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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 dodecyl sulfate was also tested as potential micellar catalyst.

Introduction

During the last two decades, 1,3-dipolar cycloadditions (1,3-DC) in water or aqueous media have been recognized as a 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 focusing 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

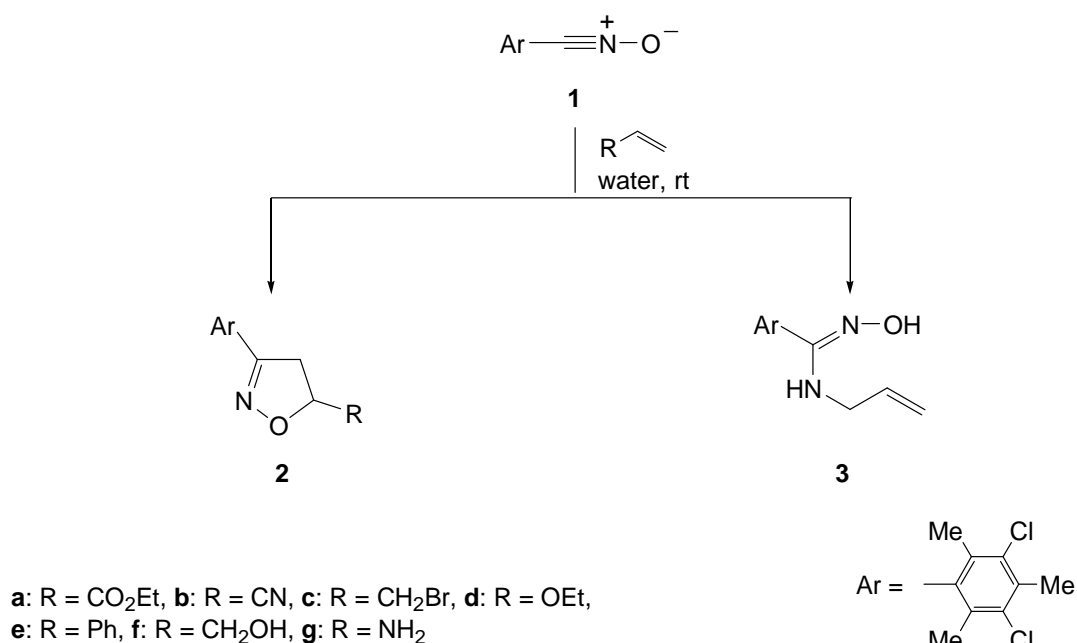
both a mechanistic⁶ and synthetic⁷ standpoint. To date, however, no systematic studies of stable nitrile oxide 1,3-DC in pure water have been performed. In fact, nitrile oxides are almost always generated *in situ* from the whole array of their precursors⁵ which are usually fully insoluble in water. As a result, an organic cosolvent is very often required giving rise to a variety of experimental conditions spanning from homogeneous⁸ 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.

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

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 control¹² 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.



Scheme 1

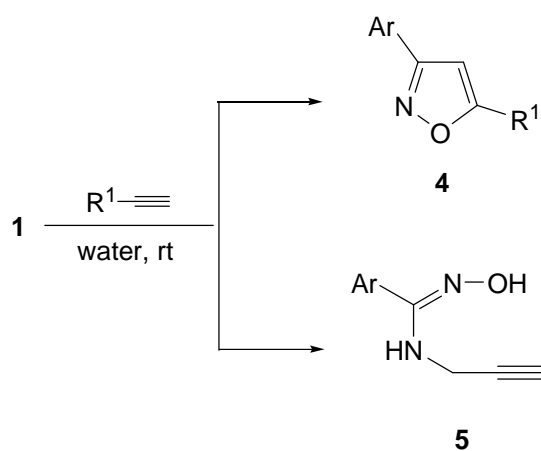
Table 1. Cycloaddition between nitrile oxide **1** and monosubstituted ethylenes in water.^a

