Nitrile Oxide 1,3-Dipolar Cycloadditions in Water: Novel Isoxazoline and Cyclophane Synthesis

Kason Bala, Helen C. Hailes*

Department of Chemistry, University College London, 20 Gordon Street, London WC1H 0AJ, UK
Fax +44(20)76797463; E-mail: h.c.hailes@ucl.ac.uk

Received 14 September 2005

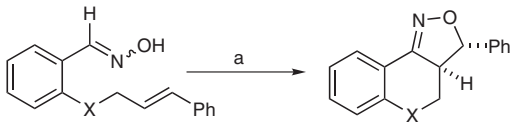
Abstract: Facile examples of one-pot 1,3-dipolar cycloadditions in water are described to generate novel benzopyran, quinoline and cyclophane isoxazolines.

Key words: pericyclic reaction, 1,3-dipolar cycloaddition, cyclophane, nitrile oxide, reactions in water

The use of water as a solvent for organic reactions offers many potential advantages over organic solvents including safety and cost. In the early 1980s Breslow and Rideout highlighted other benefits of using water for Diels–Alder reactions where rate enhancements and different stereoselectivities were observed.[1] These were attributed to the hydrophobic effect,[1,2] and since then the use of aqueous media has been exploited in a wide range of organic transformations: the importance of hydrogen bond interactions has also been recognised.[3] Another pericyclic reaction, the 1,3-dipolar cycloaddition has by comparison not been extensively investigated in aqueous media. The formation and reactivity of substituted benzonitrile oxides in aqueous solution was first reported by Hegarty et al., who highlighted that benzohydroxamoyl chloride could be converted to the corresponding 1,3-dipole in water which was then used as a medium for the cycloaddition.[4] Lee subsequently reported the cyclization of nitrile oxides with dipolarophiles in aqueous–organic biphasic systems through generation of the nitrile oxide from the corresponding oxime in situ: several of the cycloadditions also required the addition of a catalytic amount of organic base, typically triethylamine.[5] The reaction of preformed 2,6-dichlorobenzonitrile *N*-oxide with 2,6-diisopropyl-*p*-benzoquinone has been described in aqueous ethanol mixtures where enhanced rates were observed compared to that in chloroform.[6] However, a more recent kinetic study explored the pericyclic reaction between preformed benzonitrile *N*-oxide and a range of dipolarophiles in aqueous and organic media.[7] It was concluded that with electron-rich dipolarophiles the cycloaddition was accelerated in water and protic solvents, but no special effects were observed with electron-poor dipolarophiles.[7]

Biphasic or homogeneous mixed solvent systems have been used when carrying out 1,3-dipolar cycloaddition reactions in aqueous media and the application of water only as a medium is less common. Examples include work by Rohloff et al. who used dibromoformaldoxime in a one-pot reaction which decomposed to a nitrile oxide in alkaline water and was then coupled to water-soluble olefins and acetylenes.[8] Also the reaction of a benzonitrile *N*-oxide with a cyclodextrin-supported alkene terminated acylamide, however, as is often the case the nitrile oxide was preformed.[9] Nevertheless, there are significant advantages to using water alone as a solvent including facile product isolation if it has a low solubility in water. Herein we describe studies to investigate the feasibility of using water as a reaction solvent in a one-pot reaction for the intramolecular 1,3-dipolar cycloaddition of **1** to generate benzopyran and quinoline-based isoxazolines **2**, useful synthetic intermediates for the synthesis of bifunctional compounds. The effect of substrate hydrophobicity through incorporation of a hydrophilic spacer has also been explored.

In initial experiments 2-{[(*E*)-3-phenylprop-2-enyl]oxy}benzaldehyde, selected as a substrate to give an aromatic group on the isoxazoline cycloadduct, was prepared as previously reported.[10] The benzaldoxime **1a** was readily formed using hydroxylamine in 97% yield and found to be relatively insoluble in a number of organic solvents, however was sparingly soluble in THF. The addition of sodium hypochlorite in water to **1a** in THF resulted in the formation of **2a** in 90% yield (Scheme 1, Table 1, entry 1). When the reaction was performed in water only under the same conditions **2a** was formed in 24% yield, but extension of the reaction time increased the yield to 90% (Table 1, entries 2,3). No nitrile oxide intermediates or side-products were isolated. Notably, one key advantage of using water was that the product **2a** could be isolated directly by filtration, rather than phase separation and removal of the organic solvent, and no undissolved starting material remained. Also in these cycloadditions, the addition of a base was not required as had been reported by Lee who converted *o*-allyloxybenzaldoxime to the corresponding benzopyran in a biphasic reaction system.[5]



1a X = O
1b X = NH

2a X = O
2b X = NH

Scheme 1 Reagents and conditions: a) solvent and time (see Table 1), r.t., NaOCl

SYNTHESIS 2005, No. 19, pp 3423–3427
Advanced online publication: 14.11.2005
DOI: 10.1055/s-2005-918471; Art ID: C07105SS
© Georg Thieme Verlag Stuttgart · New York

Downloaded by: University of Pittsburgh. Copyrighted material.

