A green chemical approach for the *N*-alkylation of aldoximes to form nitrones in organized aqueous media and their *in situ* cycloaddition with olefins†

Sandip K. Hota, Amrita Chatterjee, Pranab K. Bhattacharya‡ and Partha Chattopadhyay*

Received 13th August 2008, Accepted 9th October 2008
First published as an Advance Article on the web 11th November 2008
DOI: 10.1039/b812290c

Aldoximes react with α,β-unsaturated carbonyl and sulfonyl compounds in organized aqueous media (nanoreactor system) using dodecylbenzenesulfonic acid (DBSA) as surfactant to generate *N*-alkylated nitrones, which undergo intermolecular cycloaddition in the same pot with maleimides to give the desired cycloadduct in absence of any organic solvent and catalyst. Divinyl sulfone was successfully used for both *N*-alkylation and intramolecular cycloaddition, affording only one cycloadduct. This is a new example of green chemistry and provides a new aspect of reactions in water.

Introduction

The concept of green chemistry[1] and its application[2] in synthetic chemistry, has emerged as a major solution for the development of cleaner and more benign chemical processes. Various methodologies and routes have been developed for this purpose. Use of water as a solvent[3] is undoubtedly the best alternative as there will be no use of hazardous and toxic organic solvents and no need for vigorous drying of the solvents. The problem of insolubility and hydrolytic decomposition of many organic compounds in water may be solved by the use of a surfactant, which in water forms an organized medium.[4] The border between the homogeneous (solution phase) and heterogeneous phases consists of micellar, reverse micellar, microheterogeneous, colloidal phases *etc.* During the course of surfactant catalyzed reactions, the organized medium acts as a nanoreactor,[5] which solubilizes and conforms hydrophobic organic compounds into its hydrophobic cores and thus protects water labile substances from decomposition.[6] Although different research groups have developed various types of reactions in aqueous media,[3,4] the preparation of nitrones by *N*-alkylation of aldoximes[7] in water appears to be the first example of this type of useful reaction, attempted so far. In the course of developing efficient organic reactions in water, our group earlier reported a one-pot process for nitrone formation in water, followed by its intermolecular cycloaddition to form isoxazolidines.[4b] Recently, we also reported stereoselective synthesis of chiral oxepanes and pyrans through intramolecular nitrone cycloaddition in organized aqueous media.[4c] These studies led us to investigate the formation of nitrones through *N*-alkylation of oximes in organized aqueous media.

Nitrones are well-known 1,3-dipoles in thermal cycloaddition reactions with multiple bond systems to provide different heterocyclic five membered ring systems.[8] Various uses and reactions of nitrones are well established.[9] There are many standard routes for the formation of nitrones.[10] Most of them include anhydrous conditions or dehydrative agents. For example, one of the most convenient methods of nitrone generation is the reaction of oximes with various alkylating agents or dipolarophiles.[11] When oximes are *N*-alkylated in this process, the formed nitrones have different functionalities and can take part in various types of reactions leading to the synthesis of biologically active natural products.[11a,12] Cycloaddition reaction with externally added dipolarophiles is the most common reaction of the formed nitrones. However, most of the processes use anhydrous conditions, toxic organic solvents and different catalysts (non-green process), along with high temperature and long reaction times.

Results and discussion

Intermolecular pathway

We hereby report for the first time the formation of nitrone through the *N*-alkylation of aldoximes in water and its subsequent cycloaddition (Table 1). Aldoximes react with α,β-unsaturated carbonyl and sulfonyl compounds to give *N*-alkylated nitrones in moderate to good yields, which then undergo intermolecular cycloaddition with maleimide to give the desired cycloadduct. We used dodecylbenzenesulfonic acid (DBSA) as surfactant to form the desired organized media. Dynamic light scattering (DLS), *i.e.* a particle size analyzer study,[5a] proved the formation of the nanoreactor system (Fig. 1). We also obtained the optical micrograph of the aqueous media containing DBSA as surfactant (Fig. 2).

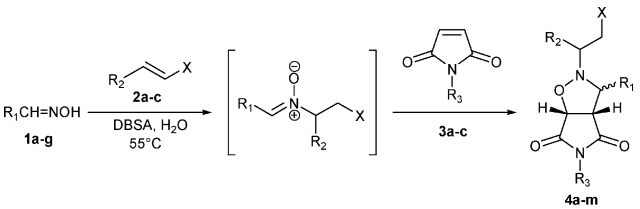
The applicability of the resultant *N*-alkylated nitrone, such as its reaction with some dipolarophiles through intermolecular

Chemistry Division, Indian Institute of Chemical Biology, 4, Raja S. C. Mullick Road, Jadavpur, Kolkata, 700 032, India. E-mail: partha@iicb.res.in

† Electronic supplementary information (ESI) available: NMR spectra of all the cycloaddition products and synthetic procedures of the reactants. CCDC reference number 686184. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/b812290c

‡ Deceased.

Table 1 Surfactant-catalyzed conjugate additions of oximes to α,β-unsaturated carbonyl and sulfonyl compounds and intermolecular nitrone cycloaddition with various *N*-substituted maleimides in organised aqueous media



1a-g: R_1 = Ph, 3-BrC_6H_4, 4-$NO_2C_6H_4$, (*E*)-C_6H_4CH=CH, $CH_3CH_2CH_2$, 2-$NO_2C_6H_4$, 3-$NO_2C_6H_4$
2a: R_2 = H, X = CO_2Et; **2b:** R_2 = Ph, X = COPh; **2c:** R_2 = H, X = SO_2Ph
3a-c: R_3 = Ph, Me, $CH_2CH_2CH_3$

Entry	Oximes	R_1	Acceptors	Maleimide	Time/h	Product[a] (Yield) (%)	Product[b] (*exo*:*endo*)
1	**1a**	Ph	**2a**	**3a**	20	**4a** (58)	100:0
2	**1a**	Ph	**2b**	**3a**	20	**4b** (68)	60:40
3	**1b**	3-BrC_6H_4	**2a**	**3b**	26	**4c** (55)	100:0
4	**1b**	3-BrC_6H_4	**2b**	**3b**	26	**4d** (68)	59:41
5	**1c**	4-$NO_2C_6H_4$	**2a**	**3a**	28	**4e** (53)	100:0
6	**1c**	4-$NO_2C_6H_4$	**2b**	**3a**	28	**4f** (66)	77:23
7	**1d**	(*E*)-PhCH=CH	**2a**	**3a**	22	**4g** (57)	100:0
8	**1e**	n-C_3H_7	**2a**	**3a**	22	**4h** (70)	100:0
9	**1e**	n-C_3H_7	**2b**	**3a**	20	**4i** (75)	100:0
10	**1f**	2-$NO_2C_6H_4$	**2b**	**3a**	30	**4j** (55)	59:41
11	**1g**	3-$NO_2C_6H_4$	**2a**	**3c**	26	**4k** (58)	68:32
12	**1a**	Ph	**2c**	**3b**	25	**4l** (53)	100:0
13	**1c**	4-$NO_2C_6H_4$	**2c**	**3a**	32	**4m** (52)	100:0

[a] after purification by column chromatography. [b] *exo*:*endo* ratio is determined by ^1H and ^{13}C spectra.

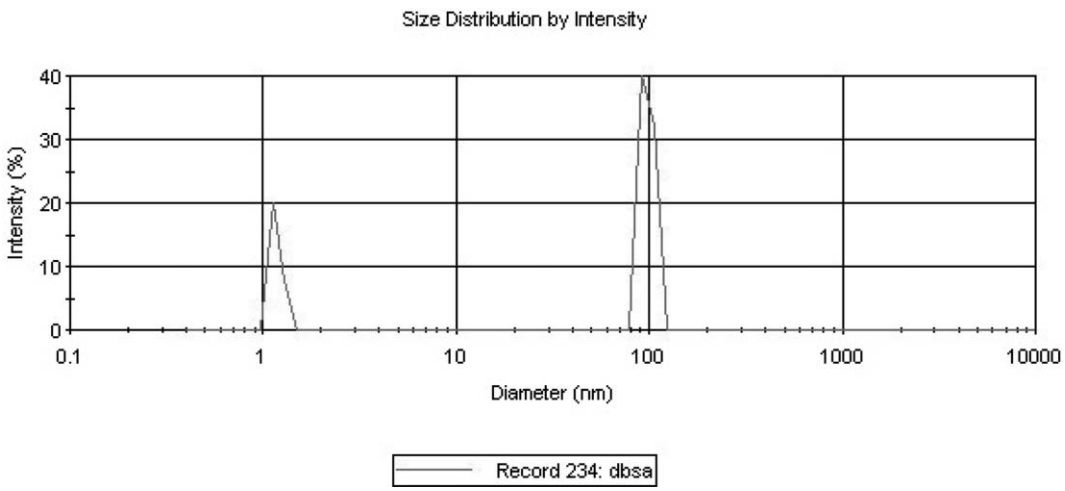


Fig. 1 Dynamic light scattering (DLS) data of the organised media using DBSA as surfactant.

