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Stable nitrile oxide dipolar cycloadditions in pure water

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ABSTRACT

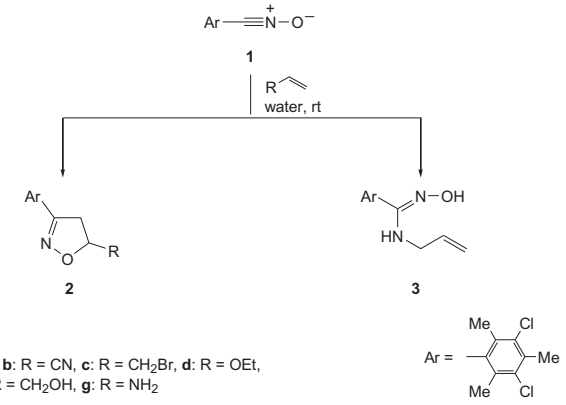
A systematic study on the behaviour of stable 2,4,6-trimethyl-3,5-dichlorobenzonitrile oxide versus a number of mono-, bi- and trisubstituted dipolarophiles in water was pursued obtaining simple as well as annulated isoxazolines. Reaction conditions changed with the dipolarophilic species, according to their solubility in water and the degree of substitution of the reactive carbon–carbon multiple bond. The presence of sodium dodecylsulfate was also tested as potential micellar catalyst.

1. Introduction

During the last two decades, 1,3-dipolar cycloadditions (1,3-DC) in water or aqueous media have been recognized as an useful, non-conventional method with wide application in the synthesis of a huge number of five-membered heterocyclic rings.[1] This is primarily due to the straightforward features of water as the reaction medium. In fact, despite the aggressive nature of water towards a number of organic functionalities, water itself displays a number of desirable features: (i) the pH of the reaction medium is often easily controlled, (ii) reaction rates can be dramatically increased by means of the hydrophobic effect, (iii) product separation and/or reaction workup is generally greatly simplified and (iv) environmentally-friendly procedures can be successfully elaborated. Early contributions by Grundmann described nitrile oxide cycloadditions in biphasic aqueous–organic mixtures.[2] Later, further examples of dipolar cycloadditions in water or aqueous media have been exploited,[3] leading to some successful synthetic methodologies (the well-known 'click' azide–alkyne cycloaddition).[4] By focussing on the field of nitrile oxide chemistry,[5] some papers have appeared in recent years describing the 1,3-dipolar activity of such species in aqueous systems from both a mechanistic[6] and synthetic[7] standpoint. To date, however, no systematic studies of stable nitrile oxide 1,3-DC in pure water have been performed. In fact, nitrile oxides are almost always generated in situ from the whole array of their precursors,[5] which are usually fully insoluble in water. As a result, an organic cosolvent is very often required giving rise to a variety of experimental conditions spanning from homogeneous[8] to biphasic systems.[9] We argued that a thermally stable nitrile oxide could tolerate the use of pure water as the reaction medium thus circumventing the use of organic solvent. Hence, in the present work we undertook a systematic investigation on the behaviour of the stable 2,4,6-trimethyl-3,5-dichlorobenzonitrile oxide onto a variety of alkenyl-, alkynyl- and hetero- dipolarophiles in water.

2. Results and discussion

As a suitable dipolar species, nitrile oxide **1** (Scheme 1) was prepared according to literature procedures.[10] This nitrile oxide was submitted to reaction with a number of dipolarophilic species in pure water at room temperature as summarised in Schemes 1–4 and Tables 1–3. The results were satisfactory, provided that very short reaction times and mild conditions were in place with respect to some reactions carried out in organic solvent as control experiments (vide infra, note 14), and very good isolation yields were always experienced. Furthermore, reaction workup was a very simple matter since the crude product was collected by filtration, thus avoiding any chromatographic separation. Further



a: R = CO_2Et, **b**: R = CN, **c**: R = CH_2Br, **d**: R = OEt, **e**: R = Ph, **f**: R = CH_2OH, **g**: NH_2

Scheme 1.

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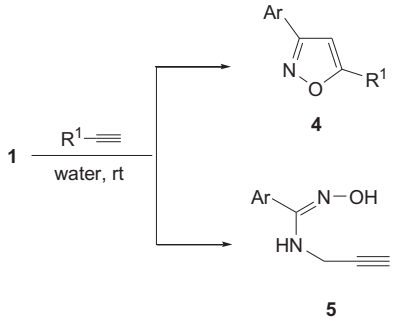
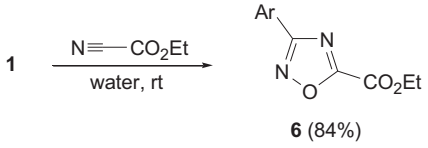
crystallisation gave analytically pure products **2**–**13** whose structures were established unambiguously on the basis of spectroscopic as well as spectrometric data.