Table 1 Reaction Conditions and Results for 1,3-Dipolar Cycloadditions in Scheme 1[a]

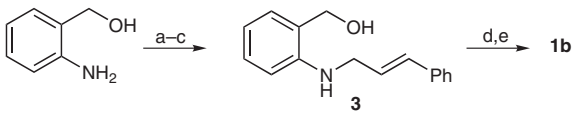
Entry	Conditions	Time (h)	Product	Yield (%)
1	H_2O–THF (3:7)	18	**2a**	90
2	H_2O	18	**2a**	25
3	H_2O	72	**2a**	90
4	H_2O–THF (9:1)	18	**2a**	33
5	H_2O–THF (1:1)	18	**2a**	60
6	H_2O–THF (1:9)	18	**2a**	91
7	90 mM SDS in H_2O	72	**2a**	24
8	CH_2Cl_2/H_2O (95:5)	72	–	0
9	CH_2Cl_2/H_2O (9:1)	18	**2b**	90
10	H_2O	18	**2b**	40
11	H_2O	48	**2b**	92
12	90 mM SDS in H_2O	18	**2b**	40

[a] NaOCl (2.5 equiv as 11% aqueous solution) was used.

Further investigations into the effect of water on the reaction were carried out using different ratios of water–THF as the solvent. An increased proportion of water led to a suppression of the cycloaddition reaction and formation of the adduct **2a** in a lower yield (Table 1, entries 4–6). The use of aqueous surfactant media was explored to enhance solubilisation of the benzaldoxime **1a** with sodium dodecyl sulfate (SDS) solution.[11] No effect was observed, **1a** still had low solubility in the aqueous media and **2a** was isolated in 24% yield (Table 1, entry 7). When dichloromethane–water was used as a solvent no reaction was observed perhaps reflecting the poor solubility of **1a** in dichloromethane (Table 1; entry 8).

For comparison purposes, the formation of the nitrile oxide was investigated using Grundmann's methodology[12] with subsequent cyclisation. Initially **1a** was treated with *N*-bromosuccinimide and triethylamine in anhydrous DMF but no cyclised product was generated. Modification of the reaction conditions, using aqueous ethanol rather than DMF and sodium hydroxide as base generated the cyclised product **2a** after 18 hours in 24% yield. Overall, the outcome of these reactions is likely to be a balance between the enforced aggregation of reacting functionalities as a consequence of the hydrophobic effect, since the reaction proceeds more readily in aqueous-based media, and hydrogen-bond interactions and the solubilities of starting material and product. The one-pot reaction could readily be performed in water alone, ensuring the facile isolation of product, however the reactions proceeded more slowly in water than in a biphasic THF–water mixture.

Having established the feasibility of using water alone as a solvent, formation of the corresponding quinoline-based isoxazoline **2b** from benzaldoxime **1b** was explored. Compound **1b** was prepared as shown in Scheme 2.



Scheme 2 Reagents and conditions: a) CH_2Cl_2, TBDMSCl, Et_3N, r.t., 18 h (90%); b) (*E*)-cinnamaldehyde, toluene, Dean–Stark apparatus, 18 h (97%); c) $NaBH_3CN$, HCl to pH 2, r.t., 10 h (96%); d) Fetizon's reagent, toluene, Dean–Stark apparatus, 18 h (95%); e) $NH_2OH{\cdot}HCl$, NaOH, EtOH–H_2O (4:1) (97%)

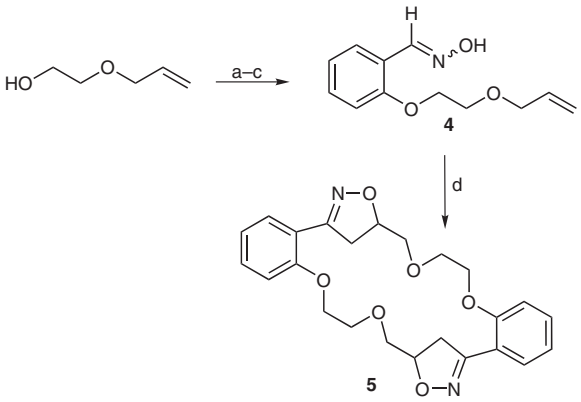
2-Aminobenzyl alcohol was protected using *tert*-butyldimethylsilyl chloride, then reacted with (*E*)-cinnamaldehyde to give the imine as previously described.[13] Reduction of the imine was carried out using sodium cyanoborohydride under acidic conditions[14] which also led to removal of the silyl protecting group in 96% yield to give **3**. Finally, oxidation to the aldehyde using Fetizon's reagent[15] and reaction with hydroxylamine gave the benzaldoxime **1b** in high yield.

