Asian Journal of Chemistry Vol. 22, No. 2 (2010), 1231-1244

Study of The Reactivity of Aromatic Nitrones Towards Acrylonitrile in Microemulsion: A Green Chemistry

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Cycloaddition reaction of a series of synthesized aromatic nitrones with acrylonitrile (ACN) was studied in toluene and in microemulsions made of water/ACN/(sodium dodecylsulfate/*n*-butanol = ½). The phase diagram of the latter system was worked out and revealed a wide domain of microemulsions, particularly in the vicinity of the water-borne region. Of these microemulsions, the oil-rich ones (W/O) gave the best results in the cycloaddition reaction. In the conventional medium (toluene), the reaction afforded mixtures of four diastereoisomers of isoxazolidines in moderate overall yields (*ca.* 30-70 %). However, the reactions in microemulsions were featured with relatively milder conditions (lower temperatures and shorter reaction times) and better yields, 60-80 % after 6 h at 25 ºC. Enhancement of the yields (80-100 %) was effected under the same reaction conditions, employing metal triflates Lewis acid catalysts in the microemulsion systems. A linear relationship between the temperature and the reaction time was found; a 25 ºC rise in temperature led to a reaction time drop of about 90 % to achieve nearly the same yield.

Key Words: Isoxazolidine, Lewis acid, Microemulsion, Nitrone.

INTRODUCTION

The use of water and water-based systems as substitutes for organic conventional media in organic synthesis is one of the principles of the green chemistry[1,2]. A survey of the literature within the last two decades reveals the great success of a large number of organic reactions in aqueous media[3,4]. Yet, some organic reactions suffer from some drawbacks related to the lower water-solubility of the most organic compounds and to the decomposition and/or the deactivation of most reagents and catalysts by water molecules. Nevertheless, they can be circumvented by carrying out the reactions in organized and well-ordered systems with the aid of surfactants[5,6]

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that may prove beneficial for high reactivity and regio/stereoselectivity[7]. Among them, the microemulsions are of particular interest because of their peculiar properties, *i.e.*, they are thermodynamically stable, optically isotropic, transparent and clear solutions[8]. In addition, they are distinguished by a high dissolving power[9] and by an easy and continuous switchover of the micelle from one nature into another[10]. The latter intrinsic property is quite profitable when one of the microemulsion components is consumed by a reaction while the monophasic state of the medium is being unaltered[11].

Diels-Alder reactions have been successfully run in aqueous solutions and organized media, affording unexpectedly excellent kinetics and yields[12-14]. Because of its kinship to Diels-Alder reactions, the 1,3-dipolar cycloaddition reaction is expected to proceed similarly, the dipolorphile acting as a dienophile[11,15].

We are herein presenting the results of the effect of the medium on the outcome of the cycloaddition reactions of some synthesized aromatic nitrones with acrylonitrile. Customarily, these reactions occur in aromatic solvents such as benzene and toluene, which are deleterious to the health and the environment and either at reflux for *ca.* 10 h[16] or at room temperature for longer times[17]. As the environmentally benign and friendly media are nowadays sought for and are the chemists' ongoing concerns, microemulsion (water-based system) was evaluated, in this work, as a substitute for conventional organic solvents.

EXPERIMENTAL

Chemicals and solvents were purchased from the following companies: Fluka, Prolabo and Merck. They were supplied in purities higher than 95 %. Acrylonitrile was purified by distillation before use.

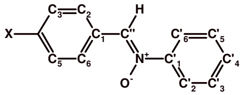
Melting points were determined by using a Büchi 512 oil bath. Electron impact mass spectra were drawn by means of an apparatus of type Nermag R 10-10. FTIR spectra (KBr pellets, room temperature) were recorded on a Perkin-Elmer 550 spectrometer. UV-visible spectra were taken on a Shimadzu 160 double beam spectrophotometer. ^{1}H and ^{13}C NMR spectra were determined on a Bruker AC 200 instrument, using $CDCl_3$ and TMS (tetramethylsilane) as solvent and internal standard, respectively. Elemental analyses were performed using a microanalyzer (EA1110 instrument). The different weighings were made with a Scaltec OSI 9001 analytical balance.

Syntheses of nitrones: β-Phenylhydroxylamine used in the syntheses of nitrones was prepared by known method[18]. The synthesis protocol of nitrones was as follows:

To a solution of 0.018 mol of aldehyde in 50 mL of ethanol was added to a solution of 2 g of β-phenylhydroxylamine in 50 mL of ethanol. The reaction mixture was refluxed for 3 h under an intensive magnetic stirring. Afterwards, the mixture was cooled to room temperature, which allowed the formation of a solid material. The latter was isolated by filtration and then recrystallized in ethyl acetate to give the nitrone in form of either a crystal or a powder. The different characteristics of the synthesized nitrones are presented in Table-1.