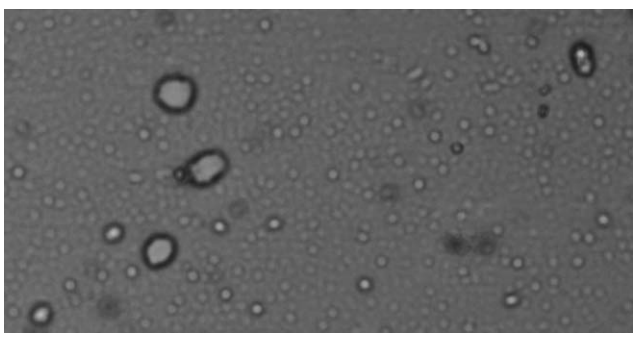
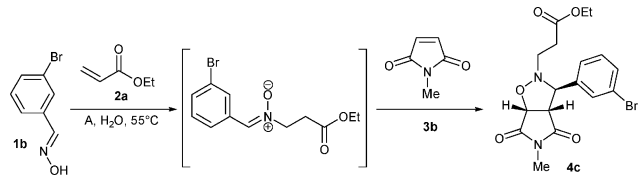


Fig. 2 Optical micrograph of the aqueous media containing DBSA as surfactant.

nitrone cycloaddition, has not been investigated much except for some reports in organic solvents.[11b,13] Kanemasa *et al.* have reported[7] *N*-alkylation of aldoximes in organic solvents such as benzene, dichloromethane and toluene in the presence of Lewis acid catalysts like ZnI_2 and $BF_3.OEt_2$ and the subsequent intermolecular cycloaddition with maleimides. In many cases, they had to reflux the hazardous organic solvents for many hours to get a good yield.

The present unique and safe approach for the preparation of nitrones by *N*-alkylation of aldoximes and their *in situ* intermolecular cycloaddition with various maleimides provides important cycloaddition products. As a part of our process we prepared seven aldoximes (**1a–g**; see ESI†). The aldoximes

Table 2 Effect of surfactants in the nitrone formation and intermolecular cycloaddition reaction in water



Entry	A	Time/h	Yield (%)
1	Surfactant DBSA	26	55
2	—	> 50	nil
3	Surfactant CTAB	> 50	10–15
4	Surfactant SDS	> 50	5–10
5	Surfactant Tween 80	> 50	not detected
6	Toluene-4-sulfonic acid	> 50	-do-
7	Toluene-4-sulfonic acid + Surfactant CTAB	> 50	25

were successfully reacted with α,β-unsaturated carbonyl compounds in presence of the surfactant in aqueous media to give *N*-alkylated nitrones in moderate to good yield (Table 1). We used ethyl acrylate and *trans*-chalcone as α,β-unsaturated carbonyl compounds and phenyl vinyl sulfone as α,β-unsaturated sulfonyl compound for this purpose. The progress of the reaction was monitored by TLC. Between ethyl acrylate and *trans*-chalcone, formation of the *N*-alkylated nitrone was better with the former, possibly due to the absence of any substituent at the β-position.

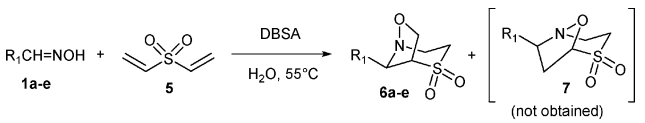
As the conjugate addition step of aldoximes to α,β-unsaturated carbonyl compounds towards formation of *N*-alkylated nitrones was found to be a slow process, *N*-substituted maleimide was added directly to the reaction mixture after formation of nitrone (~70%) to drive the equilibrium towards the end product.

We selected the reaction of 3-bromobenzaldoxime (**1b**) with ethyl acrylate (**2a**) and subsequent intermolecular cycloaddition with *N*-methylmaleimide (**3b**) as a model reaction (Table 2). We performed this reaction in various conditions including the use of different types of surfactants *i.e.* cationic, anionic, nonionic and acidic surfactants. Excellent results were obtained by using acidic surfactant DBSA. Yields were not good with cationic (CTAB), anionic (SDS) or nonionic (Tween 80) surfactants. There were no reactions in neat conditions or in water without surfactant. So it was evident that acidic surfactants had a prominent role in the *N*-alkylation of aldoximes towards the formation of the cycloadducts.

To confirm whether any non-surfactant type acid can promote nitrone formation under this condition, we carried out the reaction using a non-surfactant acid (toluene-4-sulfonic acid). As no product could be detected, the role of surfactant was established. The reaction also occurred in much lower yield when toluene-4-sulfonic acid was used in conjunction with a non-acidic surfactant (CTAB). Thus, the dual role of DBSA in ensuring the success of the reaction is established.

Moderate to excellent yields (52–75%) were obtained (Table 1) in this reaction. We observed that the nature of the alkyl or aryl components present in the aldoxime moiety influenced the course of the reaction. Generally electron donating substituents gave better results by enhancing the nucleophilicity of the oxime

Table 3 Reaction of oximes with divinyl sulfones



a-e: R_1 = Ph, 3-BrC_6H_4, 4-$NO_2C_6H_4$, (*E*)-$C_6H_4CH{=}CH$, $CH_3CH_2CH_2$

Entry	Oxime	Time/h	Product	Yield[a] (%)
1	**1a**	16	**6a**	57
2	**1b**	17	**6b**	55
3	**1c**	20	**6c**	52
4	**1d**	17	**6d**	53
5	**1e**	15	**6e**	53

[a] after purification by column chromatography.

nitrogen atom and thus promoting the Michael addition (or ene-like step). It was also found that the majority of the aldoximes afforded a single product (*exo*) with ethyl acrylate (**2a**) but a mixture of diastereomers with *trans*-chalcone (**2b**). Only the aliphatic aldoxime, butyraldehyde oxime (**1e**) produced solely the *exo* product with both the nucleophiles. The structures of the products were deduced on the basis of analytical and spectroscopic data. For example, the relative configurations among the three methine protons (3-H, 3a-H, and 6a-H) of **4c** were deduced by COSY and NOESY. From NOESY, it was evident that the 3a-H and 6a-H methine protons are in *cis* orientation, whereas 3-H is *trans* to 6a-H *i.e. trans* to 3a-H also. These results confirmed the *exo* structure. Exclusive or predominant formation of *exo* product in most of the reactions (Table 1) can be rationalised, as *endo* approach is sterically hindered. The minor *endo* adducts were not separated and the diastereomeric ratio was determined by NMR spectroscopy.

Intramolecular pathway

Aldoximes reacted with divinyl sulfone (**5**), a 1,4-diene, *via* a tandem process involving an *N*-(4-alkenyl) nitrone intermediate and gave rise to a bridged-ring product (**6**). Although the intermediate *N*-(4-alkenyl) nitrones can undergo cycloaddition in two different ways to yield the cycloadduct (**6**) or (**7**), we got only **6a–e**. The reaction of various aldoximes with divinyl sulfone afforded only one product each, *i.e.* 8-aryl/alkyl-7-oxa-4-thia-1-aza-bicyclo[3.2.1]octane 4,4-dioxide exclusively. Though Grigg *et al.* had reported[14] the formation of two types of bridged-ring products in boiling xylene, we found only one in good yield (Table 3). Here also, the nucleophilicity of the oxime nitrogen atom controls the rate of the reaction by regulating the Michael addition step. We observed that the greater the electron-density on the oxime nitrogen atom, greater is the yield of the product. The structure of the product was deduced from spectroscopic and analytical data and confirmed from X-ray crystal structure[15] determination (Fig. 3).