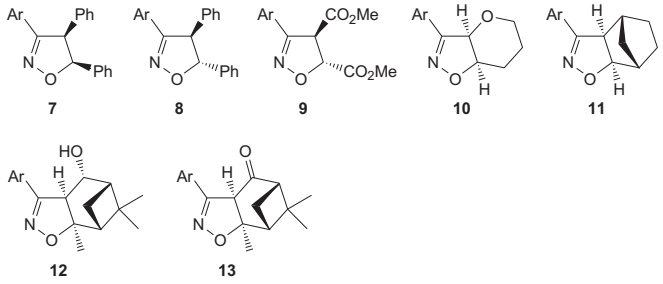


a: $R^1 = CO_2Me$, **b**: $R^1 = CH_2Cl$, **c**: $R^1 = Ph$, **d**: $R^1 = CH_2OH$, **e**: $R^1 = CH_2NH_2$

Scheme 2.



Scheme 3.



Scheme 4.

Table 1
Cycloaddition between nitrile oxide **1** and monosubstituted ethylenes in water[a]

Entry	R	Catalyst	Time (h)	Products and yields (%)[b]	
				2	**3**
1	CO_2Et	SDS[c]	2	84	—
2	CO_2Et	—	2	81	—
3	CN	SDS	2	85	—
4	CN	—	2.5	84	—
5	CH_2Br	SDS	2.5	69	—
6	CH_2Br	—	3	76	—
7	OEt	SDS	3	77	—
8	OEt	—	4	81	—
9	Ph	SDS	3	76	—
10	Ph	—	3	78	—
11	CH_2OH	SDS	4	0	—
12	CH_2OH	—	4	0	—
13[d]	CH_2OH	—	3	88	—
14	CH_2NH_2	SDS	4	0	—
15	CH_2NH_2	—	4	0	—
16[d]	CH_2NH_2	—	3	0	90

[a] At room temperature.
[b] Isolated product yield after crystallisation with diisopropyl ether.
[c] Sodium dodecylsulfate.
[d] In 4.0 M aqueous sodium chloride.

Table 2
Cycloaddition between nitrile oxide **1** and monosubstituted acetylenes in water[a]

Entry	R^1	Catalyst	Time (h)	Products and yields (%)[b]	
				4	**5**
1	CO_2Me	SDS[c]	1.5	88	—
2	CO_2Me	—	1.5	83	—
3	CH_2Cl	SDS	2.5	63	—
4	CH_2Cl	—	2.5	72	—
5	Ph	SDS	2.5	71	—
6	Ph	—	3	78	—
7	CH_2OH	SDS	4	0	—
8	CH_2OH	—	4	0	—
9[d]	CH_2OH	—	2.5	83	—
10	CH_2NH_2	SDS	4	0	—
11	CH_2NH_2	—	4	0	—
12[d]	CH_2NH_2	—	2.5	—	87

[a] At room temperature.
[b] Isolated product yield after crystallisation with diisopropyl ether.
[c] Sodium dodecylsulfate.
[d] In 4.0 M aqueous sodium chloride.

Table 3
Cycloaddition between nitrile oxide **1** and bi- or trisubstituted ethylenes in boiling water

Entry	Ethylene	Product	Time (h)	Product yield (%)[a]
1	*cis*-Stilbene	**7**	2	88
2	*trans*-Stilbene	**8**	2.5	84
3	Dimethylfumarate	**9**	3	76
4	1,4,5,6-Tetrahydropyran	**10**	2	67
5	Norbornene	**11**	2	85
6	(*S*)-*cis*-Verbenol	**12**[b]	3.5	89
7	(1*S*)-(−)-Verbenone	**13**[b]	3	91

[a] Isolated product yield after crystallisation with diisopropyl ether.
[b] Enantiomeric excess was >95:5 as determined by ^{1}H NMR in the presence of tris [heptafluoropropyl-hydroxymethylene-(+)-camphorato]europium-(III).

As far as monosubstituted ethylenic dipolarophiles were concerned (Scheme 1, Table 1) several issues deserve to be highlighted. First, it can be noted that the extent of cycloaddition is satisfactory provided that the mentioned dipolarophilic counterparts are liquids, which are insoluble or sparingly soluble in water. This finding is substantiated by the fact that no reaction occurred in the presence of water-soluble dipolarophiles like allyl alcohol (Table 1, entries 11, 12) and allylamine (Table 1, entries 14, 15) since in these latter two cases unreacted **1** was recovered. It is likely that nitrile oxide cycloadditions in water take place due to the hydrophobic effect.[11] A fully soluble reactant (dipolarophile) cannot be forced in a close space with **1** and by consequence a fruitful reaction is ruled out. To circumvent this solubility problem, we reasoned that aqueous solutions of salts, which enhance the ionic strength of the reaction medium would be able to squeeze out the (dipolarophilic) organic liquid thus allowing reaction with **1**. Thus, both reactions with allyl alcohol and allylamine were repeated in 4 M aqueous sodium chloride at room temperature. While allyl alcohol behaves as a good dipolarophile in these conditions giving the desired isoxazoline in 88% yield (Table 1, entry 13), the marked nucleophilic character of allylamine precluded the formation of the corresponding cycloadduct, instead giving the open-chain product **3** (Table 1, entry 16). As a further remark concerning the present nitrile oxide cycloadditions with monosubstituted ethylenes, the regioselectivity issue occupies a prominent place. It can be noted that only the 5-substituted isoxazolines **2** were formed from these reactions. This general behaviour is expected on the basis of the predicted energies and shapes of the FMO's involved in the cycloadditions.[12] It can be that in the case of electron-rich dipolarophiles the LUMO-dipole controlled process, which works in vacuo (e.g., within solvents with a low dielectric constant) may be reinforced in water due to the lesser hydrogen-bonding stabilisation of dipolarophiles FMO's with respect to that of the nitrile oxide.[13] With electron-poor dipolarophiles, the known nitrile oxide-HOMO control[12] should