Entry	R	Catalyst	Time (h)	Products and yields (%) ^b	
				2	3
1	CO ₂ Et	SDS ^c	2	84	—
2	CO ₂ Et	—	2	81	—
3	CN	SDS	2	85	—
4	CN	—	2.5	84	—
5	CH ₂ Br	SDS	2.5	69	—
6	CH ₂ Br	—	3	76	—
7	OEt	SDS	3	77	—
8	OEt	—	4	81	—
9	Ph	SDS	3	76	—
10	Ph	—	3	78	—
11	CH ₂ OH	SDS	4	0	—
12	CH ₂ OH	—	4	0	—
13 ^d	CH ₂ OH	—	3	88	—
14	CH ₂ NH ₂	SDS	4	0	—
15	CH ₂ NH ₂	—	4	0	—
16 ^d	CH ₂ NH ₂	—	3	0	90

^aAt room temperature. ^bIsolated product yield after crystallisation with diisopropyl ether.

^cSodium dodecylsulfate. ^dIn 4.0 M aqueous sodium chloride.

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



a: R¹ = CO₂Me, b: R¹ = CH₂Cl, c: R¹ = Ph, d: R¹ = CH₂OH, e: R¹ = CH₂NH₂

Scheme 2

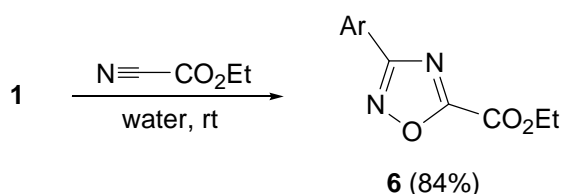
Table 2. Cycloaddition between nitrile oxide **1** and monosubstituted acetylenes in water.^a

Entry	R ¹	Catalyst	Time (h)	Products and yields (%) ^b	
				4	5
1	CO ₂ Me	SDS ^c	1.5	88	—
2	CO ₂ Me	—	1.5	83	—
3	CH ₂ Cl	SDS	2.5	63	—
4	CH ₂ Cl	—	2.5	72	—
5	Ph	SDS	2.5	71	—
6	Ph	—	3	78	—
7	CH ₂ OH	SDS	4	0	—
8	CH ₂ OH	—	4	0	—
9 ^d	CH ₂ OH	—	2.5	83	—
10	CH ₂ NH ₂	SDS	4	0	—
11	CH ₂ NH ₂	—	4	0	—
12 ^d	CH ₂ NH ₂	—	2.5	—	87

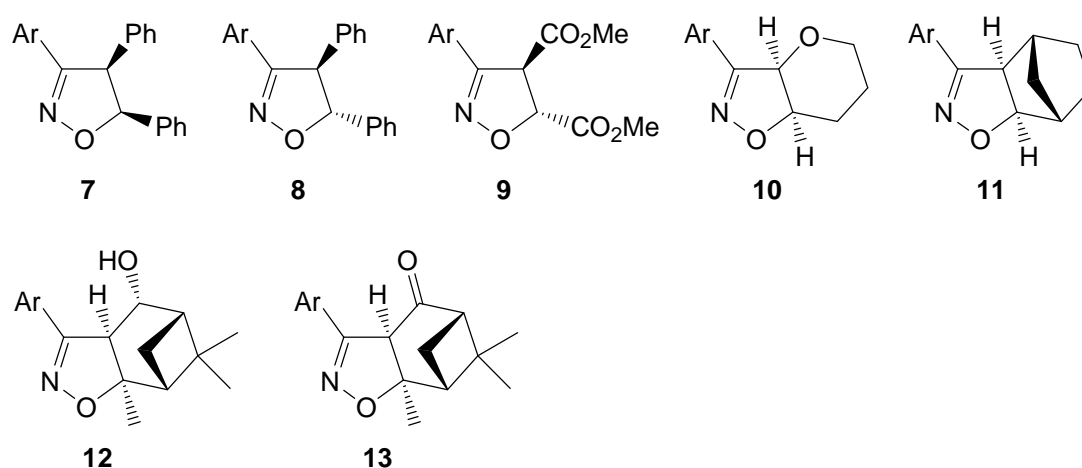
^aAt room temperature. ^bIsolated product yield after crystallisation with diisopropyl ether.