In situ formation of the nitrile oxide precursor and 1,3-dipolar cycloaddition were then explored. Compound **1b** was soluble in dichloromethane which was used in initial studies. Accordingly, dichloromethane/water (95:5) as solvent and sodium hypochlorite as the oxidant readily led to formation of the isoxazoline in 90% yield (Scheme 1, Table 1, entry 9). Using water alone as a solvent led to the formation of **2b** under the same conditions in 40% yield, however, on extending the reaction time **2b** was isolated in 92% yield (Table 1, entries 10 and 11). Both the benzaldoxime and product had low solubilities in water and no intermediates such as the nitrile oxide were isolated. Again this suggested that the solubility of **1b** in water may reduce the rate of chlorination and subsequent nitrile oxide formation, however, the ease of product isolation at the end of the reaction by filtration made the reaction extremely facile. Use of the surfactant SDS had no effect on solubilising the oxime and the product **2b** was isolated in the same yield as when water was alone used (Table 1, entry 12).

Having established a straightforward protocol for synthesis of the isoxazolines in water, the methodology was extended to the synthesis of a novel cyclophane where it was envisaged that performing the cycloaddition reaction in water and exploiting any templating effects may be of benefit. Accordingly the benzaldoxime precursor **4** was prepared (Scheme 3): 2-allyloxyethanol was activated with methanesulfonyl chloride which was coupled to salicylaldehyde in 75% yield. Reaction with hydroxylamine hydrochloride generated the benzaldoxime **4** in high yield as before which appeared to have limited solubility in water, although on mixing with sodium hypochlorite resulted in formation of a homogeneous solution from which a precipitate was generated. After 18 hours, a product was isolated and determined to be the dimeric species **5**, formed in 97% yield. Compound **5** existed as a mixture of two diastereoisomers (ratio 4:1 by analytical HPLC). A com-

Downloaded by: University of Pittsburgh. Copyrighted material.

parable yield and isomer ratio were observed when using a mixed dichloromethane/water (95:5) solution containing sodium hypochlorite for the reaction, and in both cases no monomeric cycloadducts were isolated. This was most likely due to complexation of the ethylene glycol units from each unit around sodium during the cyclisation. To confirm the effect of sodium cations, treatment of **4** with *N*-bromosuccinimide and triethylamine in DMF to generate the nitrile oxide then afforded **5** in only 10% yield, together with a resinous material, most likely a polymer. This confirmed that the chelation effect by sodium enhances formation of the dimeric species rather than polymerization. Notably, related benzaldoximes comprised of aliphatic spacers have undergone 1,3-dipolar cycloaddition in organic media: monomeric isoxazoles were formed in low yield together with traces of a dimer (depending on the spacer used) and large quantities of a polymer.[16] Our approach highlights the highly selective nature of the reaction through the incorporation of ethylene glycol units and use of aqueous media for a one-pot reaction.



Scheme 3 Reagents and conditions: a) $MeSO_2Cl$ (95%); b) salicylaldehyde (75%), NaH, DMF; c) $NH_2OH{\cdot}HCl$, NaOH, EtOH–H_2O (4:1) (97%); d) NaOCl (2.5 equiv as 11% aqueous solution) (97%)

In summary, facile examples of one-pot 1,3-dipolar cycloadditions have been described in water to generate a novel benzopyran, quinoline and cyclophane isoxazoline. The reaction times to form **2a** and **2b** were longer using water alone as a solvent rather than a mixed solvent system, perhaps reflecting the low solubilities of the benzaldoximes in water. One major advantage of using water was the ease of isolation because the products precipitated out of solution and no starting material remained. Also when using aqueous media, the novel cyclophane was formed without formation of polymeric side-products. This approach can now be applied to the formation of related materials including cyclophanes comprised of alternative ring sizes.

Chemicals were purchased from Aldrich or Lancaster and used as received. Unless otherwise stated, H_2O refers to the use of deionised H_2O. Solvents were purchased from BDH Ltd unless indicated otherwise and used as received. Anhyd reaction solvents were HPLC grade and freshly distilled over CaH_2 (CH_2Cl_2, toluene, Et_3N) or sodium (THF). Anhyd DMF (Aldrich) was used as received. ^1H NMR spectra were recorded on a Bruker instrument at 300 MHz, 400 MHz or 500 MHz as indicated, and ^{13}C NMR spectra at 75 MHz or 125 MHz. Residual protic solvent was taken as internal standard with $CDCl_3$. Mass spectrometry was performed at UCL (EI, FAB) or London School of Pharmacy using an Autospec Q, VG 7070, VG 7070B or a ZAB-SE instrument. High resolution accurate mass spectra were performed at the London School of Pharmacy (FAB). Elemental analyses were carried out at the UCL microanalytical service. IR were recorded on a Perkin-Elmer 983G or FT-IR 1605 instrument. Melting points were determined using a Gallenkamp melting point apparatus and are uncorrected. HPLC analyses were performed using a Gilson M303 instrument and a HiChrom normal phase column and UV-visible detector.