Conclusions

In conclusion, we have demonstrated a useful and 'green' approach to the preparation of nitrones through the *N*-alkylation of aldoximes in organized aqueous media and subsequent intermolecular or intramolecular cycloaddition reactions in the

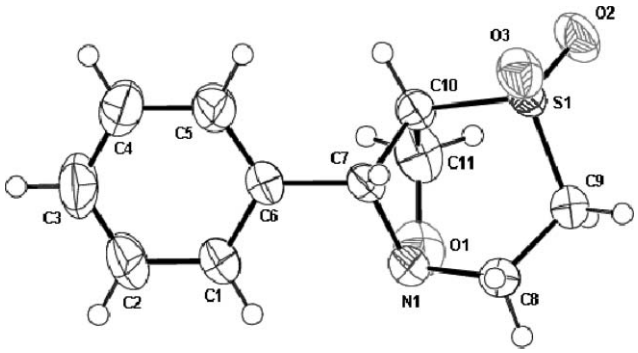


Fig. 3 X-Ray structure of the compound **6a**.

same pot. This process leads to the formation of only one product in most of the cases. This concept of a nanoreactor, formed in the organized aqueous media, could be applicable to various other types of reactions.

Experimental

General

Some reagents were obtained from commercial sources and used without purification. The solvents used were of technical grade, and freshly distilled prior to use. ^{1}H (300 MHz, 600 MHz) and ^{13}C (75 MHz, 150 MHz) NMR spectra were recorded using $CDCl_3$ as solvent and tetramethyl silane (TMS) as internal standard on Bruker DPX 300 MHz and Bruker DRX 600 MHz NMR instruments at ambient temperature. Chemical shifts are stated in parts per million in δ scales. COSY and NOESY experiments have been carried out in order to assign the ^{1}H spectra completely. Infrared spectra were recorded on a JASCO-FT-IR Model-410. Spectra were calibrated against the polystyrene absorption at 1601 cm^{-1}. IR spectra were measured using a KBr pellet or in neat condition. Mass spectra were measured mostly in ESIMS (+) and some in EIMS mode. DI-EIMS were recorded on a GCMS-Shimadzu-QP5050A and ESIMS were done on a Waters® Micromass® Q-TOF micro™ Mass Spectrometer. X-Ray crystallographic data of single crystals were collected on Bruker Kappa Apex II with Mo-Kα radiation ($\lambda = 0.71073$ Å). Dynamic light scattering (DLS) was performed by Malvern Instruments (Model: Nano ZS 80). Optical micrograph was taken at 10x magnification in a Nikon ECLIPSE (Model: E200) microscope. The surfactants used were dodecyl benzene sulfonic acid (DBSA), cetyl trimethyl ammonium bromide (CTAB), sodium dodecyl sulfate (SDS) and polyoxyethylene(20) sorbitan monooleate (Tween 80). TLC was performed on pre-coated plates (0.25 nm, silica gel 60 F_{254}). Organic extracts were dried over anhydrous sodium sulfate. Column chromatography and flash chromatography were carried out using commercial-grade silica gel (100–200 mesh or 230–400 mesh). PS and EA stand for petroleum spirit (60–80 °C) and ethyl acetate, respectively.

Experimental procedure for *N*-alkylation of aldoximes and subsequent cycloaddition reaction in organized aqueous media

An aromatic or aliphatic aldoxime (0.5 mmol) and an α,β-unsaturated carbonyl compound (0.5 mmol, 1.0 equiv.) were added successively to a solution of the surfactant (DBSA, 0.05 mmol) in H_2O (2 mL) at room temperature in a 25 mL round-bottom flask. The reaction was sonicated§ for 10 minutes, then stirred at 55 °C and monitored by TLC. After satisfactory formation of the *N*-alkylated nitrone, *N*-alkyl or aryl maleimide (0.6 mmol) was added and the stirring of the reaction mixture was continued at that temperature. After stirring at that temperature for the period of time listed in Table 1, the product was extracted with ethyl acetate. Then it was washed with brine, dried over Na_2SO_4, and concentrated in rotavapor. The crude product was then purified by silica gel column chromatography.

3-(4,6-Dioxo-3,5-diphenyl-hexahydro-pyrrolo[3,4-d]isoxazol-2-yl)-propionic acid ethyl ester (4a)

Grayish solid; yield 58% (eluent PS-EA, 4:1); mp. 145 °C; only *exo* product is formed; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.20 (t, $J = 7.1$ Hz, 3H), 2.51–2.62 (m, 2H), 2.85–3.03 (m, 2H), 3.84 (dd, $J = 3.3$, 7.3 Hz, 1H), 4.08 (q, $J = 7.1$ Hz, 2H), 4.37 (bs, 1H), 5.07 (d, $J = 7.3$ Hz, 1H), 7.31–7.50 (m, 10H); ^{13}C NMR ($CDCl_3$, 150 MHz): δ 14.1 (CH_3), 33.1 (CH_2), 53.7 (CH_2), 60.4 (CH_2), 68.4 (CH), 75.8 (CH), 79.1 (CH), 126.3 (Ar-CH), 128.2 (Ar-CH), 128.8 (Ar-CH), 128.9 (Ar-CH), 129.0 (Ar-CH), 129.0 (Ar-CH), 129.2 (Ar-CH), 129.3 (Ar-CH), 131.3 (C), 171.8 (C), 172.3 (C), 174.3 (C); IR (KBr) ν_{max}: 3449, 2915, 1713, 1497, 1389, 1324, 1193, 1070 cm^{-1}; ESIMS (*m*/*z*): 395 ($M^+ + 1$), 417 ($M^+ + 23$). Elemental analysis for $C_{22}H_{22}N_2O_5$: Calcd. C, 66.99; H, 5.62; N, 7.10. Found: C, 67.13; H, 5.73; N, 6.97.

2-(3-Oxo-1,3-diphenyl-propyl)-3,5-diphenyl-tetrahydro-pyrrolo[3,4-d]isoxazole-4,6-dione (4b)

Yellowish sticky liquid; yield 68%; (eluent PS-EA, 4:1); mixture of diastereomers; *exo*:*endo* = 60:40; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 3.23 (dd, $J = 4.9$, 17.5 Hz, 1H), 3.53 (dd, $J = 6.6$, 16.9 Hz, 1H), 3.58 (t, $J = 8.1$ Hz, 2H), 3.85 (d, $J = 8.7$ Hz, 1H), 4.04–4.14 (m, 2H), 4.27 (t, $J = 8.5$ Hz, 1H), 4.59–4.68 (m, 2H), 4.84 (t, $J = 5.6$ Hz, 1H), 4.94 (d, $J = 7.3$ Hz, 1H), 5.26 (d, $J = 8.2$ Hz, 1H), 6.65–6.68 (m, 1H), 7.08 (d-like, $J = 6.8$ Hz, 2H), 7.18–7.54 (m, 32H), 7.97 (t-like, $J = 8.0$ Hz, 4H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 42.4 (CH_2), 43.7 (CH_2), 53.5 (CH), 54.1 (CH), 61.0 (CH), 64.0 (CH), 68.5 (CH), 69.0 (CH), 75.5 (CH), 78.0 (CH), 125.9 (Ar-CH), 127.6 (Ar-CH), 127.8 (Ar-CH), 128.0 (Ar-CH), 128.1 (Ar-CH), 128.2 (Ar-CH), 128.4 (Ar- CH), 128.5 (Ar-CH), 128.6 (Ar-CH), 128.7 (Ar-CH), 128.9 (Ar-CH), 129.0 (Ar-CH), 130.1 (Ar-CH), 130.8 (Ar-CH), 131.2 (Ar-CH), 132.8 (Ar-CH), 133.0 (Ar-CH), 133.2 (Ar-CH), 134.6 (C), 135.3 (C), 136.8 (C), 137.0 (C), 171.6 (C), 171.9 (C), 172.7 (C), 174.2 (C), 197.8 (C); IR (neat) ν_{max}: 3492, 3062, 3028, 2923, 2342, 1958, 1785, 1722, 1684, 1597, 1496, 1451, 1381, 1288, 1205 cm^{-1}; EIMS (*m*/*z*): 502(M^+). Elemental analysis for $C_{32}H_{26}N_2O_4$: Calcd. C, 76.48; H, 5.21; N, 5.57. Found: C, 76.39; H, 5.33; N, 5.66.