TABLE-1

RESULTS OF THE REACTIONS AFFORDING NITRONES



Nitrone	X	MM (g)	Yield (%)	m.p. (ºC)	R_f (a)	Elemental analysis (%)		UV-Visible (c)		IR (b) (cm^{-1})	MS (m/z)		^{1}H NMR (d) δ (ppm), *J* (Hz)	^{13}C NMR δ (ppm), *J* (Hz)
						Calcd.	Found	λ_{max} (nm)	ε		Base peak	M$^+$		
I (1)	NO_2	242.230	79	191	0,32	C:64.46 H:4.16 N:11.56	C:63.53 H:3.81 N:11.52	351.5 265.0 203.5	20660 9600 19620	(N-O):1074.5 (C=N):1595.4 (C-X):1342.0 -1510	242	91	8.10 (H, H''-S), 8.56 (2H, H-2, 6-dd), 7.80 (2H, H-2', 6'-dd), 8.35 (2H, H-3, 5-d), 7.56-7.51 (3H, H-3', 4',5'-m)	132.3(CH, C''), 136.21(C, C-1), 129.40(CH, C-2, 6), 123.94(CH, C-3, 5), 148.00(C, C-4), 148.92(C, C-1'), 121.73(CH, C-2', 6'), 129.23 (CH, C-3', 5'), 130.74 (CH, C-4')
II (2)	Cl	231.677	76	157	0,35	C:67.33 H:4.33 N:6.04	C:67.00 H:4.28 N:6.18	319.0 256.5 204.0	26020 7160 18920	(N-O):1072.3 (C=N):1542.9 (C-X):840.9	231	91	7.92(H, H''-S), 8.39(2H, H-2, 6-dd), 7.78(2H, H-2', 6'-dd), 7.43(2H, H-3, 5-d), 7.50(3H, H-3', 4',5'-m)	133.37(CH, C''), 129.22(C, C-1), 129.45(CH, C-2, 6), 129.18(CH, C-3, 5), 136.34(C, C-4), 148.92(C, C-1'), 121.68(CH, C-2', 6'), 128.92 (CH, C-3', 5'), 129.63(CH, C-4')
III (3)	Br	276.129	71	162	0,34	C:56.55 H:3.65 N:5.07	C:56.41 H:3.42 N:5.21	319.5 258.5 203.5	25420 6650 17970	(N-O):1072.3 (C=N):1542.9 (C-X):686.6	276.1	293.2	7.9(H, H''-S), 8.30(2H, H-2, 6-dd), 7.75(2H, H-2', 6'-dd), 7.60(2H, H-3, 5-d), 7.48 (3H, H-3', 4',5'-m)	133.43(CH, C''), 129.57(C, C-1), 131.89(CH, C-2, 6), 130.30(CH, C-3, 5), 124.78(C, C-4), 148.95(C, C-1'), 121.67(CH, C-2', 6'), 129.23 (CH, C-3', 5'), 130.14 (CH, C-4')
IV (2)	H	197.233	68	125	0,31	C:79.09 H:5.57 N:7.09	C:78.80 H:5.45 N:7.37	312.5 230.5 203.5	21890 10840 18410	(N-O):1063.4 (C=N):1504.6	197	91	7.49 (H, H''-S), 8.42 (2H, H-2, 6-dd), 7.80 (2H, H-2', 6'-dd), 7.50 (2H, H-3, 5-d), 7.42 (3H, H-3', 4',5'-m)	134.57(CH, C''), 131.99(C, C-1), 129.74(CH, C-2, 6), 129.09(CH, C-3, 5), 130.99(C, C-4), 149.08(C, C-1'), 122.35(CH, C-2', 6'), 129.67(CH, C-3', 5'), 130.67(CH, C-4')
V (2)	OCH_3	227.259	59	120	0,19	C:73.99 H:5.77 N:6.16	C:74.01 H:5.78 N:6.10	330.0 237.5 203.0	26710 10050 18330	(N-O):1064.6 (C=N):1550.7 (C-X):1257.5	227	212.3	7.865(H, H''-S), 8.41(2H, H-2, 6-dd), 7.77(2H, H-2', 6'-dd), 7.01(2H, H-3, 5-d), 7.44(3H, H-3', 4',5'-m), 3.88 (3H, CH_3)	134.1(CH, C''), 123.78(C, C-1), 131.6(CH, C-2, 6), 114.4(CH, C-3, 5), 161.53(C, C-4), 148.95(C, C-1'), 121.65(CH, C-2', 6'), 129.11(CH, C-3', 5'), 129.62(CH, C-4'), 55.7(CH_3)
VI (2)	OC_2H_5	241.285	58	135	0,23	C:74.67 H:5.81 N:6.27	C:74.67 H:5.81 N:6.35	331.5 237.5 202.5	27830 10400 19480	(N-O):1063.9 (C=N):1553.6 (C-X):1256.9	241	242.2	7.86(H, H''-S), 8.43(2H, H-2, 6-dd), 7.8(2H, H-2', 6'-dd), 7.00(2H, H-3, 5-d), 7.48(3H, H-3', 4',5'-m), 4.15(2H, CH_2), 1.47(3H, CH_3)	134.24 (CH, C''), 123.58(C, C-1), 131.18 (CH, C-2, 6), 114.51 (CH, C-3, 5), 160.98(C, C-4), 148.97(C, C-1'), 121.66 (CH, C-2', 6'), 129.10 (CH, C-3', 5'), 129.59 (CH, C-4'), 14.71 (CH_2), 63.65 (CH_3)

(1) Yellow powder; (2) White crystals; (3) White powder; (a) TLC plate, silica gel, eluent:diethylether – petroleum ether (50:50 V/V).
(b) KBr pellets; (c) Methanol (10^{-4}moles/L), 25°C.; (d) s: singlet; d: doublet ; m: multiplet.