2-{[(*E*)-3-Phenylprop-2-enyl]oxy}benzaldehyde was prepared as previously described.[10] 2-(*tert*-Butyldimethylsilyloxymethyl)phenyl-1-amine and 2-(*tert*-butyldimethylsilyloxymethyl)phenyl-1-[(*E*)-3-phenylprop-2-enylidene]imine were prepared as previously reported.[13]

2-{[(*E*)-3-Phenylprop-2-enyl]oxy}benzaldehyde Oxime (1a)

2-{[(*E*)-3-Phenylprop-2-enyl]oxy}benzaldehyde (6.00 g, 25.2 mmol), NaOH (5.00 g, 125 mmol) and $NH_2OH{\cdot}HCl$ (2.74 g, 39.4 mmol) were added to a solution of 80% aq EtOH (50 mL) and the mixture stirred at r.t. for 8 h. The crude product was extracted into EtOAc (3 × 25 mL) and the combined organic extracts dried ($MgSO_4$). The solvent was removed in vacuo and the crude product recrystallised from EtOH to afford **1a** as yellow crystals (6.18 g, 97%); mp 104–106 °C (EtOH).

IR (KBr): 3293, 2960, 1593 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 4.67 (2 H, dd, *J* = 5.7, 1.2 Hz, CH_2O), 6.32 (1 H, td, *J* = 16.0, 5.7 Hz, =C*H*CH_2O), 6.66 (1 H, d, *J* = 16.0 Hz, C=C*H*Ph), 6.91 (2 H, m, ArH), 7.20–7.36 (6 H, m, ArH), 7.77 (1 H, dd, *J* = 8.0, 1.6 Hz, ArH), 8.52 (1 H, s, HC=N).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 69.2 (CH_2O), 112.6 (C-3), 121.1, 124.1, 126.6, 126.8, 128.0, 128.3, 128.6, 131.1, 133.2, 136.3, 146.6, 156.8.

MS (EI): *m*/*z* (%) = 253 (M^+, 3), 236 (10), 117 (100).

HRMS: *m*/*z* calcd for $C_{16}H_{16}NO_2$ [MH^+]: 254.1181; found: 254.1170.

Anal. Calcd for $C_{16}H_{15}NO_2$: C, 75.87; H, 5.97; N, 5.53. Found: C, 75.49; H, 5.90; N, 5.42.

3-Phenyl-3a,4-dihydro-3*H*-chromeno[4,3-*c*]isoxazole (2a)

To **1a** (0.253 g, 1.00 mmol) in the solvent indicated (Table 1, 15 mL) was added aq NaOCl (11% Cl_2 content, 1.62 mL, 2.50 mmol) at 5 °C. The reaction was stirred for 10 min, then at r.t. for 18 h. When an organic solvent was used, H_2O (30 mL) was added, the organic layer separated and remaining product extracted from the aqueous layer using CH_2Cl_2 (15 mL). The combined organic extracts were washed with H_2O (15 mL), dried ($MgSO_4$) and the solvent was removed in vacuo. The crude product was purified by precipitation with cold Et_2O to afford **2a** as colourless crystals. When H_2O was used as a reaction solvent, the precipitate formed was isolated by filtration under reduced pressure and washed with cold Et_2O (2 × 5 mL) to give **2a**; mp 80–82 °C (Et_2O).

IR (KBr): 2954, 1649, 1607, 1500 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 3.82 (1 H, ddd, *J* = 12.6, 12.3, 5.8 Hz, 3a-H), 4.15 (1 H, dd, *J* = 12.3, 10.4 Hz, C*H*HO), 4.50 (1 H, dd, *J* = 10.4, 5.8 Hz, CH*H*O), 5.15 (1 H, d, *J* = 12.6 Hz, 3-H), 6.85 (1 H, d, *J* = 8.4 Hz, 6-H), 6.91 (1 H, dd, *J* = 7.7, 7.3 Hz, 8-H), 7.24 (1 H, ddd, *J* = 8.4, 7.3, 1.6 Hz, 7-H), 7.34 (5 H, m, C_6H_5), 7.76 (1 H, dd, *J* = 7.7, 1.6 Hz, 9-H).

Downloaded by: University of Pittsburgh. Copyrighted material.

^{13}C NMR (75 MHz, $CDCl_3$): δ = 53.0 (C-3a), 69.2, 85.9, 113.3, 117.6, 122.0, 125.7, 126.7, 129.01, 129.04, 132.6, 137.4, 153.4, 156.7.

FAB-MS: *m*/*z* (%) = 252 (MH^+, 100), 236 (10), 117 (100).

HRMS: *m*/*z* calcd for $C_{16}H_{14}NO_2$ [MH^+]: 252.1025; found: 252.1015.

2-[(*E*)-3-Phenylprop-2-enylamino)]phenylmethanol (3)

To a solution of $NaBH_3CN$ (0.28 g, 4.44 mmol) in aq acidic MeOH (pH 2, 10 mL) was added 2-(*tert*-butyldimethylsilyloxymethyl)phenyl-1-[(*E*)-3-phenylprop-2-enylidene]imine[13] (1.00 g, 2.96 mmol). The mixture was stirred at r.t. for 10 h and the solvent removed in vacuo. On addition of H_2O (10 mL), the crude product was extracted into EtOAc (3 × 20 mL), washed with brine (2 × 20 mL), H_2O (20 mL) and the combined organic extracts were dried ($MgSO_4$). The solvent was removed in vacuo and the product was purified using flash silica chromatography (EtOAc–hexane, 2:1) to give **3** as yellow crystals (0.68 g, 96%); mp 124–126 °C (EtOAc–hexane).

