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Stereoselective Synthesis of Chiral Oxepanes and Pyrans through Intramolecular Nitrone Cycloaddition in Organized Aqueous Media

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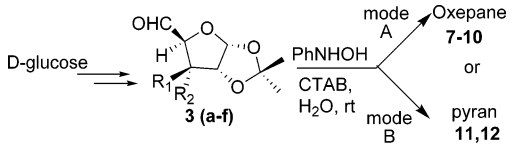

A highly stereoselective surfactant-catalyzed intramolecular nitrone (formed by dehydration in water) cycloaddition in aqueous media leading to exclusive formation of a single isomer is reported. Either oxepane or pyran is formed from 3-*O*-allyl furanoside derivatives, which constitute the framework of a large number of biologically active compounds. Therefore, the environmentally friendly, efficient, and highly stereoselective syntheses of these chiral intermediates are still a meaningful pursuit.

The design of reaction systems for environmentally benign conditions (green chemistry)[1] and highly stereoselective production is the cherished goal now. From the standpoint of green chemistry and its 12 principles,[1g,h] water is the solvent of choice,[2−6] being both cheap and nontoxic. In recent years organic reactions in aqueous media attracted a great deal of attention, because these reactions eliminate both the use of volatile organic solvents (toxic) and the necessity of vigorous drying of solvents and substrates.[3] Also, water has unique physical and chemical properties, and these sometimes lead to reactivity or selectivity that cannot be attained in organic solvents.[3c,d]

The problem of insolubility of most organic compounds in water may be solved by the use of a surfactant, which in water forms an organized media at the border between the homogeneous (solution phase) and heterogeneous phase. This border region is a gray area consisting of micellar, reverse micellar, microheterogeneous, colloidal phase, etc. Studies of new reactions in organized media, with the exception of kinetic studies, are not very common. Although various efficient catalytic systems in water have been developed,[2,4−6] there are still many reactions that are difficult to carry out in water. One such reaction is dehydration. Although water as a solvent impedes dehydration, there are some examples of dehydration reactions in water.[2d,5a] In the course of developing efficient organic reactions in water, we recently reported nitrone formation in water, followed by its intermolecular cycloaddition to isoxazolidines in a one-pot process.[2d] During the course of surfactant-catalyzed reactions,[2b−e,4f,g,5] the organized media acts as a nanoreactor,[6] which solubilizes and conforms hydrophobic organic compounds into its hydrophobic cores where dehydration, i.e., nitrone formation, occurs. A dynamic light scattering study[6c] shows that the surfactant in aqueous solution is self-assembled with hydrodynamic radii of 1.296 nm (29.36%) and 295.3 nm (70.64%) to form the nanoreactor. Although the steric disposition of the substrate inside the organized media is expected to be achiral since the media is formed from achiral surfactant, we noted that when chiral substances are used along with the achiral surfactant some stereoselectivity is observed.[2d] Therefore, a chiral substrate along with an achiral surfactant in aqueous media might produce better selectivity than in organic solvents. To investigate the concept, we report here the use of arious 3-*O*-allyl analogues of carbohydrate in stereoselective

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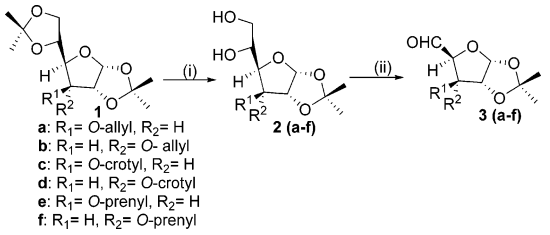
intramolecular nitrone cycloadditions.[7] Dipolar cycloadditions of nitrones[7,8] to alkenes have received much synthetic interest[7g–l] because the newly generated ring systems are highly amenable to further transformations leading to versatile intermediates. Also, sugar-based chiral cyclic ethers constitute the framework of a large number of naturally occurring biologically active compounds such as ciguatoxin,[9] other marine toxins,[10] zoapatanol,[11] sepholenol,[12] laurencin,[13] etc. The high importance of these systems resulted in the development of number of synthetic methods,[14] including nitrone cycloaddition.[7]