^cSodium dodecylsulfate. ^dIn 4.0 M aqueous sodium chloride.

In order to complete the picture concerning the reactivity of **1** toward 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.

**Scheme 3**

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).



Scheme 4

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

Entry	Ethylene	Product	Time (h)	Product yield (%) ^a
1	<i>cis</i> -Stilbene	7	2	88
2	<i>trans</i> -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	(<i>S</i>)- <i>cis</i> -Verbenol	12^b	3.5	89
7	(1 <i>S</i>)-(-)-Verbenone	13^b	3	91

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

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 Figure 1, in the same way to that previously found onto similar annulated pyrazoles.¹⁷

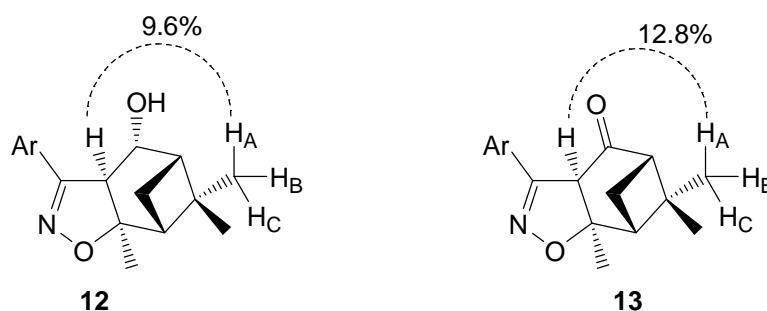


Figure 1

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.

Conclusions

The reactivity of stable nitrile oxide **1** toward 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 enhancer of the reaction medium ionic strength. The presence of SDS as 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. Elemental analysis were performed on a Perkin-Elmer 2400 CHN/O analyzer.

Experimental Section

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. ¹H NMR (300 MHz) and ¹³C NMR (75 MHz) spectra were taken with a Bruker AMX 300 instrument (in CDCl₃ solutions at room temperature). Chemical shifts are given as ppm from tetramethylsilane. Coupling constants (*J*) values are given in Hz 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.

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**.

3-(2,4,6-Trimethyl-3,5-dichloro)phenyl-5-ethoxycarbonyl-4,5-dihydroisoxazole **2a**: White powder, m.p. 135-137°C; ¹H NMR (300 MHz, CDCl₃): 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); ¹³C NMR (75 MHz, CDCl₃): 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): $\nu = 1740 \text{ cm}^{-1}$; 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.

3-(2,4,6-Trimethyl-3,5-dichloro)phenyl-5-cyano-4,5-dihydroisoxazole **2b**: White powder, m.p. 110-113°C; 1H NMR (300 MHz, $CDCl_3$): $\delta = 2.37$ (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, $CDCl_3$): $\delta = 18.2$ (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): $\nu = 2250 \text{ cm}^{-1}$; 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.

3-(2,4,6-Trimethyl-3,5-dichloro)phenyl-5-bromomethyl-4,5-dihydroisoxazole **2c**: Pale yellow powder, m.p. 128-130°C; 1H NMR (300 MHz, $CDCl_3$): $\delta = 2.32$ (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, $CDCl_3$): $\delta = 17.7$ (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): $\nu = 680 \text{ cm}^{-1}$; 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.

3-(2,4,6-Trimethyl-3,5-dichloro)phenyl-5-ethoxy-4,5-dihydroisoxazole **2d**: White powder, m.p. 106-109°C; 1H NMR (300 MHz, $CDCl_3$): $\delta = 1.29$ (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, $CDCl_3$): $\delta = 15.02$ (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): $\nu = 1140 \text{ cm}^{-1}$; 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.