also work in water due to the comparable stabilisation of both reactants FMO's.[13] In fact, we observed short reaction times irrespective of the electronic features of the dipolarophile. In some control experiments, ethyl acrylate and ethylvinyl ether were submitted to reaction with **1** in boiling carbon tetrachloride obtaining the corresponding cycloadducts **2a** and **2d** after 7 h.[14]

Due to the ability of some surfactants to speed-up 1,3-DC in water,[15,16] all the above reactions involving monosubstituted alkenyl dipolarophiles were also performed in the presence of sodium dodecylsulfate (SDS). By setting the SDS concentration as 15 mM, the formation of micelles can be expected, provided that the critical micellar concentration (CMC) of SDS is known to be 8.2 mM in water.[15] Close inspection of the reaction times reported in Table 1 reveal that a mechanistic picture involving some kind of micellar catalysis can be ruled out, i.e., the presence of SDS did not enhance significantly reaction times.

All the above considerations may be roughly applied to monosubstituted acetylenic dipolarophiles as can be inferred from both Scheme 2 and Table 2.

In order to complete the picture concerning the reactivity of **1** towards monosubstituted dipolarophiles, our attention was turned to ethylcyanoformate as a valuable heterodipolarophile (Scheme 3). After 2 h at room temperature the expected 1,2,4-oxadiazole **6** was obtained in 84% yield.

The results described and discussed up to this point show the ease of reaction between **1** and monosubstituted dipolarophiles. However, when attempting the reaction between **1** and norbornene under the same conditions, unchanged reactants were recovered. It could be likely that enthalpic factors are responsible for this disappointing outcome. Thus, we decided to submit bi- and trisubstituted ethylenes to reaction with **1** in boiling water. As can be seen from Table 3, isolation yields of products **7**–**13** (Scheme 4) were quite satisfactory in these latter conditions. The obtainment of isoxazolines **7**–**9** as single diastereoisomers is particularly significant since it points out the concerted nature of nitrile oxide 1,3-DC in water, i.e., the stereochemistry of the corresponding 1,2-disubstituted ethylenes is retained through the 1,3-DC's (Table 3, entries 1–3).

As a further step of the present work, two naturally-occurring oxygenated monoterpenes of the pinane family, namely (*S*)-*cis*-verbenol and (1*S*)-(−)-verbenone, were reacted with **1** giving cycloadducts **12** and **13**, respectively, as single diastereoisomers in the enantiopure form (Table 3, entries 6, 7 and Table 3, footnote b). Structures **12** and **13** were assigned on the basis of NOESY experiments having observed NOE enhancement between H and H_{A-C} as depicted in Fig. 1, in the same way to that previously found onto similar annulated pyrazoles.[17]

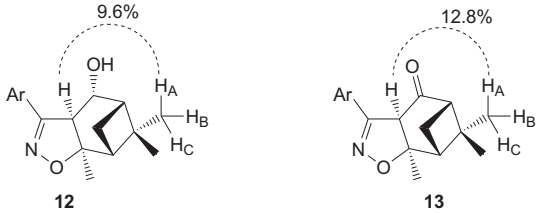


Fig. 1. NOE enhancements for products **12** and **13**.

In these latter two cases, the severe steric hindrance exerted by the two methyl groups placed onto the cyclobutyl ring of the dipolarophiles is responsible for the observed complete stereoselectivity.

3. Conclusions

The reactivity of stable nitrile oxide **1** towards a number of dipolarophiles has been exploited in pure water giving an array of simple as well as annulated isoxazolines. Water insoluble or sparingly soluble monosubstituted dipolarophiles react smoothly with **1** at room temperature, while the reactivity of water-soluble species is spurred by the presence of sodium chloride as an enhancer of the reaction medium ionic strength. The presence of SDS as a surfactant in the reaction mixture did not reduce significantly the reaction times. Isoxazolines **7**–**9** confirm the concerted nature of nitrile oxide cycloadditions in water, while enantiopure products **12** and **13** were obtained through complete diastereofacial-selective cycloadditions.