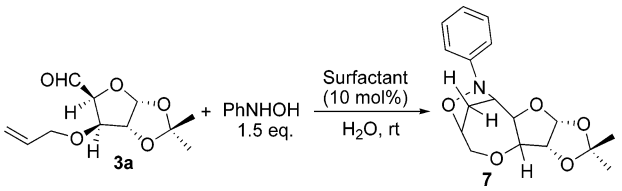
To our knowledge, stereoselective intramolecular nitrone cycloaddition in aqueous media has not been reported, and so, in continuation of our effort, we herein describe the stereoselective synthesis of chiral oxepanes and pyrans by 3-*O*-allyl carbohydrate nitrone cycloaddition starting from D-glucose. The requisite furanoside-5-aldehydes (**3**) were prepared from the corresponding 1,2:5,6-diisopropylidene-3-*O*-allyl furanosides (**1**) via a standard sequence of reactions[7g] (Scheme 1) and were

SCHEME 1. Synthesis of Furanoside Aldehydes 3[a]



[a] Reagents and conditions: (i) 75% aq CH_3COOH, rt, 15 h; (ii) $NaIO_4$, MeOH, H_2O, 3 h, 0 °C to rt.

TABLE 1. Effect of Surfactant on Intramolecular Nitrone Cycloaddition in Water



entry	surfactant	time (h)	yield (%)	entry	surfactant	time (h)	yield (%)
1		48		5	Triton X-100	30	80
2	CTAB	8	79	6	Tween-20	30	80
3	SDS	8	75	7	DBSA	16	61
4	SDBS	8	75	8	Triton CF 10	36	79

sufficiently pure to be used directly in the next step. The corresponding nitrones, formed in aqueous media catalyzed by surfactant using phenyl hydroxylamine with the respective aldehyde at room temperature, underwent stereoselective intramolecular cycloaddition (Scheme 2). By carrying out the model reaction shown in Table 1, it was found that the type of surfactant used influenced both the yield and the reaction time. Nonionic surfactants (entries 5, 6, and 8) were effective but required longer reaction time, an acidic surfactant (entry 7) reduced the yield, and anionic surfactants (entries 3 and 4) were slightly less effective than a cationic surfactant (entry 2). From these observations we concluded that CTAB is the most efficient surfactant for this reaction. When performing these reactions in water without surfactant, we recovered starting materials as reported earlier.[2d] No reaction was obtained under neat condition. We conclude that surfactants have a prominent role in nitrone formation and the subsequent cycloaddition in aqueous medium by the formation of an organized media. Similar reactions when performed in organic solvents, which require maintaining dry, refluxing condition in most cases, gave a mixture of pyrans and oxepane isomers.[7a–j] Often these cycloadditions lead to the formation of nonseparable mixture of isomers.[7a–j]

The role of solvent on the ring size selectivity was studied by Mandal et al.,[7k–m] who noted changes from five to six members when the solvent was changed from aprotic to protic for the substrate with a hydroxyl group at C-3 position. Indeed, this hydroxyl group has a profound influence over the course of cyclization, but they still obtained a mixture of products upon cyclization. However, in our case, there is no free hydroxyl group present anywhere. The most attractive observation in these surfactant-mediated intramolecular nitrone cycloaddition reactions of sugar in aqueous media is the formation of a single isomer out of the four possible isomers (Table 2). The nitrones of 3-*O*-allyl glucofuranose and the corresponding allose deriva-

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SCHEME 2. Synthesis of Oxepanes (7−10) and Pyrans (11−12)