§ It is well-known that sonication favors the formation of organized media and so we did it to obtain a shorter reaction time and better result.

3-[3-(3-Bromo-phenyl)-5-methyl-4,6-dioxo-hexahydro-pyrrolo[3,4-d]isoxazol-2-yl]-propionic acid ethyl ester (4c)

Yellow solid; yield 55% (eluent PS-EA, 4:1); mpt. 140°C; only *exo* product is formed; confirmed by COSY and NOESY; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.25 (t, J = 7.1 Hz, 3H), 2.68 (t, J = 6.9 Hz, 2H), 2.80–2.89 (m, 1H), 2.97 (s, 3H), 3.06–3.16 (m, 1H), 3.70 (t, J = 7.9 Hz, 1H), 3.93 (d, J = 8.7 Hz, 1H), 4.12 (q, J = 7.1 Hz, 2H), 4.89 (d, J = 7.2 Hz, 1H), 7.11 (d, J = 7.7 Hz, 1H), 7.23 (t, J = 7.8 Hz, 1H), 7.33 (s, 1H), 7.46 (d, J = 7.9 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz): 14.1 (CH_3), 24.8 (CH_3), 32.8 (CH_2), 51.0 (CH_2), 54.1 (CH), 60.5 (CH_2), 72.5 (CH), 76.2 (CH), 122.9 (q), 126.3 (Ar-CH), 130.3 (Ar-CH), 130.7 (Ar-CH), 132.0 (Ar-CH), 135.8 (C), 171.7 (C), 172.6 (C), 174.8 (C); IR (KBr) ν_{max}: 2986, 1786, 1731, 1707, 1564, 1437, 1385, 1322, 1290, 1180, 1131, 1070, 1045, 983, 856, 781 cm^{-1}; ESIMS (m/z): 433, 435 ($M^+ + Na^+$ for ^{79}Br, ^{81}Br). Elemental analysis for $C_{17}H_{19}BrN_2O_5$: Calcd. C, 49.65; H, 4.66; N, 6.81. Found: C, 49.56; H, 4.78; N, 6.77.

3-(3-Bromo-phenyl)-5-methyl-2-(3-oxo-1,3-diphenyl-propyl)-tetrahydro-pyrrolo[3,4-d]isoxazole-4,6-dione (4d)

Yellowish white solid; yield 68% (eluent PS-EA, 4:1); mpt. 134 °C; mixture of diastereomers; *exo*:*endo* = 59:41; further separation by column chromatography failed; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 2.75 (s, 3H), 2.89 (s, 3H), 3.26 (dd, J = 5.7, 17.6 Hz, 1H), 3.41 (t, J = 8.0 Hz, 1H), 3.58 (dd, J = 7.0, 16.9 Hz, 1H), 3.68 (d, J = 8.6 Hz, 1H), 3.92–4.05 (m, 3H), 4.36 (d, J = 9.0 Hz, 1H), 4.49 (t, J = 6.7 Hz, 1H), 4.74 (q, J = 5.9 Hz, 2H), 5.02 (d, J = 7.7 Hz, 1H), 6.99–7.03 (m, 3H), 7.17–7.33 (m, 15H), 7.44–7.48 (m, 7H), 7.94 (t, J = 7.0 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz): 24.4 (CH_3), 24.6 (CH_3), 42.5 (CH_2), 43.0 (CH_2), 53.5 (CH), 54.3 (CH), 60.9 (CH), 64.3 (CH), 67.2 (CH), 69.1 (CH), 75.4 (CH), 77.2 (CH), 122.1 (q), 122.8 (q), 126.2 (Ar-CH), 127.8 (Ar-CH), 128.0 (Ar-CH), 128.2 (Ar-CH), 128.4 (Ar-CH), 128.4 (Ar-CH), 129.6 (Ar-CH), 130.0 (Ar-CH), 130.3 (Ar-CH), 130.6 (Ar-CH), 130.8 (Ar-CH), 131.0 (Ar-CH), 131.9 (Ar-CH), 133.0 (Ar-CH), 133.1 (Ar-CH), 134.4 (C), 135.4 (C), 136.6 (C), 136.9 (C), 137.3 (C), 139.5 (C), 172.3 (C), 172.7 (C), 173.9 (C), 174.9 (C), 197.5 (C), 197.6 (C); IR (KBr) ν_{max}: 3482, 3065, 1786, 1714, 1596, 1431, 1380, 1286, 1219, 1145, 1051, 996, 791, 749, 693 cm^{-1}; ESIMS (m/z): 541, 543 (M^+ + 23 for ^{79}Br, ^{81}Br). Elemental analysis for $C_{27}H_{23}BrN_2O_4$: Calcd. C, 62.44; H, 4.46; N, 5.39. Found: C, 62.36; H, 4.38; N, 5.50.

3-[3-(4-Nitro-phenyl)-4,6-dioxo-5-phenyl-hexahydro-pyrrolo[3,4-d]isoxazol-2-yl]-propionic acid ethyl ester (4e)

Brownish sticky liquid; yield 53%; (eluent PS-EA, 4:1); only *exo* product is formed; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.22 (t, J = 7.1 Hz, 3H), 2.65 (t, J = 6.7 Hz, 2H), 2.97 (t, J = 6.7 Hz, 2H), 3.80 (dd, J = 4, 7.4 Hz, 1H), 4.11 (q, J = 7.1 Hz, 2H), 4.45 (bs, 1H), 5.09 (d, J = 7.4 Hz, 1H), 7.31–7.34 (m, 2H), 7.42–7.54 (m, 3H), 7.62 (d, J = 8.6 Hz, 2H), 8.28 (d, J = 8.7 Hz, 2H). ^{13}C NMR ($CDCl_3$, 150 MHz): δ 14.1 (CH_3), 32.9 (CH_2), 60.7 (CH_2), 75.9 (CH), 124.2 (Ar-CH), 126.2 (Ar-CH), 129.0 (Ar-CH), 129.2 (Ar-CH), 129.4 (Ar-CH), 131.0 (C), 148.1 (C), 171.5 (C), 173.7 (C). IR (neat) ν_{max}: 3381, 3078, 2926, 2855, 2453, 1788, 1722, 1599, 1521, 1383, 1348, 1195, 1108, 1015, 853, 754, 693 cm^{-1}; ESIMS (m/z): 462 (M^+ + 23), 494 (M^+ + 23 + MeOH). Elemental analysis for $C_{22}H_{21}N_3O_7$: Calcd. C, 60.13; H, 4.82; N, 9.56. Found: C, 60.25; H, 4.72; N, 9.69.

3-(4-Nitro-phenyl)-2-(3-oxo-1,3-diphenyl-propyl)-5-phenyl-tetrahydro-pyrrolo[3,4-d]isoxazole-4,6-dione (4f)

Yellowish orange solid; yield 66%; (eluent PS-EA, 4:1); mp. 192°C; mixture of diastereomers; *exo*:*endo* = 77:23; ^{1}H NMR ($CDCl_3$, 600 MHz): δ 3.35 (dd, J = 5.4, 16.8 Hz, 2H), 3.66 (t, J = 8.1 Hz, 2H), 3.94 (d, J = 8.4 Hz, 2H), 4.25 (dd, J = 8.4, 16.8 Hz, 1H), 4.28 (t, J = 8.4 Hz, 1H), 4.58 (dd, J = 5.4, 8.4 Hz, 2H), 4.98 (d, J = 7.5 Hz, 2H), 6.79 (d, J = 8.1 Hz, 1H), 7.00–7.02 (m, 3H), 7.22–7.24 (m, 4H), 7.31–7.58 (m, 22H), 8.03 (d, J = 8.4 Hz, 4H), 8.27 (d, J = 8.4 Hz, 4H); ^{13}C NMR ($CDCl_3$, 150 MHz): δ 42.0 (CH_2), 43.8 (CH_2), 53.7 (CH), 54.2 (CH), 61.3 (CH), 64.5 (CH), 67.6 (CH), 69.1 (CH), 75.4 (CH), 77.8 (CH), 123.4 (Ar-CH), 124.2 (Ar-CH), 125.6 (Ar-CH), 125.8 (Ar-CH), 127.8 (Ar-CH), 128.2 (Ar-CH), 128.3 (Ar-CH), 128.3 (Ar-CH), 128.6 (Ar-CH), 128.7 (Ar-CH), 128.7 (Ar-CH), 128.9 (Ar-CH), 129.0 (Ar-CH), 129.2 (Ar-CH), 130.1 (Ar-CH), 130.9 (C), 133.3 (Ar-CH), 133.4 (Ar-CH), 134.0 (C), 136.6 (C), 137.0 (C), 139.8 (C), 140.6 (C), 142.6 (C), 147.5 (C), 148.1 (C), 171.1 (C), 171.6 (C), 172.3 (C), 173.6 (C), 197.8 (2C, C); IR (KBr) ν_{max}: 3449, 3065, 1723, 1685, 1598, 1521, 1496, 1449, 1385, 1348, 1205 cm^{-1}; ESIMS (m/z): 570 (M^+ + 23). Elemental analysis for $C_{32}H_{25}N_3O_6$: Calcd. C, 70.19; H, 4.60; N, 7.67. Found: C, 70.28; H, 4.52; N, 7.80.

