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The effect of ionic liquids on the outcome of nitrile oxide cycloadditions

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ABSTRACT

Nitrile oxide cycloadditions between benzonitrile oxide and a series of alkenes were investigated in ionic liquids and molecular solvents. The regioselectivity of the process alters on changing solvent type, with the steric requirements of the reaction being increased in ionic liquids. The rate of the cycloaddition process was found to be faster in ionic liquid solvents, and a concomitant increase in the rate of dimerisation of the nitrile oxide starting material was also observed.

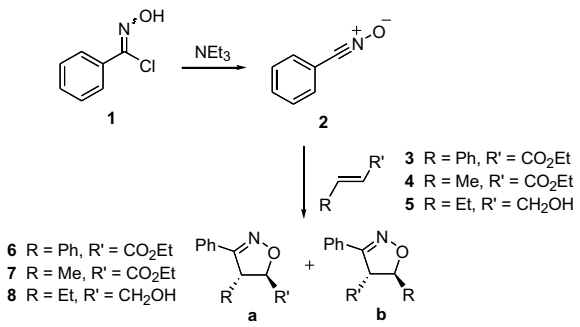
Synthetic chemistry relies heavily on the use of molecular solvents. Many of these solvents have been found to be environmentally unfriendly, so their use in industry is generating interest in alternative reaction media.[1,2] One potential answer to these problems lies with ionic liquids. Ionic liquids are versatile reaction media; changing either ion may change the physical properties of the liquid, allowing it to be altered to suit the required conditions for a certain reaction.[2] Furthermore, ionic liquids have the potential to be recycled and re-used many times,[3,4] greatly reducing waste and the impact on the environment.

These solvents may be considered to have great potential, and it has already been shown that a range of organic and inorganic syntheses can be carried out in ionic liquids.[5,6] However, the outcome of a range of reactions has been shown to be dramatically altered, both in terms of rates and product outcome, on changing from a molecular solvent to an ionic liquid, and currently such changes cannot be readily predicted.[7] For example, Diels–Alder cycloadditions have been studied extensively in ionic liquids with an increase in *endo*-selectivity and rate typically observed.[5] While these changes have been attributed to solvation parameters (such as hydrogen bonding[8,9]) which apply more generally to molecular solvents, there are concerns over the effect of the dilution of the reaction media with reagents and the fact that similar results are observed in ionic liquids based on either phosphonium[10] or pyridinium[11] cations where hydrogen bonding is greatly reduced. As such, explaining these outcomes in terms of a fundamental property that differentiates ionic liquids from molecular solvents would be useful.

A related cycloaddition process is the 1,3-dipolar cycloaddition between a nitrile oxide and an alkene to give a mixture of two dihydroisoxazoles.[12] Along with producing compounds that are synthetically versatile,[13] the ratio of the regioisomers produced is dependent on factors such as the steric and electronic properties of the reactants and the solvent.[12] As such, this reaction is well suited to studying the changes that occur on moving from a molecular solvent to an ionic liquid, and it is the investigation of these changes which is the focus of the work presented here.

Initially, the effect of changing from molecular solvents to ionic liquids on the regioselectivity of nitrile oxide cycloadditions was investigated. Benzonitrile oxide **2**, chosen as a representative nitrile oxide and generated in situ from the corresponding chloroaldoxime **1**,[14] was reacted with each of a series of alkenes **3–5** in either a molecular solvent or an ionic liquid. The alkenes **3–5** were chosen as they have differing steric and electronic effects on reaction outcome (Scheme 1).

All the ionic liquids **9–11** chosen for investigation are based on the well-described 1-butyl-3-methylimidazolium cation ([Bmim]$^+$),[15] and represent a range of properties from the hydrophobic bistriflimide salt **9** through the water-soluble dicyanimide salt **11**. The molecular solvents chosen (acetonitrile, ethyl acetate and THF) represent a collection of common solvents with empirical polarity measurements in the same range as that for the ionic liquids **9–11**.[16]



Scheme 1. Preparation of the nitrile oxide **2,** and subsequent reaction with each of the alkenes **3–5** to give the corresponding dihydroisoxazoles **6–8a,b**.

