yield: 63%, yellow semisolid; $[\alpha]^{20}_D$ +79.9° (*c* 1.08, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.39−3.44 (2H, m), 3.61−3.69 (3H, m), 3.98−4.24 (6H, m), 4.37−4.54 (3H, m), 5.14−5.31 (4H, m), 5.84−5.94 (2H, m), 7.04 (1H, s). ^{13}C NMR (75 MHz, $CDCl_3$): δ 46.9, 68.2, 69.1, 69.8, 72.4, 72.9, 73.9, 76.4, 100.8, 117.4, 117.6, 134.1, 134.9, 143.0, 154.4. IR (neat, cm^{-1}): 925, 1003, 1091, 1146, 1196, 1647, 1725, 2861, 2922. EI-MS (*m*/*z*): 307 (M^+), 180, 153, 125. HR-MS (*m*/*z*) for $C_{16}H_{21}NO_5$: calcd 307.1420, found 307.1419.

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Supporting Information Available: General methods, experimental procedures, elucidation of structure by 2D NMR, spectroscopic data, and spectra for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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