4. Experimental section

4.1. General

Melting points were determined on a Büchi apparatus in open tubes and are uncorrected. IR spectra were recorded on a Perkin–Elmer 1725 X spectrophotometer. Mass spectra were determined on a VG-70EQ apparatus. ^{1}H NMR (300 MHz) and ^{13}C NMR (75 MHz) spectra were taken with a Bruker AMX 300 instrument (in $CDCl_3$ solutions at room temperature). Chemical shifts are given as parts per million from tetramethylsilane. Coupling constants (*J*) values are given in hertz and are quoted to ±0.1 Hz consistently with NMR machine accuracy. NOESY experiments were performed by setting the following parameters: relaxation delay (d1) 2 s, irradiation power (dl2) 74 dB and total irradiation time (for each signal) 1.8 s. Optical rotations were recorded on a Perkin–Elmer 241 polarimeter at the sodium D-line at 25 °C.

4.2. Reaction between nitrile oxide 1 and monosubstituted dipolarophiles in water: general procedure

A mixture of **1** (0.12 g, 0.52 mmol) and the appropriate monosubstituted dipolarophile (0.78 mmol) in water (3.5 mL) was mechanically shaken at room temperature for the time indicated in Tables 1 and 2. The resulting mixture was filtered, the solid material was washed with water (5 mL) and dried in vacuo. Further crystallisation with diisopropyl ether gave pure **2**, **4** or **6**.

4.2.1. 3-(2,4,6-Trimethyl-3,5-dichloro)phenyl-5-ethoxycarbonyl-4,5-dihydroisoxazole ***2a***. White powder, mp 135–137 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ=1.35 (3H, t, *J*=7.1), 2.29 (6H, s), 2.53 (3H, s), 3.38–3.43 (2H, m), 4.30 (2H, q, *J*=7.1), 5.17 ppm (1H, dd, *J*=7.7, 2.0); ^{13}C NMR (75 MHz, $CDCl_3$): δ=16.7 (q), 18.0 (q), 20.2 (q), 44.1 (t), 46.6 (t), 85.9 (d), 126.0 (s), 130.6 (s), 133.7 (s), 136.2 (s), 156.5 (s), 167.1 ppm (s); IR (Nujol): ν=1740 cm^{-1}; MS: *m*/*z*: 329 [M$^+$]; elemental analysis calcd (%) for $C_{15}H_{17}Cl_2NO_3$: C 54.56, H 5.19, N 4.24; found: C 54.60, H 5.22, N 4.29.

4.2.2. 3-(2,4,6-Trimethyl-3,5-dichloro)phenyl-5-cyano-4,5-dihydroisoxazole ***2b***. White powder, mp 110–113 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ=2.37 (6H, s), 2.55 (3H, s), 3.42 (1H, dd, *J*=11.6, 3.3), 3.58 (1H, dd, *J*=11.6, 7.2), 5.42 ppm (1H, dd, *J*=7.2, 3.3); ^{13}C NMR (75 MHz, $CDCl_3$): δ=18.2 (q), 19.8 (q), 44.0 (t), 72.4 (d), 127.2 (s), 133.6 (s), 134.4. (s), 137.8 (s), 156.6 (s), 176.9 ppm (s); IR (Nujol): ν=2250 cm^{-1}; MS: *m*/*z*: 282 [M$^+$]; elemental analysis calcd (%) for $C_{13}H_{12}Cl_2N_2O$: C 55.14, H 4.27, N 9.89; found: C 55.18, H 4.30, N 9.92.

4.2.3. 3-(2,4,6-Trimethyl-3,5-dichloro)phenyl-5-bromomethyl-4,5-dihydroisoxazole ***2c***. Pale yellow powder, mp 128–130 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ=2.32 (6H, s), 2.54 (3H, s), 3.13 (1H, dd, *J*=17.9, 7.4), 3.26 (1H, dd, *J*=17.9, 10.4), 3.58 (1H, dd, *J*=10.5, 7.5), 3.65 (1H, dd, *J*=10.5, 4.1), 4.95–5.10 ppm (1H, m); ^{13}C NMR (75 MHz, $CDCl_3$): δ=17.7 (q), 18.4 (q), 32.6 (t), 43.2 (t), 78.7 (d), 127.9 (s), 132.6 (s), 133.2 (s), 135.2 (s), 156.0 ppm (s); IR (Nujol): ν=680 cm^{-1}; MS: *m*/*z*:

350 [M^+]; elemental analysis calcd (%) for $C_{13}H_{14}BrCl_2NO$: C 44.48, H 4.02, N 3.99; found: C 44.52, H 3.98, N 4.04.