3-(2,4,6-Trimethyl-3,5-dichloro)phenyl-5-phenyl-4,5-dihydroisoxazole **2e**: Pale yellow powder, m.p. 91-92°C; 1H NMR (300 MHz, $CDCl_3$): $\delta = 2.28$ (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, $CDCl_3$): $\delta = 18.1$ (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): $\nu = 1950, 1880 \text{ cm}^{-1}$; 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.

3-(2,4,6-Trimethyl-3,5-dichloro)phenyl-5-methoxycarbonylisoxazole **4a**: White powder, m.p. 111-112°C; 1H NMR (300 MHz, $CDCl_3$): $\delta = 2.16$ (6H, s), 2.55 (3H, s), 4.02 (3H, s), 6.87 ppm (1H, s); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 18.3$ (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): $\nu = 1730 \text{ cm}^{-1}$; 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.

3-(2,4,6-Trimethyl-3,5-dichloro)phenyl-5-chloromethylisoxazole **4b**: White powder, m.p. 76-78°C; ¹H NMR (300 MHz, CDCl₃): δ = 2.16 (6H, s), 2.55 (3H, s), 4.69 (2H, s), 6.25 ppm (1H, s); ¹³C NMR (75 MHz, CDCl₃): 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 C₁₃H₁₂Cl₃NO: C 51.26, H 3.97, N 4.60; found: C 51.23, H 4.00, N 4.56.

3-(2,4,6-Trimethyl-3,5-dichloro)phenyl-5-phenylisoxazole **4c**: Pale yellow powder, m.p. 104-105°C; ¹H NMR (300 MHz, CDCl₃): δ = 2.23 (6H, s), 2.58 (3H, s), 6.44 (1H, s), 7.48-7.83 ppm (5H, m); ¹³C NMR (75 MHz, CDCl₃): 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 C₁₈H₁₅Cl₂NO: C 65.08, H 4.55, N 4.22; found: C 65.11, H 4.52, N 4.27.

3-(2,4,6-Trimethyl-3,5-dichloro)phenyl-5-ethoxycarbonyl-1,2,4-oxadiazole **6**: White powder, m.p. 167-169°C; ¹H NMR (300 MHz, CDCl₃): δ = 1.49 (3H, t, *J* = 7.0), 2.17 (6H, s), 2.53 (3H, s), 4.57 ppm (2H, q, *J* = 7.0); ¹³C NMR (75 MHz, CDCl₃): 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 C₁₄H₁₄Cl₂N₂O₃: C 51.08, H 4.29, N 8.51; found: C 51.11, H 4.29, N 8.57.

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 x 10 mL), the organic layer was washed with water (3 x 10 mL) and dried over sodium sulfate. Evaporation at reduced pressure gave a residue which was crystallised with diisopropylether giving pure **2**, **4** or **6**.

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

A mixture of **1** (0.12 g, 0.52 mmol), the appropriate monosubstituted dipolarophile (0.78 mmol) in 4M 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 x 5 mL) and dried *in vacuo*. Further crystallisation with diisopropyl ether gave pure **2-5**.

3-(2,4,6-Trimethyl-3,5-dichloro)phenyl-5-hydroxymethyl-4,5-dihydroisoxazole **2f**: White powder, m.p. 120-121°C; ¹H NMR (300 MHz, CDCl₃): 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); ¹³C NMR (75 MHz, CDCl₃): 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 C₁₃H₁₅Cl₂NO₂: C 54.18, H 5.25, N 4.86; found: C 54.22, H 5.22, N 4.90.

3-(2,4,6-Trimethyl-3,5-dichloro)phenyl-5-hydroxymethylisoxazole **4d**: White powder, m.p. 97-99°C; ¹H NMR (300 MHz, CDCl₃): 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); ¹³C NMR (75 MHz, CDCl₃): 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 C₁₃H₁₃Cl₂NO₂: C 54.57, H 4.58, N 4.89; found: C 54.60, H 4.60, N 4.93.