Cycloaddition in toluene: isoxazolidines: To a solution of 0.005 mol of nitrone in 50 mL of toluene was added a solution of 0.1 mol of acrylonitrile in 50 mL of toluene. The reaction mixture was then refluxed for 12 h. After cooling the system to room temperature and evaporation of the solvent, a viscous liquid was obtained. Petroleum ether was added to this liquid and the mixture was gently heated for few minutes. The precipitate formed during cooling was isolated by filtration, dried and then recrystallized in pentane/CH_2Cl_2 (4:1). The different characteristics of the synthesized isoxazolidines are given in Table-2 (each of the reported isoxazolidine is actually a mixture of the four diastereoisomers).

Cycloaddition in microemulsions

Microemulsions tested: Three microemulsions **A**, **B** and **C**, based on the water/acrylonitrile/(sodium dodecylsulfate-*n*-butanol = ½) were prepared according to the compositions shown in Table-3. The performance of microemulsion on the cycloaddition reaction was ascertained by dissolving 0.2 g of nitrone **IV** in 2 mL of the microemulsion and the reaction was followed as described below.

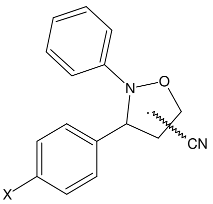
Calibration curves: A mother solution of nitrone-microemulsion system was prepared by diluting 10 μL of this mixture in 1 mL of methanol. Then, samples of different concentrations (C) were made in 5 mL of methanol by diluting different volumes, which were drawn off from the mother solution. The UV-visible absorbances (Abs) were measured for all samples at the corresponding absorption wavelengths of the nitrones and the Abs = f (C) graphs were drawn.

Typical procedure for nitrone IV: In a 25 mL round-bottomed flask were introduced 2 mL of a microemulsion in which 0.2 g of nitrone **IV** was dissolved. The clear and transparent mixture was stirred with a magnetic bar at 25 °C. Every 10 min of the reaction, 2 μL of the reaction mixture was sampled, diluted in 4 mL of methanol and analyzed by UV-visible spectrometry. After realizing the disappearance of the characteristic band of the nitrone, the organic phase was isolated by extraction with CH_2Cl_2. After the drying operation with anhydrous $MgSO_4$ and the removal of drying agent by filtration, the dichloromethane was evaporated to afford a mixture of isoxazolidines.

Procedure for the effect of Lewis acid: To a 2 mL of the microemulsion **B** were added 0.2 g of nitrone **IV** and 0.2 equiv of Lewis acid with respect to the amount of nitrone (61 mg, $La(OTf)_3$; 65 mg, $Yb(OTf)_3$; 51 mg, $Sc(OTf)_3$; 37 mg, $Cu(OTf)_2$). The reaction course was carried out as described above.

Procedure for the effect of the substituent on C-arylnitrone: To a 2 mL of the microemulsion **B** were added 0.076 mg (1.49 mmol) of $Sc(OTf)_3$ and nitrone in an optimal amount that microemulsion can dissolve. The maximum amounts of the nitrones dissolved and used were as follows: 0.23 mg, **I**; 0.32 mg, **II**; 0.26 mg, **III**; 0.54 mg, **V**; 0.87, **VI**. The reaction course was carried out as described above.

TABLE-2
RESULTS OF THE REACTIONS IN TOLUENE AFFORDING ISOXAZOLIDINES



Isoxazolidine	X	MM (g)	Yield (%)	R_f (a)	Elemental analysis (%)		UV-Visible (c)		IR (b) (cm^{-1})	MS (m/z)	
					Calcd.	Found	λ_{max} (nm)	ε		Base peak	M^+
I’ (1)	NO_2	295.293	69	0.33 0.43 0.58 0.68	C:65.08 H:4.44 N:14.23	C:65.38 H:4.59 N:14.33	265 203	324 851	(C-N):1110.9 (C-O):1257.5 (N-O):1033.8 (C-X):1342.4 (C≡N):2445.6	91	295
II’ (2)	Cl	284.740	48	0.5 0.63 0.75 0.81	C:67.43 H:4.56 N:9.83	-	225 204	345 1499	(C-N):1087.8 (C-O):1257.5 (N-O):1041.5 (C-X):840.9 (C≡N):2360.7	284	284
III’ (2)	Br	329.191	46	0.5 0.61 0.75 0.81	C:58.38 H:3.98 N:8.51	C:58.35 H:3.73 N:8.66	226 202	355 824	(C-N):1069.6 (C-O):1256.6 (N-O):1050.0 (C-X):896.0 (C≡N):2428.57	77	328
IV’ ‘(3)	H	250.295	46	0.51 0.61 0.66 0.71	C:76.09 H:5.60 N:11.18	-	238.5 203	179 688	(C-N):1026.1 (C-O):1257.5 (N-O):1026.1 (C≡N):2241.1	91	250
V’ (1)	OCH_3	280.321	39	0.43 0.51 0.56 0.58	C:72.77 H:5.70 N:9.98	-	230 202.5	475 967	(C-N):1110.9 (C-O):1249.8 (N-O):1029.9 (C-X):1300.0 (C≡N):2245	172	280
VI’ (1)	OC_2H_5	294.348	31	0.48 0.58 0.63 0.66	C:73.45 H:6.16 N:9.52	C:74.04 H:6.45 N:9.63	230.5 202.5	511 1045	(C-N):1118.6 (C-O):1172.6 (N-O):1049.2 (C-X):1242.1 (C≡N):2368.4	77	294

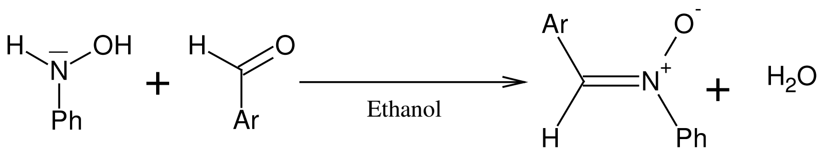
(1) Oily; (2) Pasty; (3) Colorless crystals; (a) TLC plates, silica gel, eluent:diethylether – petroleum ether (50/50 V/V). (b) KBr pellets; (c) Methanol (10^{-4}moles/L), 25°C.