4.2.4. 3-(2,4,6-Trimethyl-3,5-dichloro)phenyl-5-ethoxy-4,5-dihydroisoxazole ***2d***. White powder, mp 106–109 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ=1.29 (3H, t, J=7.1), 2.32 (6H, s), 2.57 (3H, s), 2.95 (1H, dd, J=17.8, 1.2), 3.26 (1H, dd, J=17.8, 6.3), 3.68 (1H, dq, J=14.2, 7.0), 3.98 (1H, dq, J=14.2, 7.2), 5.70 ppm (1H, dd, J=6.3, 1.2); ^{13}C NMR (75 MHz, $CDCl_3$): δ=15.02 (q), 18.0 (q), 18.9 (q), 45.9 (t), 63.7 (t), 102.4 (d), 128.8 (s), 133.3 (s), 133.5 (s), 135.5 (s), 157.7 ppm (s); IR (Nujol): ν=1140 cm^{-1}; MS: m/z: 301 [M^+]; elemental analysis calcd (%) for $C_{14}H_{17}Cl_2NO_2$: C 55.64, H 5.67, N 4.63; found: C 55.60, H 5.70, N 4.67.

4.2.5. 3-(2,4,6-Trimethyl-3,5-dichloro)phenyl-5-phenyl-4,5-dihydroisoxazole ***2e***. Pale yellow powder, mp 91–92 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ=2.28 (6H, s), 2.56 (3H, s), 3.09 (1H, dd, J=17.4, 8.3), 3.56 (1H, dd, J=17.4, 10.9), 5.82 (1H, dd, J=10.9, 8.3), 7.34–7.43 ppm (5H, m); ^{13}C NMR (75 MHz, $CDCl_3$): δ=18.1 (q), 18.9 (q), 47.6 (t), 82.1 (d), 125.6 (d), 128.3 (d), 128.8 (d), 133.2 (s), 133.6 (s), 135.5 (s), 140.7 (s), 156.5 ppm (s); IR (Nujol): ν=1950, 1880 cm^{-1}; MS: m/z: 333 [M^+]; elemental analysis calcd (%) for $C_{18}H_{17}Cl_2NO$: C 64.68, H 5.13, N 4.19; found: C 64.71, H 5.11, N 4.22.

4.2.6. 3-(2,4,6-Trimethyl-3,5-dichloro)phenyl-5-methoxycarbonylisoxazole ***4a***. White powder, mp 111–112 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ=2.16 (6H, s), 2.55 (3H, s), 4.02 (3H, s), 6.87 ppm (1H, s); ^{13}C NMR (75 MHz, $CDCl_3$): δ=18.3 (q), 18.8 (q), 43.8 (q), 107.8 (d), 127.6 (s), 128.7 (s), 133.2 (s), 133.8 (s), 134.1 (s), 162.1 (s), 168.0 ppm (s); IR (Nujol): ν=1730 cm^{-1}; MS: m/z: 313 [M^+]; elemental analysis calcd (%) for $C_{14}H_{13}Cl_2NO_3$: C 53.52, H 4.17, N 4.46; found: C 53.57, H 4.20, N 4.49.

4.2.7. 3-(2,4,6-Trimethyl-3,5-dichloro)phenyl-5-chloromethylisoxazole ***4b***. White powder, mp 76–78 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ=2.16 (6H, s), 2.55 (3H, s), 4.69 (2H, s), 6.25 ppm (1H, s); ^{13}C NMR (75 MHz, $CDCl_3$): δ=18.7 (q), 19.1 (q), 34.4 (t), 105.0 (d), 128.4 (s), 133.6 (s), 133.9 (s), 135.8 (s), 162.3 (s), 168.3 ppm (s); IR (Nujol): ν=775 cm^{-1}; MS: m/z: 303 [M^+]; elemental analysis calcd (%) for $C_{13}H_{12}Cl_3NO$: C 51.26, H 3.97, N 4.60; found: C 51.23, H 4.00, N 4.56.

4.2.8. 3-(2,4,6-Trimethyl-3,5-dichloro)phenyl-5-phenylisoxazole ***4c***. Pale yellow powder, mp 104–105 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ=2.23 (6H, s), 2.58 (3H, s), 6.44 (1H, s), 7.48–7.83 ppm (5H, m); ^{13}C NMR (75 MHz, $CDCl_3$): δ=18.5 (q), 18.8 (q), 107.7 (d), 123.9 (d), 125.2 (d), 128.2 (d), 128.7 (s), 132.6 (s), 133.4 (s), 133.7 (s), 137.8 (s), 156.2 (s), 163.7 ppm (s); IR (Nujol): ν=1970, 1840 cm^{-1}; MS: m/z: 331 [M^+]; elemental analysis calcd (%) for $C_{18}H_{15}Cl_2NO$: C 65.08, H 4.55, N 4.22; found: C 65.11, H 4.52, N 4.27.