1-Allylamino-(2,4,6-trimethyl-3,5-dichloro)benzaldehyde oxime **3**: Yellow powder, m.p. 57-59°C; ¹H NMR (300 MHz, CDCl₃/D₂O): 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 C₁₃H₁₆Cl₂N₂O: C 54.37, H 5.62, N 9.75; found: C 54.41, H 5.59, N 9.71.

1-Propargylamino-(2,4,6-trimethyl-3,5-dichloro)benzaldehyde oxime **5**: Yellow powder, m.p. 66-67°C; ¹H NMR (300 MHz, CDCl₃/D₂O): 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 C₁₃H₁₄Cl₂N₂O: C 54.75, H 4.95, N 9.82; found: C 54.77, H 4.95, N 9.79.

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 x 5 mL) and dried *in vacuo*. Further crystallisation with diisopropyl ether gave pure **7-13**, respectively.

3-(2,4,6-Trimethyl-3,5-dichloro)phenyl-4(*R**),5(*S**)-diphenyl-4,5-dihydroisoxazole **7**: White powder, m.p. 89-90°C; ¹H NMR (300 MHz, CDCl₃): 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); ¹³C NMR (75 MHz, CDCl₃): 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 C₂₄H₂₁Cl₂NO: C 70.25, H 5.16, N 3.41; found: C 70.26, H 5.19, N 3.48.

3-(2,4,6-Trimethyl-3,5-dichloro)phenyl-4(*R**),5(*R**)-diphenyl-4,5-dihydroisoxazole **8**: White powder, m.p. 114-116°C; ¹H NMR (300 MHz, CDCl₃): 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); ¹³C NMR (75 MHz, CDCl₃): 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 C₂₄H₂₁Cl₂NO: C 70.25, H 5.16, N 3.41; found: C 70.28, H 5.16, N 3.45.

3-(2,4,6-Trimethyl-3,5-dichloro)phenyl-4(*R**),5(*R**)-bis-methoxycarbonyl-4,5-dihydroisoxazole **9**: Pale yellow powder, m.p. 124-127°C; ¹H NMR (300 MHz, CDCl₃): 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); ¹³C NMR (75 MHz, CDCl₃): 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 C₁₆H₁₇Cl₂NO₅: C 51.35, H 4.58, N 3.74; found: C 51.35, H 4.61, N 3.79.

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, m.p. 79-81°C; ¹H NMR (300 MHz, CDCl₃): 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); ¹³C NMR (75 MHz, CDCl₃): 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 C₁₅H₁₇Cl₂NO₂: C 57.34, H 5.45, N 4.46; found: C 57.35, H 5.48, N 4.50.

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, m.p. 88-89°C; ¹H NMR (300 MHz, CDCl₃): 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); ¹³C NMR (75 MHz, CDCl₃): 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 C₁₇H₁₉Cl₂NO: C 62.97, H 5.91, N 4.32; found: C 63.01, H 5.95, N 4.28.

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, m.p. 147-148°C; [α]_D²⁵ = -31.0 (c = 0.10, CH₂Cl₂); ¹H NMR (300 MHz, CDCl₃/D₂O): 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); ¹³C NMR (75 MHz, CDCl₃/D₂O): 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 C₂₀H₂₅Cl₂NO₂: C 62.83, H 6.59, N 3.66; found: C 62.86, H 6.61, N 3.70.

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, m.p. 131-134°C; [α]_D²⁵ = -63.3 (c = 0.13, CH₂Cl₂); ¹H

NMR (300 MHz, CDCl₃): 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); ¹³C NMR (75 MHz, CDCl₃): 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 C₂₀H₂₃Cl₂NO₂: C 63.16, H 6.10, N 3.68; found: C 63.19, H 6.12, N 3.72.