3-(4,6-Dioxo-5-phenyl-3-styryl-hexahydro-pyrrolo[3,4-d]isoxazol-2-yl)-propionic acid ethyl ester (4g)

Brown liquid; yield 57%; (eluent PS-EA, 4:1); only *exo* product is formed; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.22 (t, J = 7.1 Hz, 3H), 2.60–2.73 (m, 2H), 2.84–2.92 (m, 1H), 3.29–3.39 (m, 1H), 3.62 (t, J = 8.3 Hz, 1H), 3.76 (t, J = 7.5 Hz, 1H), 4.07–4.16 (m, 2H), 4.98 (d, J = 7.3 Hz, 1H), 5.99 (dd, J = 8.9, 15.8 Hz, 1H), 6.77 (d, J = 15.8 Hz, 2H), 7.29–7.50 (m, 5H); ^{13}C NMR ($CDCl_3$, 150 MHz): δ 14.2 (CH_3), 33.0 (CH_2), 50.7 (CH_2), 52.8 (CH), 60.5 (CH_2), 72.3 (CH), 75.7 (CH), 121.2 (Ar-CH), 126.3 (Ar-CH), 127.0 (Ar-CH), 128.5 (Ar-CH), 128.6 (Ar-CH), 128.9 (Ar-CH), 129.2 (Ar-CH), 129.3 (Ar-CH), 131.4 (C), 135.8 (C), 137.0 (Ar-CH), 172.0 (C), 172.4 (C), 173.9 (C); IR (neat) ν_{max}: 2982, 1720, 1597, 1497, 1450, 1383, 1193, 1094, 1028, 969, 860, 754, 693 cm^{-1}; ESIMS (m/z): 443 (M^+ + 23). Elemental analysis for $C_{24}H_{24}N_2O_5$: Calcd. C, 68.56; H, 5.75; N, 6.66. Found: C, 68.69; H, 5.86; N, 6.79.

3-(4,6-Dioxo-5-phenyl-3-propyl-hexahydro-pyrrolo[3,4-d]isoxazol-2-yl)-propionic acid ethyl ester (4h)

Brownish orange sticky liquid; yield 70%; (eluent PS-EA, 4:1); only *exo* product is formed; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.0 (t, J = 6.8 Hz, 3H), 1.24 (t, J = 7.1 Hz, 3H), 1.52–1.73 (m, 4H), 2.66 (t, J = 6.9 Hz, 2H), 3.00–3.09 (m, 1H), 3.14–3.24 (m, 1H), 3.41 (bs, 1H), 3.54 (dd, J = 3.5, 7.5 Hz, 1H), 4.13 (q, J = 7.1 Hz, 2H), 4.90 (d, J = 7.5 Hz, 1H), 7.29–7.50 (m, 9H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 13.9 (CH_3), 14.1 (CH_3), 19.3 (CH_2), 29.8 (CH_2), 33.2 (CH_2), 51.0 (CH_2), 54.3 (CH), 60.5 (CH_2), 69.7 (CH), 76.3 (CH), 126.1 (Ar-CH), 126.3 (Ar-CH), 128.8 (Ar-CH), 129.1 (Ar-CH), 129.2 (Ar-CH), 131.4 (C), 171.8 (C), 174.8 (C);

IR (neat) ν_{max}: 3489, 2961, 2935, 2873, 1784, 1724, 1597, 1498, 1456, 1382, 1189, 1061, 1028, 858, 736, 692 cm^{-1}; ESIMS (*m*/*z*): 383 (M^+ + 23), 415 (M^+ + 23 + MeOH). Elemental analysis for $C_{19}H_{24}N_2O_5$: Calcd. C, 63.32; H, 6.71; N, 7.77. Found: C, 63.22; H, 6.63; N, 7.62.

2-(3-Oxo-1,3-diphenyl-propyl)-5-phenyl-3-propyl-tetrahydro-pyrrolo[3,4-d]isoxazole-4,6-dione (4i)

Yellowish orange sticky liquid; yield 75%; (eluent PS-EA, 4:1); only *exo* product is formed; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 0.68 (t, J = 6.7 Hz, 3H), 0.87–0.97 (m, 2H), 1.32–1.42 (m, 2H), 3.54 (d, J = 8.1 Hz, 1H), 3.64 (dd, J = 9.5, 17.3 Hz, 1H), 3.74–3.78 (m, 1H), 3.97 (dd, J = 3.0, 17.3 Hz, 1H), 4.51 (dd, J = 3.0, 9.0 Hz, 1H), 5.04 (d, J = 8.1 Hz, 1H), 7.20–7.27 (m, 5H), 7.33–7.41 (m, 3H), 7.45–7.60 (m, 6H), 7.83 (d, J = 7.5 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 13.3 (CH_3), 19.3 (CH_2), 37.7 (CH_2), 44.4 (CH_2), 54.9 (CH), 65.2 (CH), 67.5 (CH), 78.7 (CH), 126.3 (Ar-CH), 126.5 (Ar-CH), 127.9 (Ar-CH), 128.1 (Ar-CH), 128.2 (Ar-CH), 128.3 (Ar-CH), 128.4 (Ar-CH), 128.5 (Ar-CH), 128.7 (Ar-CH), 128.7 (Ar-CH), 129.1 (Ar-CH), 129.1 (Ar-CH), 129.2 (Ar-CH), 129.5 (Ar-CH), 131.4 (C), 133.0 (Ar-CH), 136.9 (C), 139.3 (C), 173.8 (C), 175.4 (C), 197.5 (C); IR (neat) ν_{max}: 3064, 3029, 2960, 2874, 1785, 1720, 1683, 1596, 1496, 1453, 1380, 1189, 1078, 858, 750, 690 cm^{-1}; ESIMS (m/z): 491 (M^+ + 23), 523 (M^+ + 23 + MeOH). Elemental analysis for $C_{29}H_{28}N_2O_4$: Calcd. C, 74.34; H, 6.02; N, 5.98. Found: C, 74.42; H, 5.96; N, 6.09.