IR (KBr): 3490, 2840, 1651, 1574, 1512 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 3.90 (2 H, dd, *J* = 5.8, 1.6 Hz, CH_2N), 4.60 (2 H, s, CH_2OH), 6.28 (1 H, dt, *J* = 15.9, 5.8 Hz, NCH_2CH), 6.55 (1 H, d, *J* = 15.9 Hz, CHPh), 6.60 (1 H, ddd, *J* = 8.1, 7.4, 1.3 Hz, Ar 5-H), 6.65 (1 H, d, *J* = 8.1 Hz, Ar 3-H), 6.99 (1 H, dd, *J* = 7.4, 1.3 Hz, Ar 6-H), 7.15–7.29 (6 H, m, ArH).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 45.7 (CH_2N), 64.8 (CH_2OH), 111.1, 116.7, 124.5, 126.3, 127.0, 127.5, 128.5, 129.1, 129.7, 131.4, 136.9, 147.3.

MS (EI): *m*/*z* (%) = 239 (M^+, 15), 220 (16), 117 (100).

HRMS: *m*/*z* calcd for $C_{16}H_{17}NO$ [M^+]: 239.1310; found: 239.1300.

Anal. Calcd for $C_{16}H_{17}NO$: C, 80.30; H, 7.16; N, 5.85. Found: C, 80.08; H, 7.09; N, 5.69.

2-[(*E*)-3-Phenylprop-2-enylamino)]benzaldehyde

To a solution of **3** (1.05 g, 4.40 mmol) in anhyd toluene (50 mL) was added Fetizon's reagent[15] (Ag_2CO_3/Celite 1.80 mmol/g; 4.88 g, 4.40 mmol). The reaction mixture was refluxed for 18 h with the azeotropic removal of H_2O. Insoluble material was then removed by filtration and the filtrate was evaporated in vacuo. The crude product was purified by flash silica chromatography (EtOAc–hexane, 1:1) to afford the title compound as a yellow oil (0.99 g, 95%).

IR (film): 3332, 2850, 1689, 1651, 1574, 1512 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.98 (2 H, ddd, *J* = 5.7, 5.7, 1.5 Hz, CH_2N) 6.23 (1 H, td, *J* = 16.0, 5.7 Hz, NCH_2CH), 6.50 (1 H, d, *J* = 16.0 Hz, CHPh), 6.63 (2 H, m, Ar 3-H, 5-H), 7.20–7.30 (6 H, m, ArH), 7.40 (1 H, dd, *J* = 7.0, 1.5 Hz, Ar 6-H), 8.64 (1 H, br s, NH), 9.80 (1 H, s, CHO).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 44.5 (CH_2N), 111.2, 115.2, 118.7, 125.7, 126.4, 127.6, 128.6, 131.7, 135.7, 136.66, 136.7, 150.6, 194.0 (C=O).

APCI + MS: *m*/*z* (%) = 237 (M^+, 15), 134 (14), 117 (100).

HRMS: *m*/*z* calcd for $C_{16}H_{15}NO$ [M^+]: 237.1154; found: 237.1144.

Anal. Calcd for $C_{16}H_{15}NO$: C, 80.78; H, 6.37; N, 5.90. Found: C, 80.78; H, 6.24; N, 5.70.

2-[(*E*)-3-Phenylprop-2-enylamino]benzaldehyde Oxime (1b)

To 2-[(*E*)-3-phenylprop-2-enylamino]benzaldehyde (0.410 g, 1.72 mmol) in 80% aq EtOH (10 mL), were added NaOH (0.10 g, 2.60 mmol) and NH_2OH·HCl (0.48 g, 4.88 mmol). The mixture was stirred at r.t. for 18 h and then diluted with H_2O (10 mL). The crude product was extracted into EtOAc (3 × 25 mL) and the combined organic extracts were washed with brine (2 × 20 mL), H_2O (20 mL) and dried ($MgSO_4$). The solvent was removed in vacuo to yield **1b** as a yellow oil (0.42 g, 97%).

IR (film): 3332, 2950, 1616, 1575, 1520 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 4.02 (2 H, dd, *J* = 5.3, 4.3 Hz, CH_2N), 6.26 (1 H, td, *J* = 16.0, 5.3 Hz, NCH_2CH), 6.65 (1 H, d, *J* = 16.0 Hz, CHPh), 6.68 (2 H, m, Ar 3-H, 5-H), 7.01 (1 H, br s), 7.11 (1 H, m, Ar 4-H), 7.20–7.40 (6 H, m, ArH), 8.23 (1 H, CH=N).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 45.6 (CH_2N), 111.0, 114.6, 115.9, 126.7, 127.0, 127.9, 128.9, 131.3, 131.8, 133.2, 137.3, 147.6 (C=N), 154.7.

MS (EI): *m*/*z* (%) = 252 (M^+, 25), 235 (90), 117 (100).