TABLE-3
MICROEMULSIONS COMPOSITIONS (in wt. %)

Microemulsion	ACN	Water	SDS	*n*-Butanol
A	20	50	10	20
B	50	20	10	20
C	20	20	20	40

RESULTS AND DISCUSSION

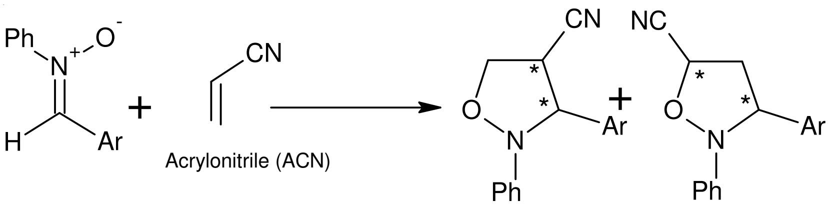
Six aromatic nitrones **I-VI** (**Scheme-I**) were prepared *via* a condensation reaction of β-phenylhydroxylamine with the corresponding aromatic aldehydes in good yields (60-80 %). The former compound was synthesized by reducing the nitrobenzene using zinc powder in the presence of ammonium chloride[18]. The different results of these reactions and the characteristics of the nitrones are gathered in Table-1.



I, Ar = *p*-NO_2Ph ; **II**, Ar = *p*-ClPh ; **III**, Ar = *p*-BrPh ;
IV, Ar = Ph ; **V**, Ar = *p*-CH_3OPh ; **VI**, Ar = *p*-C_2H_5OPh.

Scheme-I

The cycloaddition reactions of the synthesized aromatic nitrones with acrylonitrile (ACN) to yield isoxazolidines **I'-VI'** (**Scheme-II**), were examined in toluene and microemulsion.



*= asymmetric carbon

Scheme-II

Reactions in toluene: The reactions (**Scheme-II**) were first realized in toluene as a conventional medium, under reflux for 12 h. The nitrone/ACN molar ratio was set at 1/20 as suggested by Pandey *et al.*[19]. The results compiled in Table-2 show that the overall yields of isoxazolidines were low to moderate (*ca.* 30-70 %) and seemed to be substituent-dependent; *i.e.*, better yields were obtained for electron-withdrawing substituents on the aryl group (Ar). The corresponding isoxazolidines were actually mixtures of four diastereoisomers in about equal extents as revealed by TLC analyses (four spots of almost similar shapes). The isoxazolidines were identified by different physical and spectroscopic analyses.

Not only was the non stereoselectivity of 1,3-dipolar cycloaddition reaction in a classical medium deterring, but also the extreme conditions employed (reflux, 12 h) and the solvent toxicity were hampering.

Reactions in microemulsions: At first, a pseudoternary phase diagram (Fig. 1) of the water/ACN/(sodium dodecylsulfate/*n*-butanol = ½) system was worked out in order to determine the domains of the microemulsion existence. In this system, sodium dodecyl sulfate (SDS) and *n*-butanol were employed as surfactant and cosurfactant, respectively, in a ratio[20] equal to ½; *n*-butanol was selected because it does not react neither with nitrones nor with acrylonitrile. Acrylonitrile acts as the reactive oil and acting as a microemulsion component as well as a reaction reactant. The phase diagram shown in Fig. 1 interestingly discloses a vast domain of the existence of microemulsions, particularly near the water-borne side, allowing to freely and adequately choose a microemulsion of any kind for the reaction in concern.

