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Water Exclusion Reaction in Aqueous Media: Nitrone Formation and Cycloaddition in a Single Pot

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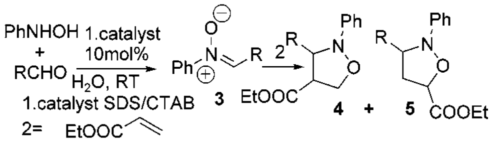
ABSTRACT



The formation of nitrone (a water exclusion reaction) in aqueous media using surfactant and subsequent cycloaddition in the same pot, a new example of green chemistry, is reported. The control of regioselectivity favors the formation of trans-5-substituted isoxazolidine. This work not only may lead to an environmentally benign system but also will provide a new aspect of reactions in water.

Environmentally benign reactions have now become the target of the synthetic organic chemists. The development of the concept of green chemistry[1] and its 12 principles[1c] act as guidelines. Catalysis plays a significant role for this purpose,[1d] and so development of alternative pathways becomes of interest. Replacement of toxic organic solvents by a nontoxic one, e.g., water,[1e−g] which is also cheap and safe, becomes one of the main features of green chemistry. However, the majority of the organic compounds are insoluble in water, and one answer to this problem is the use of surfactants, which help to solubilize the organic compounds in water.

Organized media is the border between homogeneous (solution phase) and heterogeneous phases. It is a gray area consisting of micellar, reverse micellar, microheterogeneous, colloidal phase, etc. Studies of the media are very common, but studies of new reactions in the media are not that common. The reaction studies in the media mainly focused on kinetic studies. However, some preparative studies have been done.[2]

Our studies on surfactant-catalyzed reactions revealed that emulsion droplets were formed under the reaction condition from the catalytic amount of the catalyst and the substrate. These emulsion droplets are sufficiently hydrophobic and can protect water-labile components from the hydrolytic decomposition.[2b] Therefore, dehydration reaction can be carried out in water.

Nitrones are very important due to their various uses. As therapeutic agents,[3] they are well recognized. The synthetic uses and reactions of nitrones are also well documented.[4]

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There are some standard synthetic routes to nitrones.[4,5] The majority of the reactions forming nitrones are dehydration reactions of substituted hydroxylamine and carbonyl compounds using anhydrous conditions and/or a dehydrating agent.

We hereby report for the first time the formation of nitrone in water followed by its cycloaddition. The proposed model of nitrone formation, the dehydration reaction, using substituted hydroxylamine and aldehydes in the presence of surfactant (both anionic, i.e., SDS and cationic, i.e., CTAB) as a catalyst is shown in Figure 1.

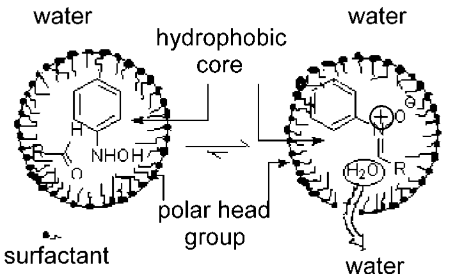


Figure 1. Proposed model of the dehydration reaction in water in the presence of catalyst (surfactant SDS or CTAB).

The emulsion droplets have a hydrophobic interior, through hydrophobic interaction. Therefore, the equilibrium position for the hydrophobic substrate would lie at the product side because, as the water molecule forms under the reaction conditions, it would be ejected from the core of the droplets. The formation of emulsion droplets in the reaction medium was confirmed by optical microscopy (Figure 2).

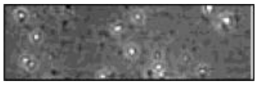
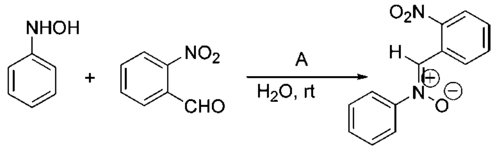


Figure 2. Optical micrograph of the reaction mixture.

Table 1. Nitrone Formation Reaction in Water



entry	A	time (h)	yield (%)
1	surfactant	1	>90
2		>48	
3	10% MeOH	>48	10

We selected the reaction of *o*-nitro benzaldehyde and phenyl hydroxylamine for the nitrone formation as a model reaction in water (Table 1). This ensures that the surfactant has the major role for the nitrone formation. During cycloaddition reaction, the control of regioselctivity favors the formation of 5-substituted isomer.

In our reaction system, phenyl hydroxylamine was reacted with various aldehydes (5 min of sonication followed by stirring; without sonication, the reaction took a longer time)[11] to form nitrone. The disappearance of aldehyde and appearance of nitrone was monitored by TLC. In the case of cinnamaldehyde, nitrone was isolated and detected by ^1H NMR and mass spectrometry. In other cases, after the formation of nitrone, the dipolarophile (ethyl acrylate) was directly added to the system and the reaction was allowed to take place at room temperature (Table 2).[6,11]

Yields are generally very good (71−91%), except in one case, i.e., the 2,5-dimethoxy phenyl system. This may be due to the activated ring system, which reduces the carbonyl character. Between the sodium dodecyl sulfate (SDS) and cetyl trimethylammonium bromide (CTAB), the latter catalyzes the reaction better, presumably due to stronger binding of the CTAB with the substrate, which is expected as CTAB has much more hydrocarbon content in its core region than

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(6) All the isoxazolidine products in Table 2 were characterized by ^1H and ^{13}C NMR. The spectral data are included in Supporting Information.