HRMS: *m*/*z* calcd for $C_{16}H_{17}N_2O$ [MH^+]: 253.1341; found: 253.1350.

3-Phenyl-3,3a,4,5-tetrahydroisoxazolo[4,3-*c*]quinoline (2b)

To a solution of **1b** (60 mg, 0.24 mmol) in solvent (5.85 mL) was added aq NaOCl (11% Cl_2 content, 0.65 mL, 1.00 mmol) at 5 °C. The mixture was stirred at r.t. for 18 h. When an organic solvent was used, H_2O (10 mL) was added, the organic layer was separated and remaining product was extracted from the aqueous layer using CH_2Cl_2 (10 mL). The combined organic extracts were washed with H_2O (10 mL), dried ($MgSO_4$) and the solvent was removed in vacuo. The crude product was purified by precipitation with cold Et_2O to afford **2b** as yellow crystals. When H_2O was used as a reaction solvent, the precipitate formed was isolated by filtration under reduced pressure and washed with cold Et_2O (2 × 5 mL) to give **2b**; mp 110–112 °C (Et_2O).

IR (KBr): 3387, 2885, 1612, 1497 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.31 (1 H, dd, *J* = 12.5, 10.8 Hz, CHHN), 3.48 (1 H, dd, *J* = 10.8, 5.8 Hz, CHHN), 3.62 (1 H, ddd, *J* = 12.5, 12.2, 5.8 Hz, 3a-H), 4.06 (1 H, br s, NH), 5.22 (1 H, d, *J* = 12.2 Hz, 3-H), 6.48 (1 H, d, *J* = 8.4 Hz, 6-H), 6.60 (1 H, dd, *J* = 7.8, 7.3 Hz, 8-H), 7.05 (1 H, ddd, *J* = 8.4, 7.3, 1.2 Hz, 7-H), 7.29 (5 H, m, C_6H_5), 7.54 (1 H, dd, *J* = 7.8, 1.2 Hz, 9-H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 45.6 (C-3a), 54.3 (C-4), 86.8 (C-3), 110.9, 115.1, 118.7, 126.0, 126.7, 128.7, 128.8, 131.9, 138.1, 145.9, 155.5.

FAB-MS: *m*/*z* (%) = 251 (MH^+, 100), 233 (16), 117 (20).

HRMS: *m*/*z* calcd for $C_{16}H_{15}N_2O$ [MH^+]: 251.1184; found: 251.1175.

Methanesulfonic Acid 2-Propenyloxyethyl Ester

The reaction was carried out under anhydrous conditions. To propenyloxyethylene glycol (6.40 mL, 60 mmol) in CH_2Cl_2 (50 mL) was added $MeSO_2Cl$ (4.64 mL, 60 mmol). Et_3N (8.34 mL, 60 mmol) was then added dropwise and the mixture was stirred at r.t. for 18 h. The triethylamine hydrochloride precipitate was removed by filtration and H_2O (50 mL) was added to the filtrate. The organic layer was separated, washed with aq sat. $NaHCO_3$ solution (3 × 100 mL) and brine (2 × 50 mL), then dried ($MgSO_4$). The solvent was removed in vacuo to afford the title compound as a yellow oil (10.26 g, 95%) which was used immediately in the next step.

IR (film): 1649, 1457, 1418 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.03 (3 H, s, SO_3CH_3), 3.65 (2 H, t, *J* = 4.6 Hz, $CH_2CH_2OSO_2CH_3$), 3.99 (2 H, dd, *J* = 5.6, 1.4 Hz, CH_2OCH), 4.32 (2 H, t, *J* = 4.6 Hz, $CH_2OSO_2CH_3$), 5.22 (2 H, dd, *J* = 10.4, 1.5 Hz, CHH=CH), 5.24 (1 H, dd, *J* = 17.1, 1.5 Hz, CHH=CH), 5.87 (1 H, tdd, *J* = 17.1, 10.4, 5.6 Hz, CH=CH_2).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 37.7 (SO_3CH_3), 67.8, 69.1, 72.4, 118.0, 134.4.

FAB-MS: *m*/*z* (%) = 181 (MH^+, 100), 123 (85), 85 (50).

HRMS: *m*/*z* calcd for $C_6H_{13}O_4S$ [MH^+]: 181.0535; found: 181.0544.

Downloaded by: University of Pittsburgh. Copyrighted material.

2-(2-Propenyloxyethoxy)benzaldehyde

The reaction was carried out under anhydrous conditions. To salicylaldehyde (4.88 g, 40.0 mmol) in anhyd DMF (50 mL) was added NaH (60 wt% in mineral oil, 1.60 g, 40 mmol) and the mixture was stirred at r.t. for 2 h. Methanesulfonic acid 2-propenyloxyethyl ester (7.24 g, 40.0 mmol) was then added the reaction heated at 70 °C for 18 h. On cooling, H_2O was added and the crude product was extracted into EtOAc (3 × 50 mL). The combined organic extracts were washed with aq sat. $NaHCO_3$ solution (2 × 20 mL), brine (20 mL), and dried ($MgSO_4$). The solvent was removed in vacuo and the crude product was purified by flash silica chromatography (hexane–EtOAc, 2:1) to afford the title compound as an oil (6.18 g, 75%).