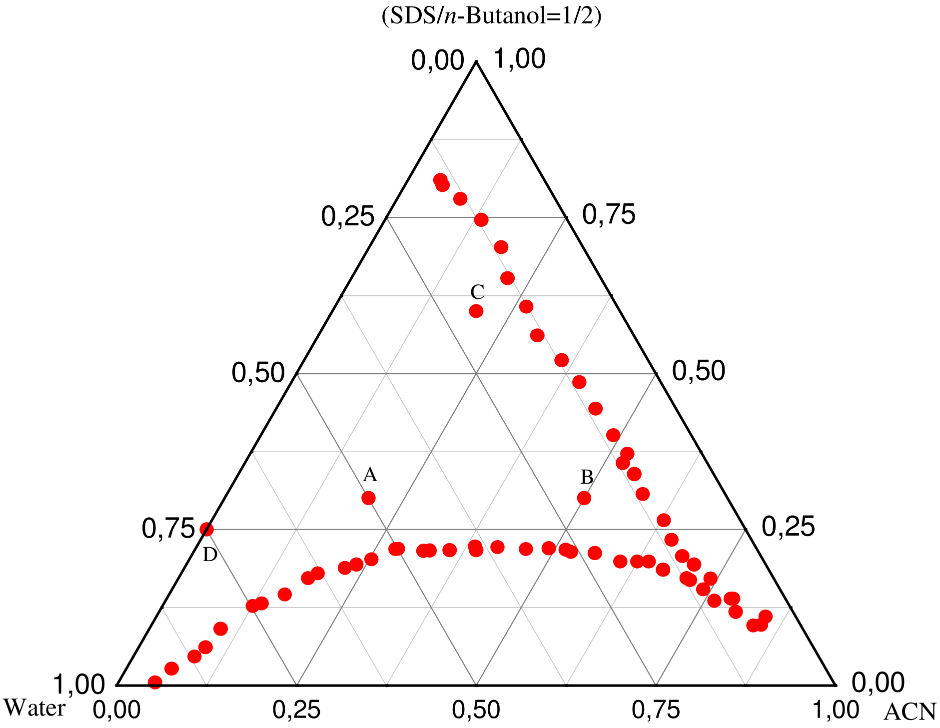


Fig. 1. Pseudoternary phase diagram of water/ACN/(sodium dodecylsulfate/*n*-butanol = ½) system. D: Titrating solution. The microemulsions chosen for the present study were: A: Water-rich microemulsion; B: Acrylonitrile-rich microemulsion; C: SDS/*n*-butanol-rich microemulsion.

Effect of the nature of microemulsion: Three different microemulsions were examined as media to study this reaction: water-rich microemulsion (**A**), acrylonitrile-rich microemulsion (**B**) and SDS/*n*-butanol-rich microemulsion (**C**). The compositions of these microemulsions are given in Table-3.

The study was mainly undertaken for diphenylnitrone **IV**, the simplest and unsubstituted nitrone. The 1,3-dipolar cycloaddition reaction of **IV** with ACN in these media was performed by adding the nitrone into the microemulsions **A**, **B** and **C** at 25 °C under intensive stirring; the microemulsions remained stable on stirring. The molar ratios of ACN/**IV** were 6.8, 31 and 6.8 in microemulsions **A**, **B** and **C**, respectively. The reaction course was easily monitored by UV-visible spectrophotometry. The important feature was that the heterogeneous facet of the mixtures did not impede this analysis. For the sake of illustration and conciseness, only the UV-visible spectra for the **IV**-microemulsion **B** system are given in Fig. 2. The UV analysis shows clearly the consumption of **IV** with time, as the **IV** nitrone absorbance at 313 nm faded out and the appearance of an isosbestic point at 253 nm, indicating the absence of intermediates and the existence of equilibrium. The absorption band of the corresponding isoxazolidine appeared at 238.5 nm. TLC analysis revealed predominantly one isomer over the remaining three diastereoisomers.

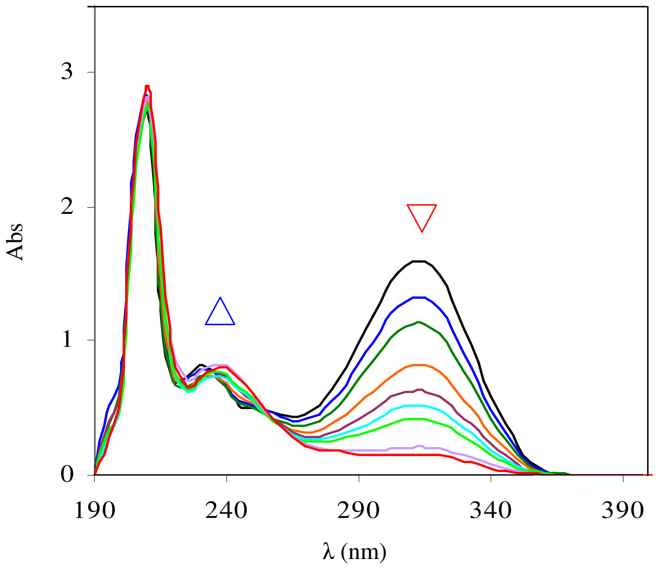


Fig. 2. UV-visible spectra as a function of time for **IV**-microemulsion B at 25 °C

The concentration of the nitrone **IV** present throughout the reaction, was estimated by the UV absorbance at 313 nm using a calibration curve for each of the **IV**-microemulsion systems.

The concentration of the residual nitrone and the reaction yield as a function of time and of the type of microemulsion medium are plotted in Fig. 3. The yield is computed from the eqn. 1, providing the nitrone was converted exclusively into isoxazolidine.

$$\text{Yield (\%)} = \frac{(C_0 - C_t)}{C_0} \times 100 \quad (1)$$

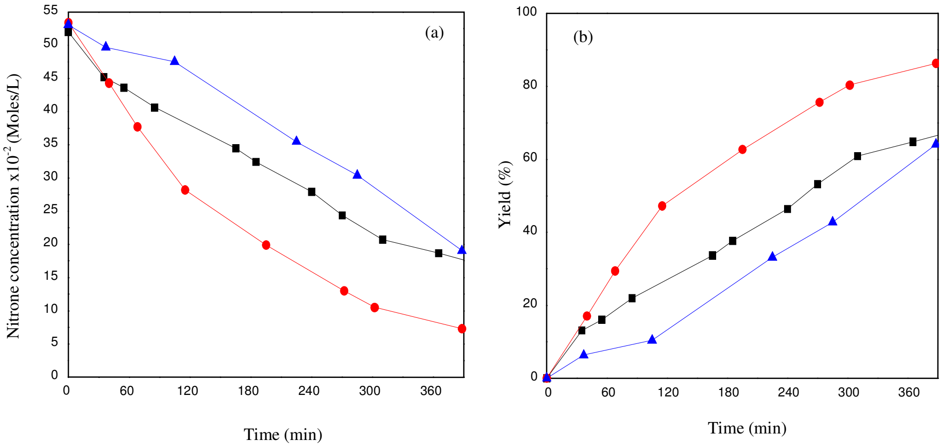
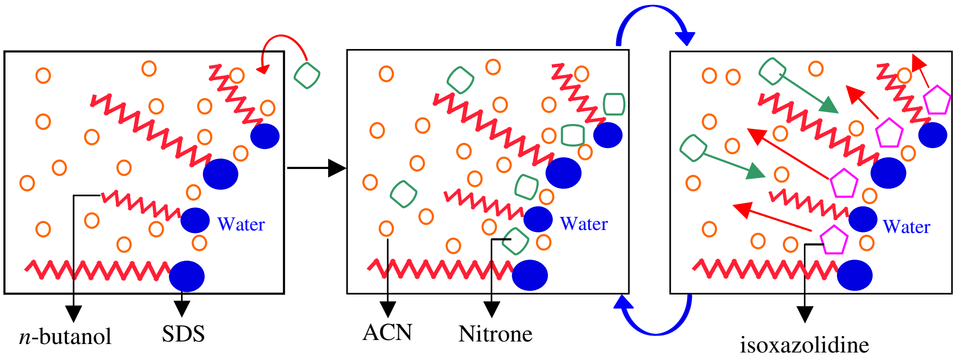


