

Preparation of diphenylisoxazoline by a dipolar cycloadditio



**ASSIGN
BUSTER**

Aims

The aims of this experiment were: to synthesise a diphenylisoxazoline by a 1, 3- dipolar cycloaddition reaction - this involved the preparation of an oxime which was oxidised to form a rather unstable nitrile oxide which was trapped in situ with an alkene to yield an isoxazoline.; to fully characterise both, the intermediate oxime and the final isoxazoline, with Infra-Red and Proton NMR spectra.

Experimental

Preparation of benzaldehyde oxime

In a fume cupboard, sodium hydroxide (3. 5g) was dissolved in water (30mL) in a 100mL conical flask containing a magnetic stirrer bar. The solution was then allowed to cool down to ambient temperature and benzaldehyde (0. 5mL) was added followed by hydroxylamine hydrochloride (0. 5g). The stirrer was set to a maximum potency to allow for vigorous stirring for about 5 minutes. The conical flask was stopped at this stage.

After 5 minutes, the stopper was removed from the flask and further portions of benzaldehyde (0. 5mL) and hydroxylamine hydrochloride (0. 5g) were added. This sequence was repeated until all the benzaldehyde (total 5. 1mL) and hydroxylamine hydrochloride (total 4. 2g) were consumed.

The reaction mixture warmed up and the solution became homogeneous - indicates complete consumption of benzaldehyde.

With the aid of a broad-range pH indicator, the reaction mixture was neutralised with glacial acetic acid (1. 6mL). At this stage a few drops of

water were added to help dissolving any sodium acetate precipitate formed. The solution was then allowed to cool and the organic material (top layer) extracted with diethyl ether (2 x 30mL) to a 100mL beaker. A few spatulas of magnesium sulphate were added to the beaker to dry the organic extracts. The mixture was filtered off into a round-bottomed flask and the solvent removed on a rotary evaporator.

The yield and the IR spectrum of the oil were recorded.

1, 3-dipolar cycloaddition reaction

Again in a fume cupboard, styrene (2.9mL) and triethylamine (0.3mL) were dissolved in dichloromethane (15mL) in a 100 mL conical flask. Sodium hypochlorite solution (25mL, ca. 10% available chlorine) was added whilst stirring with the aid of a magnetic stirrer bar already in the flask. The flask was placed into an ice bath and the oily oxime (2.5g) was added dropwise with the aid of a Pasteur pipette over a period of 15 minutes. Once addition was completed, the reaction mixture was allowed to stir in the ice bath for a further period of 45 minutes.

The whole reaction mixture was transferred to a separating funnel where it was allowed to stand for a few minutes before the lower organic phase was extracted. Afterwards, the remaining aqueous phase was extracted with further dichloromethane (15mL) and both organic extracts combined and dried over magnesium sulphate (a few spatulas as required).

The mixture was filtered into a round-bottomed flask, to remove the magnesium sulphate. The flask was placed onto a rotary evaporator to

remove any remaining solvent. The weight of the crude product was recorded and the same recrystallised from ethanol.

An IR spectrum was run through the pure product and the yield recorded.

Results

Percentage yield

Step 1: Preparation of Benzaldehyde Oxime

The first step of this experiment was to synthesise the benzaldehyde oxime.

The reaction scheme for this synthesis is as follows:

Stoichiometric ratio 1:1

Benzaldehyde used = 5.1 mL | density benzaldehyde = 1.0415 g mL⁻¹, mass = 5.31 g (3 S. F.)

Molecular mass = 106.12 g mol⁻¹, therefore n. of moles = (3 S. F.)

NH₂OH · HCl used = 4.2 g | Molecular mass = 69.5 g mol⁻¹, hence n. of moles =

NaOH used = 3.5 g | Molecular mass = 40 g mol⁻¹, hence n. of moles =

Experimental ratio

Stoichiometric ratio 1:1, hence benzaldehyde is the limiting reagent.