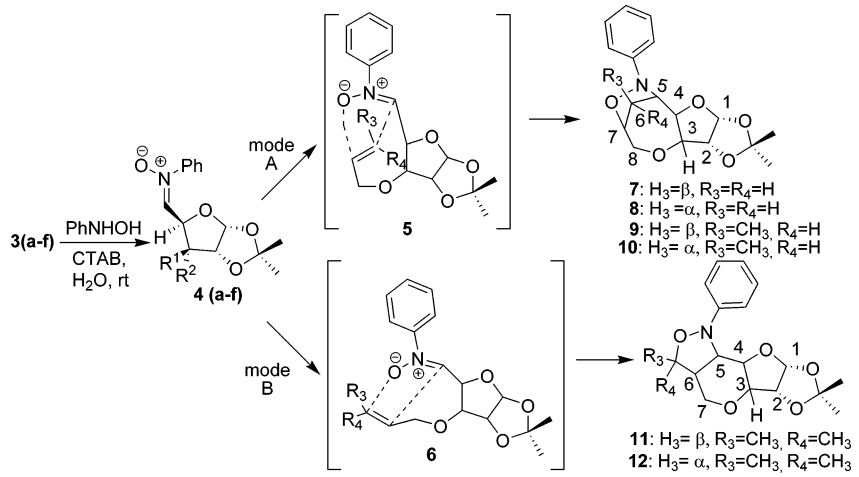
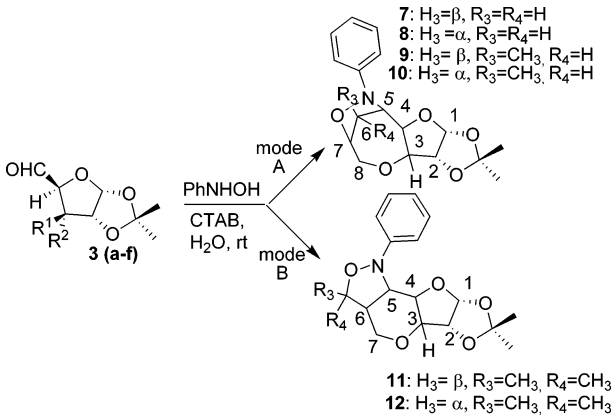


TABLE 2. Surfactant-Catalyzed Dehydrative Intramolecular Nitrone Cycloaddition of 3-*O*-Allyl Furanoside-5-aldehydes in Water



entry	RCHO	time (h)	product	yield (%)	$[\alpha]_D^{25}$ ($CHCl_3$)
1.	**3a**	8	**7**	79	−183.49, $c = 1.43$
2.	**3b**	8	**8**	84	+193.33, $c = 1.14$
3.	**3c**	24	**9**	83	−110.19, $c = 1.14$
4.	**3d**	20	**10**	85	+194.43, $c = 1.15$
5.	**3e**	36	**11**	74	−140.84, $c = 2.12$
6.	**3f**	30	**12**	78	−100.30, $c = 2.0$

tives (**4a** and **4b**) produce bridged isoxazolidines, i.e., oxepanes (**7** and **8**), as do the nitrones of crotyl derivatives **4c** and **4d** (oxepanes **9** and **10**). In contrast, nitrones of prenyl derivatives (**4e** and **4f**) produce pyrans (**11** and **12**), which may be due to the methyl−methyl steric repulsion restricting formation of the oxepane skeleton (Figure 1). The structural assignment of the carbohydrate-derived cycloadducts, particularly the stereochemistry of the newly formed centers C_5 and C_6 in the pyranoisoxazolidines (**11** and **12**), appeared to be problematic. Analysis of the relevant $^1H,^1H$ coupling constants as well as decoupling experiments led to the assigned stereochemistry. However, information about the skeletal pattern of the product, whether an oxepane or a pyran, was easily established by the ^1H and ^{13}C NMR spectral data. The appearance of a one proton multiplate near δ 2.5 in the ^1H NMR spectra due to H_6 and a methine carbon signal near δ 50.0 in the ^{13}C NMR spectra due to C_6 in **11** and **12** are proper indications of a fused isoxazolidine skeleton.[7g] The bridged isoxazolidines (i.e., oxepanes) are characterized, in the case of allyl-derivatives **7** and **8**, by the appearance of a set of a one proton doublet and a one proton multiplate near δ 2.3 due to H_{6a} and H_{6b}, respectively, and a relatively high field methylene carbon signal near δ 30.0 due to C_6 in the ^{13}C NMR spectra.[7g] For crotyl derivatives one quartet appears near δ 3.13 in ^1H NMR spectrum, confirming oxepane formation. Two-dimensional NMR studies on compound **7** showed a cross-peak between H_{8b} and H_3 in the NOESY spectrum, indicating their diaxial disposition in the seven-membered ring.[7e] Cross-peaks between H_{8a}/H_7 and H_7/H_5 established the β orientation of the bridge (Figure 2). In the case of the cyclized product of **4b**, the cross-peaks between the doublet of doublet at δ 3.9 due to H_4 and the doublet at δ 2.11 due to one of the bridge methylene protons in the NOESY spectrum established the α-orientation of the bridge in **8**.[7g] For