3-(2-Nitro-phenyl)-2-(3-oxo-1,3-diphenyl-propyl)-5-phenyl-tetrahydro-pyrrolo[3,4-d]isoxazole-4,6-dione (4j)

Brownish red sticky liquid; yield 55%; (eluent PS-EA, 4:1); mixture of diastereomers; *exo*:*endo* = 59:41; 1H NMR ($CDCl_3$, 300 MHz): δ 3.29–3.41 (m, 2H), 4.06–4.09 (m, 1H), 4.14–4.17 (m, 1H), 4.24 (dd, J = 8.4, 16.8 Hz, 2H), 4.38 (t, J = 8.4 Hz, 1H), 4.55 (t, J = 6.8 Hz, 1H), 4.81 (t, J = 5.4 Hz, 1H), 4.98 (d, J = 7.2 Hz, 1H), 5.15 (d, J = 9.2 Hz, 1H), 5.22 (d, J = 7.7 Hz, 1H), 7.00 (d, J = 6.4 Hz, 4H), 7.08–7.39 (m, 17H), 7.48 (t, J = 7.1 Hz, 6H), 7.55–7.68 (m, 6H), 7.94 (d, J = 7.1 Hz, 1H), 8.03 (d, J = 7.9 Hz, 3H); ^{13}C NMR ($CDCl_3$, 150 MHz): 41.7 (CH_2), 41.8 (CH_2), 52.8 (CH), 53.2 (CH), 61.2 (CH), 63.4 (CH), 64.0 (CH), 66.3 (CH), 75.2 (CH), 76.7 (CH), 125.2 (Ar-CH), 125.2 (Ar-CH), 125.8 (Ar-CH), 126.0 (Ar-CH), 127.3 (Ar-CH), 127.6 (Ar-CH), 127.8 (Ar-CH), 128.2 (Ar-CH), 128.3 (Ar-CH), 128.4 (Ar-CH), 128.6 (Ar-CH), 128.7 (Ar-CH), 128.7 (Ar-CH), 128.8 (Ar-CH), 128.8 (Ar-CH), 128.9 (Ar-CH), 128.9 (Ar-CH), 129.0 (Ar-CH), 129.0 (Ar-CH), 129.1 (Ar-CH), 129.2 (Ar-CH), 129.5 (Ar-CH), 129.7 (Ar-CH), 131.0 (Ar-CH), 131.1 (C), 131.4 (C), 133.3 (C), 133.4 (Ar-CH), 133.4 (C), 133.7 (C), 134.0 (Ar-CH), 136.5 (C), 137.1 (C), 140.1 (C), 148.5 (C), 149.2 (C), 171.6 (C), 172.0 (C), 173.3 (C), 173.9 (C), 197.9 (C), 198.1 (C); IR (neat) ν_{max}: 1721, 1680, 1593, 1526, 1494, 1380, 1202, 750 cm^{-1}; ESIMS (*m*/*z*): 570 (M^+ + 23). Elemental analysis for $C_{32}H_{25}N_3O_6$: Calcd. C, 70.19; H, 4.60; N, 7.67. Found: C, 70.32; H, 4.53; N, 7.56.

3-[3-(3-Nitro-phenyl)-4,6-dioxo-5-propyl-hexahydro-pyrrolo[3,4-d]isoxazol-2-yl]-propionic acid ethyl ester (4k)

Brownish red sticky liquid; yield 58%; (eluent PS-EA, 4:1); mixture of diastereomers; *exo*:*endo* = 68:32; 1H NMR ($CDCl_3$, 300 MHz): δ 0.80–0.94 (m, 9H), 1.25 (t, J = 7.1 Hz, 3H), 1.49–1.63 (m, 4H), 2.66–2.75 (m, 3H), 2.80–2.99 (m, 3H), 3.09–3.16 (m, 2H), 3.37–3.51 (m, 4H), 3.56 (dd, J = 2.9, 8.2 Hz, 1H), 3.75 (t, J = 7.9 Hz, 1H), 4.09–4.13 (m, 4H), 4.32 (dd, J = 5.6, 7.9 Hz, 1H), 4.78 (d, J = 8.2 Hz, 1H), 4.83 (s, 1H), 4.92 (d, J = 7.3 Hz, 1H), 5.27 (d-like, 1H), 6.77 (d, J = 9.6 Hz, 1H), 7.57–7.65 (m, 2H), 7.74 (d, J = 7.6 Hz, 1H), 8.08 (s, 1H), 8.19 (d, J = 7.7 Hz, 1H), 8.31 (s, 1H); ^{13}C NMR ($CDCl_3$, 150 MHz): δ 11.0 (CH_3), 11.2 (CH_3), 14.1 (CH_3), 21.1 (CH_2), 21.9 (CH_2), 32.6 (CH_2), 39.3 (CH_2), 40.7 (CH_2), 48.9 (CH), 51.0 (CH_2), 53.8 (CH), 55.7 (CH), 60.7 (CH_2), 62.4 (CH), 67.8 (CH), 72.2 (CH), 76.0 (CH), 87.1 (CH), 122.1 (Ar-CH), 122.8 (Ar-CH), 123.3 (Ar-CH), 123.9 (Ar-CH), 129.8 (Ar-CH), 129.9 (Ar-CH), 133.1 (Ar-CH), 133.9 (Ar-CH), 135.7 (C), 139.7 (C), 147.6 (C), 148.3 (C), 167.2 (C), 171.7 (C), 172.1 (C), 172.6 (C), 174.6 (C), 177.0 (C); ESIMS (*m*/*z*): 428 (M^+ + Na+). Elemental analysis for $C_{19}H_{23}N_3O_7$: Calcd. C, 56.29; H, 5.72; N, 10.37. Found: C, 56.41; H, 5.85; N, 10.45.

2-(2-Benzenesulfonyl-ethyl)-5-methyl-3-phenyl-tetrahydro-pyrrolo[3,4-d]isoxazole-4,6-dione (4l)

Yellowish orange amorphous solid; yield 53%; (eluent PS-EA, 3:1); only *exo* product is formed; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 2.92 (s, 3H), 3.37–3.39 (m, 2H), 3.65 (dd, J = 3.2, 7.2 Hz, 1H), 3.71–3.84 (m, 2H), 4.79 (t-like, 1H), 5.04 (d, J = 7.2 Hz, 1H), 7.24–7.26 (m, 3H), 7.35–7.38 (m, 5H), 7.51–7.67 (m, 1H), 7.81 (d, J = 7.4 Hz, 1H). ^{13}C NMR ($CDCl_3$, 150 MHz): δ 25.2 (CH_3), 34.4 (CH_2), 54.2 (CH), 54.3 (CH_2), 66.8 (CH), 79.8 (CH), 127.3 (Ar-CH), 127.9 (Ar-CH), 128.2 (Ar-CH), 128.3 (Ar-CH), 128.7 (Ar-CH), 128.8 (Ar-CH), 129.0 (Ar-CH), 129.1 (Ar-CH), 129.2 (Ar-CH), 133.8 (Ar-CH), 135.0 (C), 139.3 (C), 174.8 (C). IR (KBr) ν_{max}: 3454, 2938, 1709, 1439, 1382, 1289, 1141, 1047 cm^{-1}. ESIMS (*m*/*z*): 423 (M^+ + 23). Elemental analysis for $C_{20}H_{20}N_2O_5S$: Calcd. C, 59.99; H, 5.03; N, 7.00. Found: C, 60.08; H, 4.96; N, 6.88.

2-(2-Benzenesulfonyl-ethyl)-3-(4-nitro-phenyl)-5-phenyl-tetrahydro-pyrrolo[3,4-d]isoxazole-4,6-dione (4m)

Yellow sticky liquid; yield 52%; (eluent PS-EA, 3:1); only *exo* product is formed; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 3.04–3.16 (m, 2H), 3.38–3.53 (m, 2H), 3.80 (dd, J = 3.5, 6.9 Hz, 1H), 4.43 (bs, 1H), 5.00 (d, J = 7.4 Hz, 1H), 7.32 (d, J = 7.7 Hz, 2H), 7.45–7.68 (m, 8H), 7.85 (d, J = 7.7 Hz, 2H), 8.28 (d, J = 8.0 Hz, 2H). ^{13}C NMR ($CDCl_3$, 150 MHz): δ 49.1 (CH_2), 54.2 (CH_2), 56.8 (CH), 66.3 (CH), 75.9 (CH), 124.1 (Ar-CH), 124.3 (Ar-CH), 126.2 (Ar-CH), 127.8 (Ar-CH), 128.4 (Ar-CH), 128.9 (Ar-CH), 129.2 (Ar-CH), 129.4 (Ar-CH), 130.9 (Ar-CH), 134.0 (Ar-CH), 139.2 (C), 142.5 (C), 147.8 (C), 148.2 (C), 173.3 (C). IR (neat) ν_{max}: 3489, 3068, 1721, 1601, 1520, 1447, 1383, 1348, 1308, 1195, 1146, 1083 cm^{-1}. ESIMS (*m*/*z*): 508 (M^+ + 1), 530 (M^+ + 23). Elemental analysis for $C_{25}H_{21}N_3O_7S$: Calcd. C, 59.16; H, 4.17; N, 8.28. Found: C, 59.30; H, 4.26; N, 8.37.