4.2.9. 3-(2,4,6-Trimethyl-3,5-dichloro)phenyl-5-ethoxycarbonyl-1,2,4-oxadiazole ***6***. White powder, mp 167–169 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ=1.49 (3H, t, J=7.0), 2.17 (6H, s), 2.53 (3H, s), 4.57 ppm (2H, q, J=7.0); ^{13}C NMR (75 MHz, $CDCl_3$): δ=18.5 (q), 19.0 (q), 19.8 (q), 44.0 (t), 126.1 (s), 127.2 (s), 133.6 (s), 156.6 (s), 168.2 (s), 176.9 (s) ppm (s); IR (Nujol): ν=1740 cm^{-1}; MS: m/z: 328 [M^+]; elemental analysis calcd (%) for $C_{14}H_{14}Cl_2N_2O_3$: C 51.08, H 4.29, N 8.51; found: C 51.11, H 4.29, N 8.57.

4.3. Reaction between nitrile oxide 1 and monosubstituted dipolarophiles in water and in the presence of SDS: general procedure

A mixture of **1** (0.12 g, 0.52 mmol), the appropriate monosubstituted dipolarophile (0.78 mmol) and sodium dodecylsulfate (SDS) (15.1 mg, 52.4 μmol) in water (3.5 mL) was mechanically shaken at room temperature for the time indicated in Tables 1 and 2. The mixture was extracted with dichloromethane (2×10 mL), the organic layer was washed with water (3×10 mL) and dried over sodium sulfate. Evaporation at reduced pressure gave a residue, which was crystallised with diisopropyl ether giving pure **2**, **4** or **6**.

4.4. Reaction between nitrile oxide 1 and monosubstituted dipolarophiles in aqueous 4 M sodium chloride: general procedure

A mixture of **1** (0.12 g, 0.52 mmol), the appropriate monosubstituted dipolarophile (0.78 mmol) in 4 M aqueous sodium chloride (3.5 mL) was mechanically shaken at room temperature for the time indicated in Table 1, entries 13, 16 and Table 2, entries 9, 12. The resulting mixture was filtered, the solid material was washed with water (2×5 mL) and dried in vacuo. Further crystallisation with diisopropyl ether gave pure **2**–**5**.

4.4.1. 3-(2,4,6-Trimethyl-3,5-dichloro)phenyl-5-hydroxymethyl-4,5-dihydroisoxazole ***2f***. White powder, mp 120–121 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ=2.08–2.20 (1H, br s), 2.29 (6H, s), 2.53 (3H, s), 3.08 (1H, dd, J=17.8, 9.3), 3.17 (1H, dd, J=17.8, 11.1), 3.68 (1H, dd, J=12.3, 3.8), 3.95 (1H, dd, J=12.3, 2.9), 4.85–4.98 ppm (1H, m); ^{13}C NMR (75 MHz, $CDCl_3$): δ=18.3 (q), 18.8 (q), 43.6 (t), 48.8 (t), 75.2 (d), 127.7 (s), 132.9 (s), 133.7 (s), 134.1 (s), 156.8 ppm (s); IR (Nujol): ν=3420 cm^{-1}; MS: m/z: 287 [M^+]; elemental analysis calcd (%) for $C_{13}H_{15}Cl_2NO_2$: C 54.18, H 5.25, N 4.86; found: C 54.22, H 5.22, N 4.90.

4.4.2. 3-(2,4,6-Trimethyl-3,5-dichloro)phenyl-5-hydroxymethylisoxazole ***4d***. White powder, mp 97–99 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ=2.2–2.30 (1H, br s, overlapping), 2.25 (6H, s), 2.57 (3H, s), 3.14 (1H, d, J=17.6), 3.23 (1H, d, J=17.6), 6.51 ppm (1H, s); ^{13}C NMR (75 MHz, $CDCl_3$): δ=18.1 (q), 19.2 (q), 43.8 (t), 106.5 (d), 127.7 (s), 133.0 (s), 133.7 (s), 135.6 (s), 158.8 (s), 163.4 ppm (s); IR (Nujol): ν=3410 cm^{-1}; MS: m/z: 285 [M^+]; elemental analysis calcd (%) for $C_{13}H_{13}Cl_2NO_2$: C 54.57, H 4.58, N 4.89; found: C 54.60, H 4.60, N 4.93.

4.4.3. 1-Allylamino-(2,4,6-trimethyl-3,5-dichloro)benzaldehyde oxime ***3***. Yellow powder, mp 57–59 °C; ^{1}H NMR (300 MHz, $CDCl_3$/D_2O): δ=2.31 (6H, s), 2.52 (3H, s), 3.30–3.40 (2H, m), 5.00–5.13 (2H, m), 5.54–5.72 ppm (1H, m); IR (Nujol): ν=3520, 3375 cm^{-1}; MS: m/z: 286 [M^+]; elemental analysis calcd (%) for $C_{13}H_{16}Cl_2N_2O$: C 54.37, H 5.62, N 9.75; found: C 54.41, H 5.59, N 9.71.