Fig. 3. Plots of (a) the variation of the concentration (mol/L) of the residual **IV** and (b) the yields of the reactions in function of time, for the different micromulsions: A (■), B (●) and C (▶); 25 °C

where C_0 and C_t were the initial concentration of the nitrone and its concentration at a time t, respectively.

The yield and the reaction rate depended strongly on the type of microemulsion. The acrylonitrile-borne microemulsion afforded better yields and higher rate, probably because of the higher concentration of ACN as suggested by the higher molar ACN/**IV**, which is 31. In fact, the reactivity of **IV** was tested and found to be proportional to the amount of ACN. It is interesting to note that the water-rich microemulsion (**A**) was a more favoured medium than the SDS/*n*-butanol-rich microemulsion (**C**) as far as yields and kinetics were concerned. Based on these considerations, the microemulsion **B** was a preferred reaction medium, which was employed for the upcoming study. This microemulsion was in form of water microdroplets dispersed in acrylonitrile, the oily component. Once the nitrone was added, it tended to migrate towards the ACN-water interface as confirmed by a study in an emulsion medium[21]. The nitrone molecules would concentrate within the interfaces and be arranged in such a way that depends on their polarity, making them react faster and more selectively. Hence, the reaction occurred within the interfaces. The formed isoxazolidine molecules, being less polar, would have the tendency to move off, allowing the nitrone molecules to reconcentrate within the interfaces (**Scheme-III**). Thus, a significant concentration of nitrone could be maintained continuously constant[11].

Effect of Lewis acid: The reactions of **IV** in microemulsion **B** were undertaken again, but in the presence of a Lewis acid acting as a catalyst. Four metal triflates Lewis acids were evaluated *i.e.*, lanthanum triflate $La(OTf)_3$, ytterbium triflate $Yb(OTf)_3$, scandium triflate $Sc(OTf)_3$ and cupric triflate $Cu(OTf)_2$. These triflate salts are water-soluble to an appreciable extent and can be easily recovered after



Scheme-III

the workup by a simple extraction with an organic solvent[22]. As can be noticed in Fig. 4, both the reaction rates and the yields were substantially enhanced by using 0.1 equiv of the triflate-based Lewis acids. The marked effects of these catalysts on the reaction yield are quite obvious; the *ca.* 80 % yield that was observed in the absence of a catalyst after a time longer than 6 h, was obtained after only 100 min in the presence of $Cu(OTf)_2$. Overall, the efficacy of the catalysts in these reactions within the first 100 min was found to be in the following increasing order: $Yb(OTf)_3$ < $La(OTf)_3$ < $Sc(OTf)_3$ < $Cu(OTf)_2$. A hypothesis for the rationale of this finding could be the cation size effect, *i.e.*, the better catalytic activity of $Cu(OTf)_2$ owes to the smaller size of the cupric ion Cu^{2+} (ionic radius r_{Cu} = 0.72 Å; r_{La} = 1.06 Å. The small size of the cation allows a facile crossing from the aqueous phase to the organic one *via* the interfacial film; the cation will then insert within the polar heads of surfactant molecules. Yet, beyond 100 min, the catalytic effect of $Cu(OTf)_2$ started to level off, while those of the other Lewis acids still rose and even surpassed