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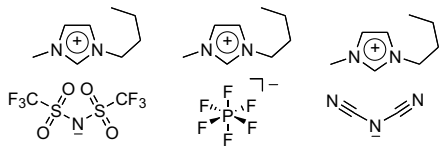

9 10 11

In each case, triethylamine was added to the reaction mixture slowly to reduce the extent to which the nitrile oxide **2** dimerises to the corresponding furoxan,[17,18] and this time of addition was optimised to maximise the extent of conversion. For reactions performed in molecular solvents, the chloroaldoxime **1** (ca. 50 mg) and the appropriate alkene (ca. 2 equiv) were dissolved in the solvent (6 mL), and triethylamine (440 μL) was added as a solution (ca. 3 mL) over ca. 6 h. Reactions in ionic liquids were performed similarly though it was found that greater extents of conversion were achieved through addition of neat triethylamine over longer time periods (12–24 h). Note that this is consistent with observed effects of ionic liquids on the dimerisation process, which will be discussed later.

The regioisomeric composition of the reaction mixtures was analysed using ^{1}H NMR spectroscopy. In the case of the reactions in molecular solvents, the solvent was removed in vacuo and the residue analysed while in the case of the reactions in ionic liquids, a small sample of the reaction mixture was analysed directly. ^{1}H NMR spectroscopy is a convenient method for the analysis of the product mixtures as each of the dihydroisoxazoles **6–8a,b** gives rise to signals in a region which is free from interferences such as signals due to residual solvent and starting materials. Further, initial studies indicated that attempted isolation of dihydroisoxazoles from ionic liquids resulted in selective extraction of one regioisomer making analysis of such extracts inappropriate for determining the regioselectivity of the process.

The ratio of the isomers produced by any one reaction was determined by taking the ratio of the average integrations of visible signals due to the C4 and C5 protons on the dihydroisoxazole products, and the extent of conversion was calculated through comparison of these integrations with that for the signals due to the residual alkene protons (Fig. 1). Separate T_1 studies were conducted to ensure appropriate choice of delay times between scans, and hence reliability of the signal integration. The values for these

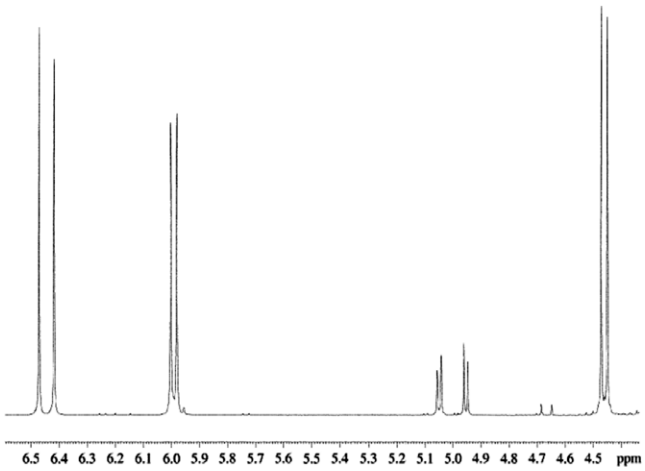

Figure 1. ^{1}H NMR spectrum (300 MHz, $CDCl_3$) of the reaction between the nitrile oxide **2** and the alkene **3** showing the signals used to calculate the ratio of the isomers **6a** and **6b** produced (δ 4.95 and 5.05, 4.46 and 5.99) and extent of conversion (above plus δ 6.44).

regioisomeric ratios are given in Table 1, with each ratio being the average of at least three replicate reactions in a given solvent.

Initially, ethyl *trans*-cinnamate (**3**) was considered as the electronic and steric effects on the regioselectivity of the nitrile oxide cycloaddition favour the formation of the same regioisomer, dihydroisoxazole **6b**. As such, it is unsurprising that this isomer is favoured over the other, **6a**, in a ratio of ca. 5.5:1 in molecular solvents. When the solvent is changed from a molecular solvent to an ionic liquid, there is a dramatic change in the regioselectivity, with the ratio of isomers **6a**:**6b** being 1:>10. That is, any effects that favour the formation of isomer **6b** in molecular solvents are magnified in the ionic liquids **9–11**.

It is worth noting that the extent of reaction in the water-soluble ionic liquid **11** was very small, even after optimisation, and none of the minor isomer **6a** could be detected. While the origin of the decrease in extent of conversion is unknown, as a result, this solvent was omitted from subsequent studies.

