A cyclodextrin to reverse the regioselectivity of nitrile oxide cycloaddition to a terminal alkene

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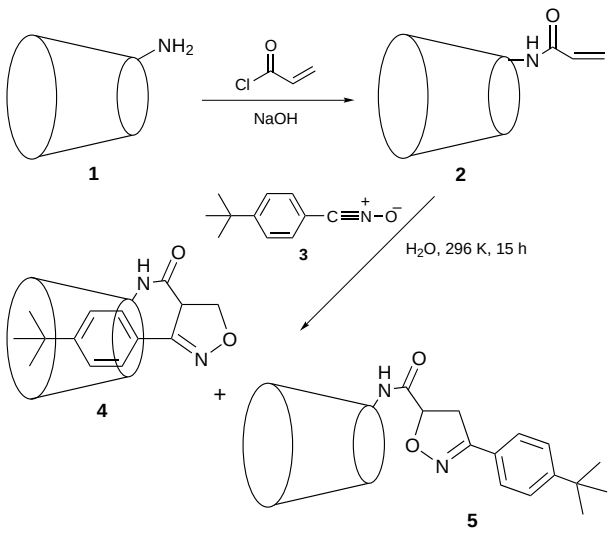
The 1,3-dipolar cycloaddition of 4-*tert*-butylbenzonitrile oxide with 6^A-acrylamido-6^A-deoxy-β-cyclodextrin in aqueous solution favours formation of the 4-substituted isoxazoline, in contrast to the normal predominance of the 5-substituted regioisomer from reactions of monosubstituted alkenes.

Nitrile oxide cycloaddition reactions with alkenes afford isoxazolines, which are of interest as versatile precursors of a range of 1,3-bifunctional compounds.[1] With mono- and trisubstituted alkenes the regioselectivity is usually determined by steric effects and the reactions afford almost exclusively 5- and 4,5,5-substituted isoxazolines, respectively. In order to reverse this regioselectivity, we envisaged that inclusion complexes of modified cyclodextrins[2] could be exploited. There have been reports that β-cyclodextrin affects the regioselectivity of nitrile oxide cycloadditions,[3] but it has now been demonstrated that these are in error and the cyclodextrin has no affect on the course of reaction in these examples.[4] Natural cyclodextrins have been used to accelerate Diels–Alder reactions of included guests and affect the distribution of products.[5] This occurs through self-assembly of the reactants within the cyclodextrin annulus, however our aim was to control the orientation of interaction between the reactants.

To develop this strategy, the dipolarophile was tethered to the cyclodextrin as the acrylamide **2** (Scheme 1). 4-*tert*-Butylbenzonitrile oxide **3** was selected as the dipole since alkyl-substituted aromatic compounds of this type are known to form thermodynamically stable inclusion complexes with β-cyclodextrin.[6] It was anticipated that inclusion of the hydrophobic moiety of the dipole **3** within the annulus of the modified cyclodextrin **2** would then establish the alignment for the cycloaddition (Fig. 1).



Scheme 1

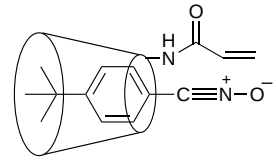
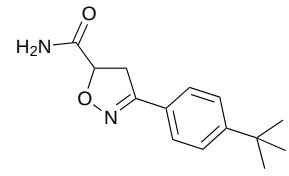


Fig. 1 Alignment of the dipole **3** and the dipolarophile **2** in the host–guest complex

Treatment of the amino-substituted cyclodextrin **1**[7] with acryloyl chloride under basic conditions gave the acrylamide **2**.† 4-*tert*-Butylbenzaldehyde reacted with hydroxylamine, then *N*-chlorosuccinimide,[8] to give the corresponding hydroximinoyl chloride, from which the nitrile oxide **3** was generated *in situ* by reaction with triethylamine. Thus the cycloaddition involved rapidly stirring a mixture of the acrylamide **2** (0.03 mmol) and the hydroximinoyl chloride (0.12 mmol) in water (2.5 ml) at 296 K for 1 h, then adding triethylamine (0.12 mmol) and stirring that mixture for a further 15 h. After work-up, this afforded a quantitative yield of a 2.3 : 1 mixture of the isoxazolines **4** and **5**,† which were separated using HPLC (Scheme 1). The ^{1}H NMR resonances due to the isoxazoline ring protons were assigned with the aid of double quantum filtered COSY experiments. When the cycloaddition reaction was repeated in DMF instead of water, the isoxazolines **4** and **5** were produced in 87% yield, as a 1 : 4 mixture.

The effect of the cyclodextrin annulus of the dipolarophile **2** was established by performing the cycloaddition of the nitrile oxide **3** with acrylamide. As expected, in either water or DMF, this reaction afforded only the 5-substituted isoxazoline **6**.†



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Therefore, the production of the 4-substituted isoxazoline **4** in the reactions of the cyclodextrin derivative **2** highlights the effect of dipole **3**–dipolarophile **2** host–guest complex formation. As expected, this effect is greater in water than in DMF because the formation of cyclodextrin inclusion complexes is favoured in aqueous solutions.

Footnotes and References

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† *Selected data* for **2**: 79%; ^{1}H NMR (500 MHz; [$^2H_6$]DMSO): δ 7.95 (1 H, br s, NH), 6.26 (1 H, dd, *J* 11.0, 17.5), 6.03 (1 H, *J* 17.5), 5.55 (1 H, d, *J* 11.0). For **4**: HPLC (Waters carbohydrate analysis column with 80% MeCN in H_2O): t_R = 25 min; ^{1}H NMR (500 MHz; [$^2H_6$]DMSO): δ 7.96 (1 H, br s, NH), 7.46 (2 H, d, *J* 8.0, ArH), 7.37 (2 H, d, *J* 8.0, ArH), 4.63 [1 H, m, isoxazoline C(5)-H], 4.60 [1 H, m, isoxazoline C(5)-H′], 4.37 [1 H, m,

isoxazoline C(4)-H]. For **5**: HPLC (as for **4**): t_R = 20 min; ^{1}H NMR (500 MHz; [$^2H_6$]DMSO): δ 7.93 (1 H, br s, NH), 7.61 (2 H, d, *J* 8.5, ArH), 7.47 (2 H, d, *J* 8.5, ArH), 5.09 [1 H, m, isoxazoline C(5)-H], 3.62 [1 H, dd, isoxazoline C(4)-H], 3.50 [1 H, dd, *J* 6.5, 17.0, isoxazoline C(4)-H′]. For **6**: ^{1}H NMR (500 MHz; [$^2H_6$]DMSO): δ 7.60 (2 H, d, *J* 8.5, ArH), 7.46 (2 H, d, *J* 8.5, ArH), 5.01 [1 H, dd, *J* 6.5, 11.5, isoxazoline C(5)-H], 3.62 [1 H, dd, isoxazoline C(4)-H], 3.50 [1 H, dd, *J* 6.5, 17.0, isoxazoline C(4)-H′].

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