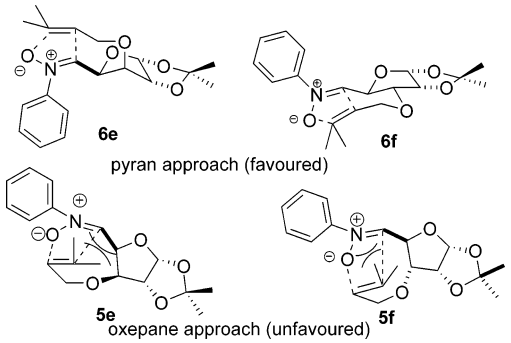


FIGURE 1. Proposed transition state favoring the pyran formation.

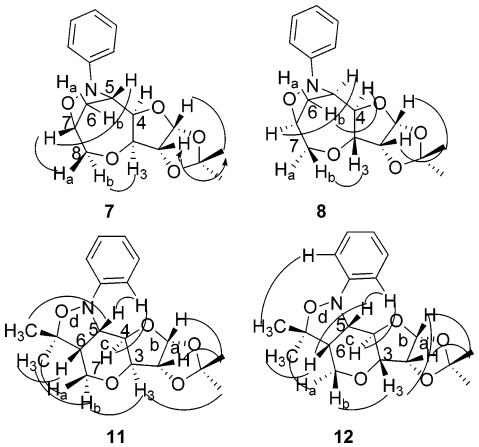


FIGURE 2. Inter-ring NOESY of **7**, **8**, **11**, and **12**

the cyclized product of β-3-*O*-crotyl nitrone (**4c**), the observation of a quartet at δ 3.13 in the ^{1}H NMR spectrum due to the bridge methine proton as well as a peak at δ 36.72 in the ^{13}C NMR spectrum due to a bridge methine carbon was a fair indication of the oxepane skeleton in **9**. The bridge -CH(CH_3)- was assigned the β-orientation in analogy with **7**. In the case of **10**, a similar analogy assigned the α-orientation of the bridge.[7g] From the ^{1}H NMR spectrum of **11**, the coupling constant of 11.7 Hz for $J_{H_6-H_7}$ indicates a 1,2-diaxial disposition in a chair conformation, and $J_{4,5} = 0$, suggests that H_5 is *trans* to H_4. Coupling constants involving the protons at the center of ring fusion are consistent with *cis*-stereochemistry for the five-membered rings a, b, and d.[7e] The inter-ring NOESY interaction shown in Figure 2 confirmed the envelop conformation for rings a and d[7e] for **11**. Similarly, the stereochemistry of the compound **12** was determined by inter-ring NOESY spectrum.

As there was no cross-peak between H_4 and H_6 in the NOESY spectrum, the stereochemistry of the ring juncture was determined to be *cis*.

In conclusion, we have demonstrated that an achiral nanoreactor is a useful and green tool for the stereoselective intramolecular 1,3-dipolar nitrone cycloaddition of chiral substrates. This reactor leads to the formation of the chiral oxepanes and pyrans with much improved stereoselectivity relative to that observed in conventional organic solvents. We expect that this reactor approach in aqueous environment will be applicable to a wide variety of reactions.

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Supporting Information Available: Spectral data for compounds **7**−**12**, DLS data, and experimental procedures. This material is available free of charge via the Internet at http://pubs.acs.org.

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