Ethyl crotonate (**4**) is similar to ethyl *trans*-cinnamate (**3**), but the bulky phenyl group is replaced with a considerably smaller methyl group. The formation of the isomer **7b** is favoured by the electronic character of the substrate **4**, while steric interactions favour the other isomer **7a**; this is in contrast to the previous case. Here, the former effect dominates with the ratio of the isomers **7a**:**7b** found to be ca. 1:2.9 in molecular solvents. This ratio decreases to ca. 1:1.9 on going from a molecular solvent to an ionic liquid. That is, the isomer whose formation is favoured by steric effects and disfavoured by electronic effects is formed to a greater extent in ionic liquids **9** and **10** than in molecular solvents.

trans-2-Penten-1-ol (**5**) has substituents on either side of the double bond which are of very similar size,[19] so the electronic effects arising from the presence of the hydroxy group might be expected to dominate in the formation of the dihydroisoxazoles **8a** and **8b**. Through consideration of related systems,[20] the hydroxy group is anticipated to result in the C3 position of the alkene **5** being more susceptible to attack by the negatively charged oxygen of the nitrile oxide **2**. Thus, the isomer **8b** is the electronically favoured one, though it is worth noting that it is also slightly sterically favoured.[19] The sum of these effects is clearly relatively small with the ratio of the isomers **8a** and **8b** being ca. 1:1.4 in molecular solvents. The change in this ratio on going to the ionic liquids **9** and **10** was small, with the ratio being ca. 1:1.2 in the ionic liquid **9** and the same, within uncertainty, as the molecular solvents for the ionic liquid **10**.

These results demonstrate the effects of using an ionic liquid rather than a molecular solvent. In the cases of the cinnamate **3** and the crotonate **4**, where both steric and electronic effects are present, it is not necessarily straightforward to immediately deconvolute the effect of changing solvent types. However, the reactions involving *trans-2*-penten-1-ol (**5**) allow simplification of the arguments. Given that difference in the size of the substituents on the alkene **5** is very small and selectivity based on any differ-

Table 1
Ratios of the dihydroisoxazoles **6–8a**:**b** produced in the cycloaddition of benzonitrile oxide **2** and the appropriate alkenes **3–5** in the solvents are shown, with average extent of conversion from the alkene given in parentheses. Each ratio is the average of at least three replicates, and the uncertainty given is the standard deviation

Solvent	**6a**:**6b**	**7a**:**7b**	**8a**:**8b**
Acetonitrile	1:6.54 ± 0.42 (44%)	1:2.88 ± 0.09 (13%)	1:1.40 ± 0.04 (19%)
Ethyl acetate	1:4.84 ± 0.63 (37%)	1:2.95 ± 0.07 (16%)	1:1.41 ± 0.02 (35%)
THF	1:5.29 ± 0.32 (38%)	1:2.95 ± 0.03 (17%)	1:1.39 ± 0.06 (33%)
9	1:15.17 ± 0.67 (29%)	1:1.91 ± 0.02 (27%)	1:1.19 ± 0.05 (14%)
10	1:12.17 ± 0.75 (84%)	1:2.20 ± 0.10 (34%)	1:1.56 ± 0.15 (12%)
11	1:>10[a] (<5%)	—	—

[a] The minor isomer was not observed and, as such, the ratio represents an estimated minimum excess of the major isomer.

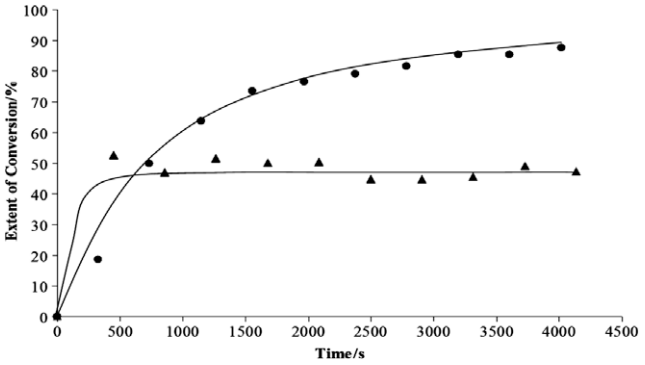

Figure 2. Extent of conversion of the cinnamate **3** to the regioisomers **6a** and **6b** with time in a mixture containing initially the cinnamate **3** and a 20-fold excess of the nitrile oxide **2** in either acetonitrile (●) or the ionic liquid **9** (▲).

ence would be expected to be minimal, the regioselectivity (and any changes in it on changing from a molecular solvent to an ionic liquid) in this case can be attributed to the electronic nature of the substrate. Hence, these results show that the selectivity based on the electronic nature of the substituents around the double bond is not largely affected by changing to an ionic solvent.