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References

- [1] (a) Molteni, G. *Heterocycles* **2006**, *68*, 2177; (b) Butler, R. N.; Coyne, A. G.; *Chem. Rev.* **2010**, *110*, 6302; (c) Moulay, C.; Touati, A. *Compt. Rend. Chim.* **2010**, *13*, 1474.
- [2] Grundmann, C.; Richter, R. *J. Org. Chem.* **1967**, *32*, 2308.
- [3] (a) Bala, K.; Hailes, H. C. *Synthesis* **2005**, 3423; (b) Lubineau, A.; Bouchain, G.; Queneau, Y. *J. Chem. Soc., Perkin Trans. 1* **1995**, 2433; (c) Wijnen, J. W.; Steiner, R. A.; Engberts, J. B. F. N. *Tetrahedron Lett.* **1995**, *36*, 5389.
- [4] (a) Gil, M. V.; Arévalo, M. J.; López, Ó. *Synthesis* **2007**, 1589; (b) Moses, J. E.; Moorhouse, A. D. *Chem. Soc. Rev.* **2007**, *36*, 1249; (c) Meldal, M.; Tornøe, C. W. *Chem. Rev.* **2008**, *108*, 2952.
- [5] Belen'kii, L. I. *Nitrile Oxides, Nitrones and Nitronates in Organic Synthesis: Novel Strategies in Synthesis*, H. Feuer, Ed.; John Wiley & Sons Inc.: Hoboken, New Jersey, 2008, pp. 1-129.
- [6] Inoue, Y.; Araki, K.; Shiraishi, S. *Bull. Chem. Soc. Jpn.* **1991**, *64*, 3079.
- [7] (a) Rolhoff, J. C.; Robinson III, J.; Gardner, J. O. *Tetrahedron Lett.* **1992**, *33*, 3113; (b) Scobie, M.; Threadgill, M. D. *J. Org. Chem.* **1994**, *59*, 7008; (c) Mineno, T.; Miller, M. J. *J. Org. Chem.* **2003**, *68*, 6591; (d) Zerresen, A.; Jäschke, A. *J. Mol. Evol.* **2005**, *61*, 236.
- [8] Adembri, G.; Poli, M. L.; Sega, A. *J. Chem. Res.* **2003**, 126 (S).
- [9] Lee, G. A. *Synthesis* **1982**, 508.
- [10] Beltrame, P.; Veglio, C.; Simonetta, M. *J. Chem. Soc. B* **1967**, 867.
- [11] (a) Lazaridis, T. *Acc. Chem. Res.* **2001**, *34*, 931; (b) Breslow, R. *Acc. Chem. Res.* **1991**, *24*, 159.

- [12] (a) Houk, K. N.; Sims, J.; Duke, R. E.; Strozier, R. W.; George, J. K. *J. Am. Chem. Soc.* **1973**, *95*, 7287; (b) Houk, K. N.; Sims, J.; Watts, C. R.; Luskus, L. J. *J. Am. Chem. Soc.* **1973**, *95*, 7301; (c) Houk, K. N.; Caramella, P. *J. Am. Chem. Soc.* **1976**, *98*, 6397.
- [13] Curran, D. P.; Kim, B. H.; Piyasena, H. P.; Loncharic, R. J.; Houk, K. N. *J. Org. Chem.* **1987**, *52*, 2137.
- [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.
- [15] van Mersbergen, D.; Wijnen, J. W.; Engberts, J. B. F. N. *J. Org. Chem.* **1998**, *63*, 8801.
- [16] (a) Molteni, G.; Ponti, A.; Orlandi, M. *New J. Chem.* **2002**, *26*, 1340; (b) Molteni, G.; Orlandi, M.; Brogini, G. *J. Chem. Soc., Perkin Trans. 1* **2000**, 3742; (c) Chatterjee, A.; Hota, S. K.; Banerjee, M.; Bhattacharya, P. K. *Tetrahedron Lett.* **2010**, *51*, 6700.
- [17] De Benassuti, L.; Garanti, L.; Molteni, G. *Tetrahedron* **2004**, *60*, 4627.

STABLE NITRILE OXIDE DIPOLAR CYCLOADDITIONS IN PURE WATER

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