IR (film): 2952, 1683, 1599, 1485 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 3.88 (2 H, t, *J* = 4.9 Hz, C*H*$_2$CH$_2$OAr), 3.99 (2 H, dd, *J* = 5.3, 1.3 Hz, CH$_2$C=), 4.32 (2 H, t, *J* = 4.9 Hz, CH$_2$OAr), 5.22 (2 H, dd, *J* = 10.4, 1.3 CH*H*=CH), 5.24 (1 H, dd, *J* = 17.2, 1.3 Hz, C*H*H=CH), 5.87 (1 H, tdd, *J* = 17.1, 10.4, 5.3 Hz, C*H*=CH$_2$), 6.98 (2 H, m, ArH), 7.53 (1 H, m, ArH), 7.76 (1 H, dd, *J* = 7.7, 1.7 Hz, Ar 6-H), 10.53 (1 H, s, CHO).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 68.7 (C-2′, *C*H$_2$OCH), 72.8, 113.3, 117.8, 121.4, 125.6, 128.7, 134.8, 136.2, 161.7, 190.1 (CHO).

FAB-MS: *m*/*z* (%) = 207 (MH^+, 25), 149 (20).

HRMS: *m*/*z* calcd for $C_{12}H_{15}O_3$ [MH^+]: 207.1021; found: 207.1030.

2-(2-Propenyloxyethoxy)benzaldehyde Oxime (4)

To 2-(2-propenyloxyethoxy)benzaldehyde (5.15 g, 25.0 mmol) in 80% aq EtOH (100 mL) were added NaOH (3.20 g, 80.0 mmol) and NH_2OH·HCl (5.65 g, 80.0 mmol). The mixture was stirred at r.t. for 10 h and then diluted with H_2O (10 mL). The crude product was extracted into EtOAc (3 × 25 mL) and the combined organic extracts were washed with brine (2 × 30 mL) and dried ($MgSO_4$). The solvent was removed in vacuo to yield **4** as a yellow oil (6.43 g, 97%).

IR (film): 3351, 2953, 1670, 1594, 1490, 1453 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 3.82 (2 H, t, *J* = 4.8 Hz, C*H*$_2$CH$_2$OAr), 4.09 (2 H, dd, *J* = 5.3, 1.4 Hz, CH$_2$C=), 4.32 (2 H, t, *J* = 4.8 Hz, CH$_2$OAr), 5.22 (2 H, dd, *J* = 10.3, 1.3 Hz, CH*H*=CH), 5.24 (1 H, dd, *J* = 17.2, 1.3 Hz, C*H*H=CH), 5.87 (1 H, tdd, *J* = 17.2, 10.3, 5.3 Hz, C*H*=CH$_2$), 6.98 (2 H, m, H-3, H-5), 7.31 (1 H, m, H-4), 7.71 (1 H, dd, *J* = 7.7, 1.7 Hz, Ar 6-H), 7.74 (NOH), 8.53 (1 H, s, CH=N).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 68.2, 68.6, 72.4, 112.6, 117.4, 121.2, 126.5, 128.3, 131.1, 134.5, 146.5, 156.9.

FABMS: *m*/*z* (%) = 222 (MH^+, 32), 206 (12).

HRMS: *m*/*z* calcd for $C_{12}H_{16}NO_3$ [MH^+]: 222.1130; found: 222.1140.

Diisoxazoline 5

To a solution of **4** (53 mg, 0.25 mmol) in H_2O (5.85 mL) was added aq NaOCl (11% Cl_2 content; 0.65 mL, 1 mmol) at 5 °C. The mixture was stirred at r.t. for 18 h and the white precipitate formed was collected by filtration. The precipitate was dried in vacuo to afford **5** as colourless crystals (53 mg, 97%) in a diastereoisomeric ratio of 4:1 [determined by normal-phase HPLC: $CHCl_3$–CH_2Cl_2, 95:5; flow rate: 0.5 mL/min; minor diastereoisomer (19.25 min), major diastereoisomer (25.77 min)].

IR (film): 1649, 1607, 1490, 1449 cm^{-1}.

FABMS: *m*/*z* (%) = 461 (MNa^+, 80), 439 (32), 176 (45).

HRMS: *m*/*z* calcd for $C_{24}H_{27}N_2O_6$ [MH^+]: 439.1869; found: 439.1850.