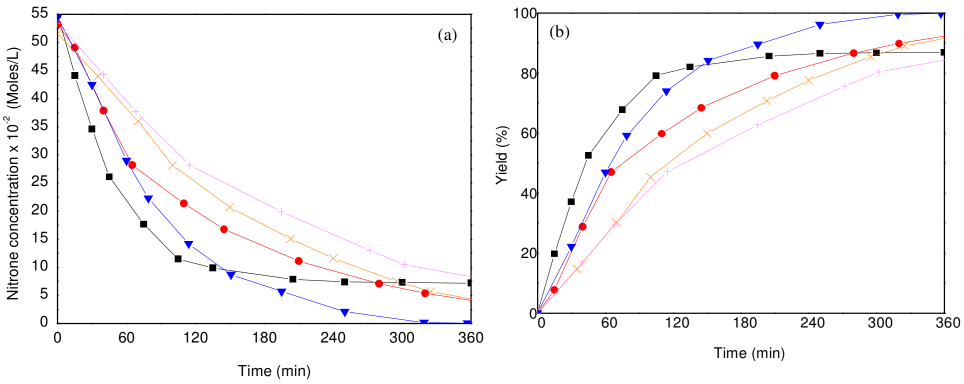
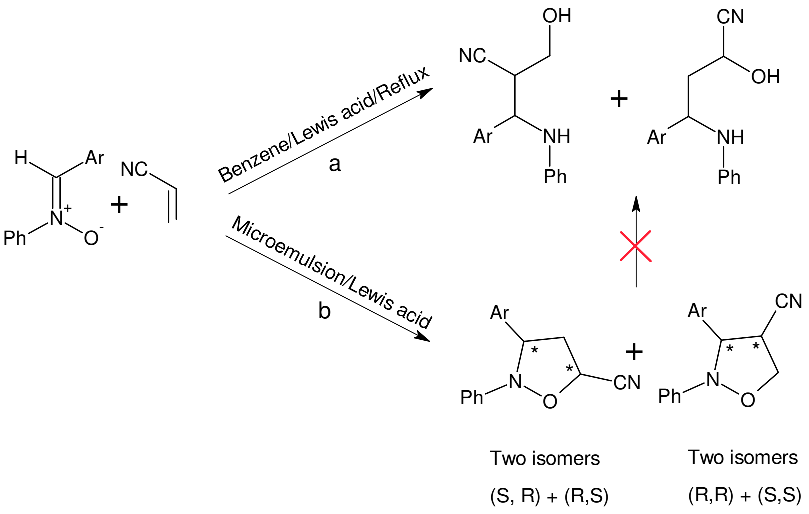


Fig. 4. Plots of (a) the variation of the concentration (mol/L) of the residual **IV** and (b) the yields of the reactions in function of time, for different Lewis acids (0.1 equiv): $Sc(OTf)_3$ (■), $La(OTf)_3$ (▶), $Yb(OTf)_3$ (●), $Cu(OTf)_3$ (*) in the absence of the catalyst (+). Microemulsion **B**; 25 °C

that of cupric triflate. This was quite expected because the latter salt can be partially hydrolyzed with time in an aqueous medium, whereas the other salts are more stable to hydrolysis[23].

The mechanism of the aldolization of aromatic aldehydes with silylenolether in an aqueous medium and in the presence of a Lewis acid has been disclosed[24]. It was found that the Lewis acid was hydrolyzed as soon as it was added into water. But, when the aldehyde is present, its molecules may compete with the water molecules for the complexation of the metallic ion, hence, the activation of aldehyde. The silylenolether will afterwards attack the latter to give the coveted aldol.

According to this mechanism, it is the nitrone that attacks the C=C double bond of acrylonitrile that was activated by the Lewis acid. It was reported that the use of Lewis acids in a 1,3-dipolar cycloaddition with electron-deficient alkenes such as ACN, often led to a reaction slowdown[25]. This can be explained by the zwitter ionic character of the nitrone, which makes it a weaker Lewis base than the dipolorphile. The Lewis acid will react with nitrone to afford a stable salt, resulting in a slow reaction[26]. On the other hand, the catalyst may promote the ring opening of the formed isoxazolidine *via* the N-O bond to give the γ-amino alcohols, as depicted in **Scheme-IVa**. Fortunately, these undesired side effects do not rise when the reaction takes place in a microemulsion medium. In fact, the interface is more replete with acrylonitrile than with nitrone, acrylonitrile being the dispersing phase (the continuous phase). Therefore, the complexation of Lewis acid would be more favourable with ACN than with nitrone. Consequently, the reactivity of the latter compound towards the Lewis acid-activated ACN will be more pronounced. In addition, the contact of Lewis acid with the produced isoxazolidine (**Scheme-IVb**) will be less probable as the latter, owing to its low polarity, sneaks off the interface (its birth place) as pictured in **Scheme-III**.



Scheme-IV

Because of its solidity to hydrolysis and its significant catalytic effect on the outcome of the reactions as shown in Fig. 4, scandium triflate was the catalyst retained for the subsequent work.

Effect of temperature: The 1,3-dipolar cycloaddition of **IV** with ACN was conducted in microemulsion **B** in the presence of 0.1 equiv of Sc(OTf)$_3$ at six different temperatures: 25, 30, 35, 40, 45 and 50 °C. It is worth mentioning that the microemulsions were stable at these temperatures. The results of the temperature influence on the reaction are illustrated in Fig. 5, indicating its strong impact on the reaction rate and the yields. The higher the temperature, the higher the yield and the reaction rate. Interestingly, a linear relationship (Fig. 6) between the temperature (T) and the reaction time (t_R) was found, for a yield as high as 98 %, obeying the equation $t_R = -10.977T + 566.81$ (t_R in min, T in °C; correlation coefficient, $R^2 = 0.9824$). So, a 25 % temperature rise led to a 255 min reaction time decrease, about a 90 % decline. The extrapolation of this plot strikingly indicates that the reaction time would not exceed a few seconds beyond 50 °C.