Using this as a starting point, it is suggested that the results for ethyl crotonate (**4**), where moving to an ionic liquid favours the sterically least hindered isomer **7a** over the electronically favoured isomer **7b**, are consistent with an increase in the regioselectivity based on steric interactions in conjunction with a small change in that due to electronic effects. For the cycloaddition of the nitrile oxide **2** with ethyl *trans*-cinnamate (**3**), where the isomer **6b** is produced to a greater extent in ionic liquids as it is favoured by both steric and electronic effects, an increase in selectivity due to steric interactions outweighs any change due to the electronic nature of the substrate on changing solvent to an ionic liquid.

The last two cases described demonstrate that changes in regioselectivity on moving from a molecular solvent to an ionic liquid are dominated by steric effects. This suggests that steric interactions in the transition state leading to the isomers **6–8a**,**b** are more significant in ionic liquids than they are in molecular solvents. Ionic liquids, due to the electrostatic interactions between their constituent ions, have higher cohesive pressures than molecular solvents.[21] Thus, the increase in regioselectivity based on steric interactions on changing from a molecular solvent to an ionic liquid can be rationalised by an increased cohesive pressure of the solvent compressing the transition state and increasing the steric interactions present. The difference between the reaction outcomes in the two ionic liquids is small when compared to the differences between ionic and molecular solvents.

It is of interest to consider the effect of carrying out these reactions in ionic liquids on the rate of the process. This is not straightforward in this case, given that competing dimerisation of the nitrile oxide **2** will complicate the process. As such, in order to observe the effect of changing solvent, a large excess (ca. 20 equiv) of the nitrile oxide **2** was generated through addition of triethylamine to the precursor **1** in the presence of the cinnamate **3** in both acetonitrile and the ionic liquid **9**. This alkene was chosen as the signals corresponding to the products **6a** and **6b** in the ^{1}H NMR spectra are most readily discernible in these systems. The reaction was followed using ^{1}H NMR spectroscopy of the reaction mixture over ca. 80 min (Fig. 2).

The most striking feature of this plot is that when the reaction is carried out in the ionic liquid **9**, the extent of conversion of the cinnamate **3** to the products **6a** and **6b** reaches ca. 50% prior to the first NMR spectrum being obtained, and does not increase further from this point. This indicates that at this time, since there is reagent **3** remaining, there must be none of the nitrile oxide **2** present, having completely dimerised to the corresponding furoxan. When the reaction is carried out in acetonitrile, the extent of reaction continues to increase, indicating that nitrile oxide **2** remains for the entirety of the experiment, thus demonstrating that the rate of dimerisation is greater in the ionic liquid **9** than in acetonitrile. This is consistent with the observation earlier that the slower addition of triethylamine (and hence generation of the nitrile oxide **2**) is necessary to maximise the extent of conversion in ionic liquids. The reaction carried out in acetonitrile reaches a corresponding extent of conversion after ca. 15 min, indicating that the rate of the nitrile oxide cycloaddition is also increased in ionic liquid **9** though clearly to a lesser extent than the dimerisation process.

In conclusion, it has been demonstrated that the regioselectivity of nitrile oxide cycloaddition reactions changes on going from a molecular solvent to an ionic liquid with the latter solvent type favouring the least sterically hindered product. This is consistent with an increased cohesive pressure resulting in a smaller, more sterically demanding transition state. The rate of the process is also increased, though an increase in the rate of the dimerisation of the nitrile oxide starting material is also observed. We are currently investigating the effect of ionic liquids on the rates and regioselectivities of other cycloaddition processes, where such reaction of the starting material is not a consideration.

Acknowledgements

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