4.4.4. 1-Propargylamino-(2,4,6-trimethyl-3,5-dichloro)benzaldehyde oxime ***5***. Yellow powder, mp 66–67 °C; ^{1}H NMR (300 MHz, $CDCl_3$/D_2O): δ=1.27 (1H, t, J=1.4), 2.27 (6H, s), 2.54 (3H, s), 3.42 ppm (2H, d, J=1.5); IR (Nujol): ν=3535, 3355 cm^{-1}; MS: m/z: 284 [M^+]; elemental analysis calcd (%) for $C_{13}H_{14}Cl_2N_2O$: C 54.75, H 4.95, N 9.82; found: C 54.77, H 4.95, N 9.79.

4.5. Reaction between nitrile oxide 1 and di- or trisubstituted ethylenes dipolarophiles in boiling water: general procedure

A mixture of **1** (0.12 g, 0.52 mmol), the appropriate di- or trisubstituted dipolarophile (0.78 mmol) in water (3.5 mL) was refluxed for the time indicated in Table 3 under vigorous mechanical shaking. The resulting mixture was cooled at room temperature and filtered. The solid material was washed with water (2×5 mL) and dried in vacuo. Further crystallisation with diisopropyl ether gave pure **7**–**13**, respectively.

4.5.1. 3-(2,4,6-Trimethyl-3,5-dichloro)phenyl-4(R),5(S*)-diphenyl-4,5-dihydroisoxazole* ***7***. White powder, mp 89–90 °C; ^{1}H NMR

(300 MHz, $CDCl_3$): δ=2.28 (6H, s), 2.48 (3H, s), 4.74 (1H, d, J=9.6), 6.15 (1H, d, J=9.6), 6.88–7.26 ppm (10H, m); ^{13}C NMR (75 MHz, $CDCl_3$): δ=18.3 (q), 18.9 (q), 66.2 (d), 88.0 (d), 123–129 (m), 133.1 (s), 134.3 (s), 135.8 (s), 136.5 (s), 138.9 (s), 141.0 (s), 158.0 ppm (s); IR (Nujol): ν=1970, 1840 cm^{-1}; MS: m/z: 409 [M^+]; elemental analysis calcd (%) for $C_{24}H_{21}Cl_2NO$: C 70.25, H 5.16, N 3.41; found: C 70.26, H 5.19, N 3.48.

4.5.2. 3-(2,4,6-Trimethyl-3,5-dichloro)phenyl-4(R),5(R*)-diphenyl-4,5-dihydroisoxazole* ***8****.* White powder, mp 114–116 °C; ^1H NMR (300 MHz, $CDCl_3$): δ=1.97 (6H, s), 2.47 (3H, s), 4.43 (1H, d, J=5.6), 6.06 (1H, d, J=5.6), 7.19–7.54 ppm (10H, m); ^{13}C NMR (75 MHz, $CDCl_3$): δ=18.2 (q), 19.0 (q), 66.9 (d), 88.5 (d), 124–129 (m), 133.5 (s), 133.9 (s), 135.4 (s), 136.3 (s), 137.4 (s), 140.7 (s), 158.3 ppm (s); IR (Nujol): ν=1990, 1820 cm^{-1}; MS: m/z: 409 [M^+]; elemental analysis calcd (%) for $C_{24}H_{21}Cl_2NO$: C 70.25, H 5.16, N 3.41; found: C 70.28, H 5.16, N 3.45.

4.5.3. 3-(2,4,6-Trimethyl-3,5-dichloro)phenyl-4(R),5(R*)-bis-methoxycarbonyl-4,5-dihydroisoxazole* ***9****.* Pale yellow powder, mp 124–127 °C; ^1H NMR (300 MHz, $CDCl_3$): δ=2.24 (6H, s), 2.54 (3H, s), 3.63 (3H, s), 3.88 (3H, s), 4.63 (1H, d, J=6.4), 5.62 ppm (1H, d, J=6.4); ^{13}C NMR (75 MHz, $CDCl_3$): δ=18.3 (q), 19.0 (q), 53.2 (q), 60.1 (t), 81.0 (d), 126.5 (s), 133.5 (s), 133.7 (s), 136.2 (s), 153.0 (s), 166.7 (s), 169.2 ppm (s); IR (Nujol): ν=1735 cm^{-1}; MS: m/z: 373 [M^+]; elemental analysis calcd (%) for $C_{16}H_{17}Cl_2NO_5$: C 51.35, H 4.58, N 3.74; found: C 51.35, H 4.61, N 3.79.

4.5.4. 1-(2,4,6-Trimethyl-3,5-dichloro)phenyl-3a(R),4,5,6,7,7a(R*)-hexahydro-pyrano[4,5-b]isoxazole* ***10****.* Pale yellow powder, mp 79–81 °C; ^1H NMR (300 MHz, $CDCl_3$): δ=1.50–2.60 (4H, m, overlapping), 2.25 (6H, s), 2.54 (3H, s), 3.45–3.60 (2H, m), 3.93 (1H, d, J=5.7), 5.74 ppm (1H, d, J=5.7); ^{13}C NMR (75 MHz, $CDCl_3$): δ=18.5 (q), 19.0 (q), 21.8 (t), 25.3 (t), 48.7 (t), 62.8 (d), 100.0 (d), 127.7 (s), 133.1 (s), 134.0 (s), 135.8 (s), 161.4 ppm (s); IR (Nujol): ν=1030 cm^{-1}; MS: m/z: 313 [M^+]; elemental analysis calcd (%) for $C_{15}H_{17}Cl_2NO_2$: C 57.34, H 5.45, N 4.46; found: C 57.35, H 5.48, N 4.50.