Experimental procedure for intramolecular nitrone cycloaddition reaction in aqueous media

An aromatic or aliphatic aldoxime (0.5 mmol) and divinyl sulfone (0.5 mmol, 1.0 equiv) were added successively to a

solution of surfactant (DBSA, 0.05 mmol) in H_2O (2 mL) at room temperature in a 25 mL round-bottom flask. The reaction was sonicated for 10 minutes and then stirred at 55 °C. After stirring at that temperature for the period of time listed in Table 3, the product was extracted with ethyl acetate. Then it was washed with brine, dried over Na_2SO_4, and concentrated in rotavapor. The crude product was then purified by silica gel column chromatography.

8-Phenyl-7-oxa-4-thia-1-aza-bicyclo[3.2.1]octane 4,4-dioxide (6a)

Colorless needles; m.p. 170 °C; yield 57%; (eluent PS-EA, 3:1); ^{1}H NMR ($CDCl_3$, 300 MHz): δ 3.04–3.16 (m, 1H), 3.36–3.48 (m, 2H), 3.74–3.90 (m, 3H), 4.50 (d, J = 9.0 Hz, 1H), 5.15 (s, 1H), 7.29–7.46 (m, 5H). ^{13}C NMR ($CDCl_3$, 150 MHz): δ 45.9 (CH_2), 53.4 (CH_2), 68.1 (CH_2), 69.1 (CH), 70.5 (CH), 125.5 (Ar-CH), 128.1 (Ar-CH), 128.8 (Ar-CH), 136.3 (C). IR (KBr) ν_{max}: 3433, 2998, 2945, 1607, 1453, 1304, 1224, 1169, 1121, 1083 cm^{-1}. ESIMS (m/z): 240 (M^+ + 1), 262 (M^+ + 23). Elemental analysis for $C_{11}H_{13}NO_3S$: Calcd. C, 55.21; H, 5.48; N, 5.85. Found: C, 55.33; H, 5.52; N, 5.92. Melting point and ^{1}H spectra are literature consistent.[14c]

8-(3-Bromo-phenyl)-7-oxa-4-thia-1-aza-bicyclo[3.2.1]octane 4,4-dioxide (6b)

Yellowish white solid; yield 55%; (eluent PS-EA, 3:1); ^{1}H NMR ($CDCl_3$, 300 MHz): δ 3.06–3.17 (m, 1H), 3.42 (d-like, J = 9.0 Hz, 2H), 3.76–3.92 (m, 3H), 4.51 (d, J = 9.0 Hz, 1H), 5.12 (s, 1H), 7.23–7.28 (m, 1H), 7.37 (d, J = 7.7 Hz, 1H), 7.46 (d, J = 7.7 Hz, 1H), 7.65 (s, 1H). ^{13}C NMR ($CDCl_3$, 150 MHz): δ 45.9 (CH_2), 53.4 (CH_2), 68.1 (CH_2), 69.0 (CH), 70.0 (CH), 123.1 (C), 124.2 (Ar-CH), 128.9 (Ar-CH), 130.4 (Ar-CH), 131.4 (Ar-CH), 138.5 (C). IR (KBr) ν_{max}: 3418, 2962, 2896, 1567, 1471, 1419, 1316, 1223, 1161, 1120 cm^{-1}. ESIMS (m/z): 341 (M^+ + 23). Elemental analysis for $C_{11}H_{12}BrNO_3S$: Calcd. C, 41.52; H, 3.80; N, 4.40. Found: C, 41.69; H, 3.88; N, 4.28.

8-(4-Nitro-phenyl)-7-oxa-4-thia-1-aza-bicyclo[3.2.1]octane 4,4-dioxide (6c)

Off white solid; m.p. 240 °C; yield 52%; (eluent PS-EA, 3:1); ^{1}H NMR ($CDCl_3$, 300 MHz): δ 3.13–3.17 (m, 1H), 3.40–3.55 (m, 2H), 3.78–3.94 (m, 3H), 4.55 (d, J = 9.8 Hz, 1H), 5.24 (s, 1H), 7.67 (d, J = 8.4 Hz, 2H), 8.26 (d, J = 8.4 Hz, 2H). ^{13}C NMR ($CDCl_3$, 150 MHz): δ 45.9 (CH_2), 53.3 (CH_2), 68.2 (CH_2), 68.9 (CH), 70.2 (CH), 124.1 (Ar-CH), 126.9 (Ar-CH), 143.2 (C), 147.8 (C). IR (KBr) ν_{max}: 3423, 3111, 2948, 1601, 1514, 1347, 1320, 1230, 1121, 1020 cm^{-1}. ESIMS (m/z): 285 (M^+ + 1), 307 (M^+ + 23). Elemental analysis for $C_{11}H_{12}N_2O_5S$: Calcd. C, 46.47; H, 4.25; N, 9.85. Found: C, 46.32; H, 4.33; N, 9.94. Melting point and ^{1}H spectra are literature consistent.[14c]

8-Styryl-7-oxa-4-thia-1-aza-bicyclo[3.2.1]octane 4,4-dioxide (6d)

Off white solid; m.p. 194 °C; yield 53%; (eluent PS-EA, 3:1); ^{1}H NMR ($CDCl_3$, 300 MHz): δ 3.03–3.07 (m, 1H), 3.36–3.44 (m, 2H), 3.70–3.79 (m, 2H), 4.15 (dd, J = 5.8, 9.7 Hz, 1H), 4.54 (d, J = 9.7 Hz, 1H), 4.72 (d, J = 5.0 Hz, 1H), 6.01 (dd, J = 5.3, 16.0 Hz, 1H), 6.78 (dd, J = 1.0, 16.0 Hz, 1H), 7.27–7.41 (m, 5H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 46.1, 53.4, 67.7, 68.8, 69.6, 123.3, 126.7, 128.5, 128.8, 129.0, 133.3, 135.7. IR (neat) ν_{max}: 2980, 1493, 1447, 1326, 1284, 1211, 1119, 965 cm^{-1}. ESIMS (m/z): 288 (M^+ + 23). Elemental analysis for $C_{13}H_{15}NO_3S$: Calcd. C, 58.85; H, 5.70; N, 5.28. Found: C, 59.01; H, 5.83; N, 5.40.

8-Propyl-7-oxa-4-thia-1-aza-bicyclo[3.2.1]octane 4,4-dioxide (6e)

Off white solid; m.p. 115 °C; yield 53%; (eluent PS-EA, 3:1); ^{1}H NMR ($CDCl_3$, 300 MHz): δ 0.96 (t, J = 7.0 Hz, 3H), 1.29–1.56 (m, 4H), 2.99–3.05 (m, 1H), 3.24–3.34 (m, 2H), 3.61–3.65 (m, 2H), 3.90 (t, J = 6.7 Hz, 1H), 4.14 (dd, J = 6.0, 9.8 Hz, 1H), 4.48 (d, J = 9.8 Hz, 1H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 13.5 (CH_3), 19.2 (CH_2), 33.7 (CH_2), 45.8 (CH_2), 53.5 (CH_2), 66.8 (CH), 68.7 (CH & CH_2). IR (neat) ν_{max}: 3434, 2949, 2871, 1455, 1325, 1282, 1195, 1121, 963 cm^{-1}. ESIMS (m/z): 206 (M^+ + 1), 228 (M^+ + 23). Elemental analysis for $C_8H_{15}NO_3S$: Calcd. C, 46.81; H, 7.37; N, 6.82. Found: C, 46.69; H, 7.49; N, 6.99.

Acknowledgements

Financial support from the Department of Science and Technology (DST), New Delhi, Government of India is gratefully acknowledged. We thank CSIR (India) for financial assistance, as well as for research fellowship to S.H. and A.C. Thanks are also due to Dr B. Achari, Emeritus Scientist, IICB for valuable suggestions and Mr S. Samanta, IICB for X-ray analysis.

Notes and references

1 (*a*) P. Anastas, L. G. Heine, T. C. Williamson, in *Green Chemical Syntheses and Processes*, Oxford University Press, New York, 2000; (*b*) M. Lancaster, in *Green Chemistry: An Introductory Text*, Royal Society of Chemistry, Cambridge, UK, 2002; (*c*) I. T. Horvath, *Acc. Chem. Res.*, 2002, **35**, 685–685; (*d*) J. Andraos, *Org. Process Res. Dev.*, 2005, **9**, 149–163; (*e*) A. S. Matlack, *Introduction to Green Chemistry*, Marcel Dekker, New York, NY, 2001.