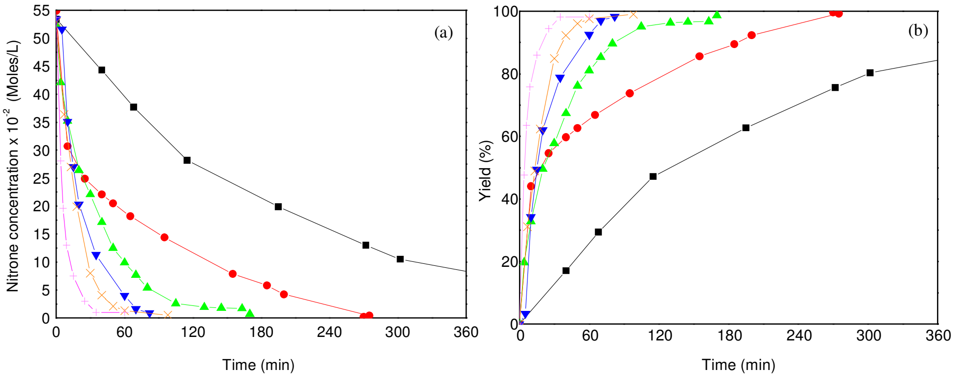


Fig. 5. Plots of (a) the variation of the concentration (mol/L) of the residual **IV** and (b) the yields of the reactions in function of time, in the microemulsion B in the presence of 0.1 equiv of Sc(OTf)$_3$: 25 °C (■); 30 °C, (●); 35 °C (▶); 40 °C (*); 45 °C (X); 50 °C (+)

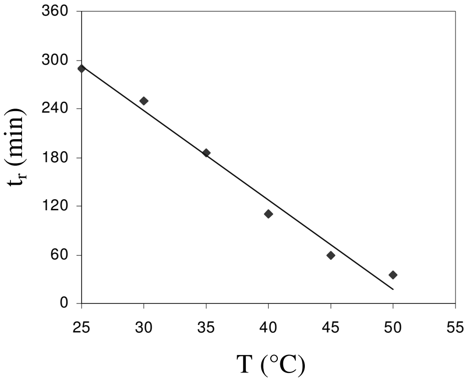


Fig. 6. Plot of the variation of the reaction time as a function of temperature: **IV**-microemulsion **B** system; yield, 98 %; Sc(OTf), 0.1 equiv.

Effect of the substituents of nitrones: After maintaining set the optimal conditions for the 1,3-dipolar cycloaddition of **IV** with ACN, the reaction was then extended to the remaining synthesized nitrones **I**, **II**, **III**, **V** and **VI**, which bear electron-withdrawing and electron-donating substituents on the aryl group. It is worth noting that some of these nitrones were insoluble neither in acrylonitrile nor in acrylonitrile-water system, even in the presence of a surfactant and upon heating[21]. However, their solubility in aqueous systems was tremendously improved in microemulsions and, the extent of the solubility is tightly bound to the nature of the substituent. This solubilization was probably due to an increase of the ACN-water interface, being the site of predilection for the nitrone molecules.

For each of the experimented nitrones, the variation of the yield with time is depicted in Fig. 7. As observed in the case of **IV** (Fig. 4b), the yields of isoxazolidines were quantitative at shorter reaction times compared to those found with other media, toluene (see above), water and emulsion[21]. For example, the reaction of the nitrone **II** with ACN under the conditions stated in the Fig. 7, produced the corresponding isoxazolidine in 90 % at only 150 min. Surprisingly, the yield seemed to be slightly substituent-dependent, *i.e.*, not in a systematic way; the influence of the substituent was not clear-cut. Yet, the effect of substitutent was evident in the case of **I** and **V** (electron-withdrawing group in **I** and electron-donating group in **V**).

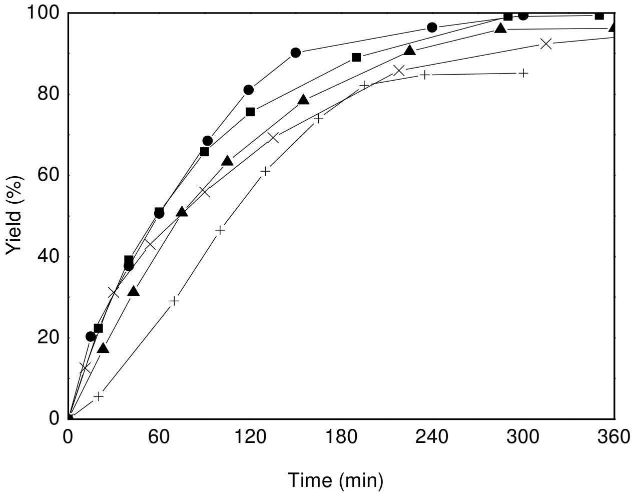


Fig. 7. Plots of the yields of the reactions in function of time for different nitrones: **I** (■), **II** (●), **III** (▶), **V**(*), **VI** (×). Microemulsion **B**; Sc(OTf), 0.1 equiv; 25 °C

Conclusion

The 1,3-dipolar cycloaddition reaction of nitrones with acrylonitrile, a vinyl compound with an electron-withdrawing substituent, occurs more rapidly in microemulsion than in a conventional medium. Of the wide spectrum of the existing microemulsions for the water/ACN/(sodium dodecylsulfate/*n*-butanol = ½) system, the W/O microemulsion is more appropriate for this reaction. A microemulsion proves to be the solubilizing system for some nitrones that defy solubility in aqueous and conventional media. More advantageously is the use of water-stable Lewis acids, the metal trifaltes, as catalysts. As a medium, the microemulsion prevents the concomitant occurrence of the hydrolysis of isoxazolidines, which can be promoted by Lewis acids. Temperature and Lewis acids reduce considerably the reaction time and favourably induce greater yields of isoxazolidines. Moreover, by using a microemulsion as a reaction medium, not only would the green chemistry enjoy a significant organic synthesis outcome but also would gain a mild and benign alternative to the toxic classical media.

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(*Received*: 12 February 2009; *Accepted*: 22 October 2009) AJC-7975