4.5.5. 1-(2,4,6-Trimethyl-3,5-dichloro)phenyl-3a(R),7a(R*)-bicyclo [2.2.1]heptano[4,5-c]isoxazole* ***11****.* White powder, mp 88–89 °C; ^1H NMR (300 MHz, $CDCl_3$): δ=0.80–1.58 (6H, m), 2.23 (6H, s), 2.81 (2H, s), 2.55 (3H, s), 3.44 (1H, dd, J=6.1, 4.4), 5.27 ppm (1H, d, J=6.1, 4.8); ^{13}C NMR (75 MHz, $CDCl_3$): δ=18.1 (q), 18.8 (q), 22.8 (t), 42.4 (d), 49.2 (t), 55.1 (d), 80.8 (d), 126.6 (s), 128.7 (s), 133.1 (s), 135.5 (s), 156.2 ppm (s); IR (Nujol): ν=850, 730 cm^{-1}; MS: m/z: 323 [M^+]; elemental analysis calcd (%) for $C_{17}H_{19}Cl_2NO$: C 62.97, H 5.91, N 4.32; found: C 63.01, H 5.95, N 4.28.

4.5.6. 1-(2,4,6-Trimethyl-3,5-dichloro)phenyl-3a(R)-methyl-5,5-dimethyl-7(S)-hydroxy-7a(S)-bicyclo [3.1.1]heptano[4,5-c]isoxazole ***12****.* Clear prisms, mp 147–148 °C; $[\alpha]_D^{25}$ −31.0 (c 0.10, CH_2Cl_2); ^1H NMR (300 MHz, $CDCl_3/D_2O$): δ=1.11 (3H, s), 1.35 (3H, s), 1.56 (3H, s), 2.0–2.6 (4H, m, overlapping), 2.32 (6H, s), 2.54 (3H, s), 3.29 (1H, d, J=3.3), 3.90 ppm (1H, dd, J=3.3, 2.0); ^{13}C NMR (75 MHz, $CDCl_3/D_2O$): δ=18.5 (q), 19.0 (q), 19.5 (q), 25.0 (q), 25.3 (t), 27.0 (q), 37.8 (s), 46.9 (d), 50.0 (d), 61.7 (d), 73.0 (d), 89.8 (s), 128.6 (s), 133.5 (s), 134.2 (s), 135.6 (s), 157.2 ppm (s); IR (Nujol): ν=3420 cm^{-1}; MS: m/z: 381 [M^+]; elemental analysis calcd (%) for $C_{20}H_{25}Cl_2NO_2$: C 62.83, H 6.59, N 3.66; found: C 62.86, H 6.61, N 3.70.

4.5.7. 1-(2,4,6-Trimethyl-3,5-dichloro)phenyl-3a(R)-methyl-5,5-dimethyl-7-oxo-7a(S)-bicyclo[3.1.1] heptano[4,5-c]isoxazole ***13****.* Clear prisms, mp 131–134 °C; $[\alpha]_D^{25}$ −63.3 (c 0.13, CH_2Cl_2); ^1H NMR (300 MHz, $CDCl_3$): δ=0.96 (3H, s), 1.48 (3H, s), 1.64 (3H, s), 2.12 (3H, s), 2.25 (3H, s), 2.33 (3H, s), 2.42–2.69 (4H, m, overlapping), 3.67 ppm (1H, s); ^{13}C NMR (75 MHz, $CDCl_3$): δ=18.4 (q), 18.8 (q), 19.5 (q), 24.9 (q), 25.4 (t), 27.6 (q), 37.7 (s), 46.6 (d), 49.5 (d), 67.1 (d), 92.4 (s), 127.7 (s), 133.4 (s), 134.6 (s), 135.1 (s), 156.0 (s), 163.1 ppm (s); IR (Nujol): ν=1690 cm^{-1}; MS: m/z: 379 [M^+]; elemental analysis calcd (%) for $C_{20}H_{23}Cl_2NO_2$: C 63.16, H 6.10, N 3.68; found: C 63.19, H 6.12, N 3.72.

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14. A solution of **1** (0.20 g, 0.86 mmol) and ethyl acrylate (90 mg, 0.90 mmol) or ethylvinyl ether (64 mg, 0.90 mmol) in carbon tetrachloride (3.5 mL) was refluxed for 7 h. Evaporation of the solvent gave a residue, which was chromatographed on a silica gel column with ethyl acetate/hexane 1:1. Further crystallisation with diisopropyl ether gave pure **2a** (0.21 g, 72%) or **2d** (0.18 g, 68%), respectively.
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