2 (*a*) M. Lancaster, in *Handbook of Green Chemistry and Technology*, ed. J. H. Clark, D. J. Macquarrie, Blackwell Publishing, Abingdon, 2002; (*b*) P. T. Anastas and M. M. Kirchhoff, *Acc. Chem. Res.*, 2002, **35**, 686–694; (*c*) *Green Chemistry: Theory and Practice*, ed. P. T. Anastas, J. C. Warner, Oxford University Press, Oxford, UK, 1998; (*d*) U. S. Environmental Protection Agency, http://www.epa.gov/greenchemistry/principles.html.

3 (*a*) U. M. Lindstrom, *Organic Recations in Water: Principles, Strategies and Application*, Blackwell Publishing, Abingdon, 2007 and references cited therein; (*b*) J. B. F. N. Engberts and M. J. Blandamer, *Chem. Commun.*, 2001, 1701–1708; (*c*) U. M. Lindstrom, *Chem. Rev.*, 2002, **102**, 2751–2772; (*d*) M. C. Pirrung and K. Das Sarma, *J. Am. Chem. Soc.*, 2004, **126**, 444–445; (*e*) D. Dallinger and C. O. Kappe, *Chem. Rev.*, 2007, **107**, 2563–2591 and references cited therein; (*f*) C.-J. Li, T.-H. Chan, *Organic Reactions in Aqueous Media*, John Wiley & Sons, New York, 1997; (*g*) C.-J. Li, *Chem. Rev.*, 2005, **105**, 3095–3166; (*h*) *Organic Synthesis in Water*, ed. P. A. Grieco, Blackie Academic and Professional, England, 1998; (*i*) Y. Kita, H. Nambu, N. G. Ramesh, G. Anilkumar and M. Matsugi, *Org. Lett.*, 2001, **3**, 1157–1160; (*j*) T. Okino and Y. Takemoto, *Org. Lett.*, 2001, **3**, 1515–1517.

4 (*a*) K. Manabe, S. Iimura, X.-M. Sun and S. Kobayashi, *J. Am. Chem. Soc.*, 2002, **124**, 11971–11978; (*b*) A. Chatterjee, D. K. Maiti and P. K. Bhattacharya, *Org. Lett.*, 2003, **5**, 3967–3969; (*c*) A. Chatterjee and P. K. Bhattacharya, *J. Org. Chem.*, 2006, **71**, 345–348.

5 (*a*) We performed the dynamic light scattering (DLS) study and observed that the surfactant in aqueous solution is self-assembled to

form the nanoreactor, with hydrodynamic radii of 1.167 nm (27.65%) and 97.75 nm (72.35%); (*b*) D. M. Vriezema, M. Comellas Aragones, J. A. A. W. Elemans, J. J. L. M. Cornelissen, A. E. Rowan and R. J. M. Nolte, *Chem. Rev.*, 2005, **105**, 1445–1490.

6 M. Lee, C.-J. Jang and J.-H. Ryu, *J. Am. Chem. Soc.*, 2004, **126**, 8082–8083.

7 For the generation of nitrones by *N*-alkylation of aldoximes in non-aqueous media, see: K. Nakama, S. Seki and S. Kanemasa, *Tetrahedron Lett.*, 2001, **42**, 6719–6722.

8 (*a*) A. Padwa, *Angew. Chem., Int. Ed. Engl.*, 1976, **15**, 123–136; (*b*) W. Oppolzer, *Angew. Chem., Int. Ed. Engl.*, 1977, **16**, 10–23; (*c*) C. P. Dell, *J. Chem. Soc., Perkin Trans. 1*, 1998, 3873–3905.

9 (*a*) M. Lombardo and C. Trombini, *Synthesis*, 2000, **6**, 759; (*b*) K. V. Gothelf and K. A. Jorgensen, *Chem. Rev.*, 1998, **98**, 863–910; (*c*) S. Kanemasa, T. Tsuruoka and H. Yamamoto, *Tetrahedron Lett.*, 1995, **36**, 5019–5022.

10 (*a*) A. Padwa, in *New Synthetic Methods*, Verlag Chemie, New York, 1979, vol. 5; (*b*) M. A. Voinov and I. A. Grigorev, *Tetrahedron Lett.*, 2002, **43**, 2445–2447; (*c*) R. Alibes, P. Blanco, P. March, M. Figueredo, J. Font, A. Alvarez-Larena and J. F. Piniella, *Tetrahedron Lett.*, 2003, **44**, 523–525.

11 (*a*) *1,3-Dipolar Cycloaddition Chemistry*, ed. A. Padwa, Wiley, New York, 1984, vol. 2, ch. 9, pp. 83–168; (*b*) M. Noguchi, H. Okada, S. Nishimura, Y. Yamagata, S. Takamura, M. Tanaka, A. Kakehi and H. Yamamoto, *J. Chem. Soc., Perkin Trans. 1*, 1999, 185–192; (*c*) H. Miyabe, K. Yoshida, V. K. Reddy, A. Matsumura and Y. Takemoto, *J. Org. Chem.*, 2005, **70**, 5630–5635; (*d*) H. A. Dondas, C. W. G. Fishwick, R. Grigg and M. Thornton-Pett, *Tetrahedron*, 2003, **59**, 9997–10007 and references cited therein.

12 (*a*) S. E. Denmark and A. Thorarensen, *Chem. Rev.*, 1996, **96**, 137–166; (*b*) R. Grigg, *Chem. Soc. Rev.*, 1987, **16**, 89–121 and references cited therein.

13 (*a*) D. Francois, A. Maden and W. V. Murray, *Org. Lett.*, 2004, **6**, 1931–1934; (*b*) R. Grigg, F. Heaney, J. Markandu, S. Surendrakumar, T.-P. Mark and W. J. William, *Tetrahedron*, 1991, **47**, 4007–4030; (*c*) A. Hassner, R. Maurya, O. Friedman, H. E. Gottlieb, A. Padwa and D. Austin, *J. Org. Chem.*, 1993, **58**, 4539–4546.

14 (*a*) P. Armstrong, R. Grigg and W. J. Warnock, *J. Chem. Soc., Chem. Commun.*, 1987, 1325–1327; (*b*) R. Grigg, J. F. Malone, M. J. Dorrity, F. Heaney, S. Rajviroongit, V. Sridharan and S. Surendrakumar, *Tetrahedron Lett.*, 1988, **29**, 4323–4324; (*c*) R. Grigg, M. J. Dorrity, F. Heaney, J. F. Malone, S. Rajviroongit, V. Sridharan and S. Surendrakumar, *Tetrahedron*, 1991, **47**, 8297–8322; (*d*) M. T. McKiernan and F. Heaney, *Tetrahedron Lett.*, 1996, **37**, 4597–4600.

15 Crystal data of compound **6a**: $C_{11}H_{13}NO_3S$, FW = 239.28, monoclinic, space group P21/c, a = 17.1392 (5) Å, b = 6.0512 (2) Å, c = 10.9857 (4) Å, β = 93.007 (2)°, V = 1137.79 (7) Å^3, Z = 4, T = 296 (2) K, d_{calcd} = 1.397 g cm^{-3}, F (000) = 504. Diffraction data were measured with Mo K_α (λ = 0.71073 Å) radiation at 296 K using a Bruker Kappa Apex 2 CCD system. A total of 2660 unique reflections were measured (θ_{max} = 30.87 °). Data analyses were carried out with the Difference Vectors program. The structures were solved by direct methods using the SHELXS-97[16] program. Refinements were carried out with a full matrix least squares method against F^2 using SHELXL-97.[17] Non-hydrogen atoms were refined with anisotropic thermal parameters. The final R value was $R1$ = 0.0456 and w$R2$ = 0.1500 with $I > 2\sigma(I)$. Crystallographic data have been deposited at the Cambridge Crystallographic Data Centre with reference numbers CCDC 686184.

16 G. M. Sheldrick, *SHELXS-97, Program for solution of crystal structures*, University of Göttingen, Germany, 1997; G. M. Sheldrick, *Acta Crystallogr. A*, 1990, **46**, 467–473.

17 G. M. Sheldrick, *SHELXL-97, Program for refinement of crystal structures*, University of Göttingen, Germany, 1997.