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(11) **General Reaction Procedure.** To a solution of surfactant (SDS or CTAB, 0.05 mmol) in H_2O (2 mL) were added an aldehyde (0.5 mmol) and phenyl hydroxylamine (0.6 mmol, 1.2 equiv) successively at room temperature in a 25 mL round-bottom flask. The reaction was sonicated for 5 min and then stirred at room temperature. The reaction was monitored by TLC. After the disappearance of aldehyde, ethyl acrylate (1 mmol, 0.1 mL) was added and the reaction mixture was stirred at room temperature. After stirring at the same temperature for the period of time listed in Table 2, the product was extracted with ethyl acetate, washed with brine, dried over Na_2SO_4, and concentrated, and purification by silica gel chromatography gave the desired product(s). In the reaction in which no sonication was used, the reaction required more time (5−6 times) for completion. It is well-known that sonication favors the formation of organized media.

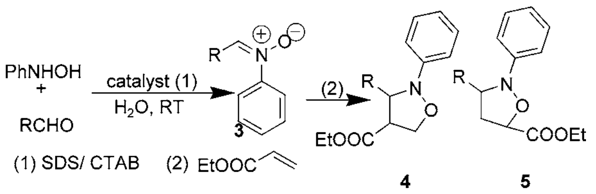
Table 2. Surfactant-Catalyzed Dehydrative Nitrone Formation from Phenyl Hydroxyl Amine and Aldehydes Followed by Cycloaddition Reaction with Ethyl Acrylate in Water at Room Temperature

entry	RCHO R = (a−i)	surfactant	time (h)	yield (%) (**4** + **5**)	**4** (exo:endo)	**5** (cis:trans)[j]
1	a = *o*-$NO_2C_6H_4$−	SDS	18	79		32:68
2	a = *o*-$NO_2C_6H_4$−	CTAB	18	85		32:68
3	b = *m*-$NO_2C_6H_4$−	SDS	30	81		46:54
4	b = *m*-$NO_2C_6H_4$−	CTAB	26	89		46:54
5	c = *p*-$NO_2C_6H_4$−	SDS	16	76	100:0	
6	c = *p*-$NO_2C_6H_4$−	CTAB	16	81	100:0	
7	d = *p*-$OMeC_6H_4$−	SDS	76	84	100:0[k]	100:0[k]
8	d = *p*-$OMeC_6H_4$−	CTAB	72	89	100:0[k]	100:0[k]
9	e = 2,5-diOMe−C_6H_3−	SDS	121	27		0:100
10	e = 2,5-diOMe−C_6H_3−	CTAB	121	38		0:100
11	f = *p*-ClC_6H_4−	SDS	40	90	100:0[l]	49:51[l]
12	f = *p*-ClC_6H_4−	CTAB	40	91	100:0[l]	49:51[l]
13	g = 3-pyridyl−	SDS	74	89		42:54
14	g = 3-pyridyl−	CTAB	70.5	91		42:54
15	h = PhCH═CH−	SDS	50	87	35:65[m]	31:69[m]
16	h = PhCH═CH−	CTAB	50	90	35:65[m]	31:69[m]
17	i = $CH_3(CH_2)_2$−	SDS	48	85		43:57
18	i = $CH_3(CH_2)_2$−	CTAB	48	85		43:57

[j] Cis:trans ratio determined with the help of NOE. [k] Ratio of **4**:**5** = 39:61. [l] Ratio of **4**:**5** = 60:40. [m] Ratio of **4**:**5** = 31:69.

SDS.[7] Cycloaddition of nitrone in organic solvent[8] leads to four different isomers, cis/trans for **5**-substituted and exo/endo for **4**-substituted isoxazolidine in 2:1 ratio. In our case, except for *p*-OMe, control of regioselectivity favors the trans-**5**-substituted product as the major one. In a few cases, the endo-**4**-substituted product predominates. Spectral studies identified the isomers. The proton attached with the carbethoxy group of structure **5** was much more downfield compared to that of structure **4**. For the *p*-nitro compound (entries 5 and 6), the other regioisomer (structure **4**) was formed exclusively.

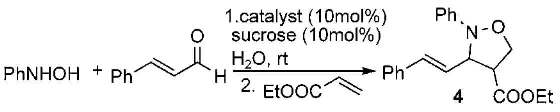
Scheme 1



In the case of the *p*-chloro compound (entries 11 and 12), the isomer is favored slightly (60%). In all the cases of isomer **4**, except cinnamaldehyde (entries 15 and 16), the endo isomer is the sole product, which was confirmed by J_{3-4} (5.5−6.0 Hz).[9] For entries 9 and 10, the lack of NOE enhancement of the C3 H for the irradiation of C5 H, and vice versa, revealed that the stereochemistry of structure **5** is trans. Comparing one of the C4 methylene protons of the above with the other products helped to determine the cis/trans isomer ratio.

When the reaction with cinnamaldehyde was conducted in the presence of sucrose (presumably capable of forming organized media[10]) and SDS (10 mol % for both cases), only one regioisomer, i.e., the 4-carbethoxy isoxazolidine system, was produced (Scheme 2).[12]

Scheme 2



In summary, water exclusion reaction in water media with the help of surfactant catalysis led to nitrone formation, and in the same pot, a cycloaddition reaction was conducted. The regio- and stereocontrol was determined. In the case of cinnamaldehyde, a similar type of experiment conducted in the presence of sucrose led to one regioisomer only. Research along this line is now under way.

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Supporting Information Available: Spectral data for the characterization of the isoxazolidine products. This material is available free of charge via the Internet at http://pubs.acs.org.

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(12) Optical rotation $[\alpha]_D = 43°$.