Major Diastereoisomer: ^1H NMR (500 MHz, $CDCl_3$): δ = 3.44 (2 H, dd, *J* = 17.6, 7.9 Hz, 2 × N=CC*H*H), 3.58 (2 H, dd, *J* = 17.6, 10.5 Hz, 2 × N=CCH*H*), 3.67 (2 H, m, 2 × OCHC*H*HO), 3.73 (2 H, m, 2 × OCHCH*H*O), 3.86 (2 H, m, 2 × C*H*HCH$_2$OAr), 3.95 (2 H, m, 2 × CH*H*CH$_2$OAr), 4.10 (2 H, m, 2 × C*H*HOAr), 4.20 (2 H, m, 2 × CH*H*OAr), 4.79 (2 H, m, 2 × C*H*ON), 6.86 (2 H, d, *J* = 8.5 Hz, ArH), 6.95 (2 H, dd, *J* = 7.7, 7.4 Hz, ArH), 7.33 (2 H, ddd, *J* = 8.5, 7.4, 1.5 Hz, ArH), 7.78 (2 H, dd, *J* = 7.7, 1.5 Hz, ArH).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 40.7 (*C*H$_2$C= N), 67.7, 69.9, 72.2, 79.5 (CHON), 111.8, 118.9, 121.0, 129.4, 131.3, 156.3, 156.5.

Minor Diastereoisomer: ^1H NMR (500 MHz, $CDCl_3$): δ = 3.46 (2 H, dd, *J* = 17.5, 7.9 Hz, 2 × N=CC*H*H), 3.63 (2 H, dd, *J* = 17.5, 10.5 Hz, 2 × N=CCH*H*), 3.67 (2 H, m, 2 × OCHC*H*HO), 3.73 (2 H, m, 2 × OCHCH*H*O), 3.89 (2 H, m, 2 × C*H*HCH$_2$OAr), 3.91 (2 H, m, 2 × CH*H*CH$_2$OAr), 4.07 (2 H, m, C*H*HOAr), 4.20 (2 H, m, 2 × CH*H*OAr), 4.79 (2 H, m, 2 × C*H*ON), 6.83 (2 H, d, *J* = 8.5 Hz, ArH), 6.91 (2 H, dd, *J* = 7.7, 7.4 Hz, ArH), 7.31 (2 H, ddd, *J* = 8.5, 7.4, 1.5 Hz, ArH), 7.82 (2 H, dd, *J* = 7.7, 1.5 Hz, ArH).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 40.1 (*C*H$_2$C=N), 67.2, 69.8, 71.5, 79.4, 112.0, 118.8, 121.0, 129.3, 131.3, 156.2, 156.5.

Acknowledgment

We thank AWE plc for a studentship to KB.

References

(1) Rideout, D. C.; Breslow, R. *J. Am. Chem. Soc.* **1980**, *102*, 7816.
(2) (a) Tanford, C. *The Hydrophobic Effect*, 2nd ed.; Wiley: New York, **1980**. (b) Blokzijl, W.; Engberts, J. B. F. N. *Angew. Chem., Int. Ed. Engl.* **1993**, *32*, 1545.
(3) For example: (a) Breslow, R. *Acc. Chem. Res.* **1991**, *24*, 159. (b) Li, C. J.; Chan, T.-H. *Organic Reactions in Aqueous Media*; Wiley: New York, **1997**. (c) Lubineau, A.; Augé, J.; Queneau, Y. *Synthesis* **1994**, 741. (d) Li, C. *Chem. Rev.* **1993**, *93*, 2023. (e) Ribe, S.; Wipf, P. *Chem. Commun.* **2001**, 299.
(4) (a) Dignam, K. J.; Hegarty, A. F.; Quain, P. L. *J. Chem. Soc., Perkin Trans. 2* **1977**, 1457. (b) Dignam, K. J.; Hegarty, A. F.; Quain, P. L. *J. Org. Chem.* **1978**, *43*, 388.
(5) Lee, G. A. *Synthesis* **1982**, 508.
(6) Inoue, Y.; Araki, K.; Shiraishi, S. *Bull. Chem. Soc. Jpn.* **1991**, *64*, 3079.
(7) Van Mersbergen, D.; Wijnen, J. W.; Engberts, J. B. F. N. *J. Org. Chem.* **1998**, *63*, 8801.
(8) Rohloff, J. C.; Robinson, J. III; Gardner, J. O. *Tetrahedron Lett.* **1992**, *33*, 3113.
(9) Meyer, A. G.; Easton, C. J.; Lincoln, S. F.; Simpson, G. W. *Chem. Commun.* **1997**, 1517.
(10) Aurrecoechea, J. M.; López, B.; Fernández, A.; Arrieta, A.; Cossío, F. P. *J. Org. Chem.* **1997**, *62*, 1125.
(11) Hailes, H. C.; Diego-Castro, M. J. *Tetrahedron Lett.* **1998**, *39*, 2111.
(12) Grundmann, C. *Synthesis* **1970**, 344.
(13) Zamboni, R.; Just, G. *Can. J. Chem.* **1978**, *56*, 2720.
(14) Orlemans, E. O. M.; Schreuder, A. H.; Conti, P. G. M.; Verboom, W.; Reinhoudt, D. N. *Tetrahedron* **1987**, *43*, 3817.
(15) (a) Fetizon, M.; Golfien, M.; Louis, J.-M. *Tetrahedron* **1975**, *31*, 171. (b) Morgans, D. J. *Tetrahedron Lett.* **1981**, *22*, 3721.
(16) Garanti, L.; Sala, A.; Zecchi, G. *J. Org. Chem.* **1975**, *40*, 2403.

Downloaded by: University of Pittsburgh. Copyrighted material.