N. of moles of benzaldehyde = n. of moles of benzaldehyde oxime

Benzaldehyde oxime yield = 4.43 g | Molecular mass = 121.139 g mol⁻¹,

thus n. of moles =

<https://assignbuster.com/preparation-of-diphenylisoxazoline-by-a-dipolar-cycloadditio/>

Step 2: 1, 3-dipolar cycloaddition reaction

The preparation of the diphenylisoxazoline by a 1, 3-dipolar cycloaddition follows the following reaction scheme:

Benzaldehyde oxime used = 2.50g | Molecular mass = 121.14 gmol⁻¹,
therefore n. of moles =

Styrene used = 2.90mL = 2.64g | Molecular mass = 104.15 gmol⁻¹, hence
n. of moles =

NaOCl (ca. 10% available Cl) used = 25 mL | density NaOCl = 1.206 gmL⁻¹,
hence 30.15g used. Molecular mass = 74.5 gmol⁻¹, therefore n. of moles =

C₆H₁₅N used = 0.3 mL | density C₆H₁₅N = 0.726 gcm⁻³, hence 0.218g
used. Molecular mass = 101.19 gmol⁻¹, therefore n. of moles =

Stoichiometric ratio of benzaldehyde oxime reacting with styrene is of 1â
%o;1

Benzaldehyde oxime is the limiting reagent

N. of moles of benzaldehyde oxime = n. of moles of diphenylisoxazoline

Yield of diphenylisoxazoline = 1.00g | molecular mass = 223.270 gmol⁻¹,
thus n. of moles =

Overall % yield

Spectroscopic data

Coupling Constants:

<https://assignbuster.com/preparation-of-diphenylisoxazoline-by-a-dipolar-cycloadditio/>

H8 at CD: 2J8, 7 = 16.4 Hz, 3J8, 6 = 8.4 Hz

H7 at CD: 2J7, 8 = 16.4 Hz, 3J7, 6 = 11.2 Hz

H6 at CE: 3J6, 7 = 11.2 Hz, 3J6, 8 = 8.4 Hz

Infra-Red Spectra

Benzaldehyde Oxime

O-H- (stretch) $\hat{\%}^{\wedge} 3500-3100 \text{ cm}^{-1}$, broad peak

C=N- $\hat{\%}^{\wedge} 1650 \text{ cm}^{-1}$

sp³ C-H $\hat{\%}^{\wedge} 3100-2750$ (including aldehyde sp³ C-H)

C=C aromatic $\hat{\%}^{\wedge} 1450-1500 \text{ cm}^{-1}$ (3 medium peaks).

N-OH $\hat{\%}^{\wedge} 960 \text{ cm}^{-1}$

3, 5-Diphenyl-2-isoxazoline

N-O $\hat{\%}^{\wedge} 920 \text{ cm}^{-1}$ (sharp, medium)

sp³ (phenyl) C-H and sp² (azoline) C-H (stretch) $\hat{\%}^{\wedge} 2800-3200 \text{ cm}^{-1}$

C-O $\hat{\%}^{\wedge} 900 \text{ cm}^{-1}$ (sharp, strong)

C=C aromatic $\hat{\%}^{\wedge} 1450-1500 \text{ cm}^{-1}$

C=N- $\hat{\%}^{\wedge} 1650 \text{ cm}^{-1}$ (sharp, weak)

Other Data

Before the organic phase was extracted, during the synthesis of benzaldehyde oxime, the reaction mixture was neutralized with glacial acetic acid, as per stated in the experimental session of this paper.

The amount of acid necessary was calculated as follows, in order to ensure an accurate amount of acid added to the reaction mixture:

N. of moles NaOH =

$\text{NH}_2\text{OH} \cdot \text{HCl}$ n. of moles =

Excess of NaOH used = % n. of moles of $\text{CH}_3\text{CO}_2\text{H}$ needed.

Molecular mass $\text{CH}_3\text{CO}_2\text{H}$ = 60.1 g mol^{-1} , hence mass of $\text{CH}_3\text{CO}_2\text{H}$ = 1.63g.

Density of $\text{CH}_3\text{CO}_2\text{H}$ = 1.049 g/mL , therefore volume needed = 1.60 mL

Discussion

Preparation of benzaldehyde oxime

The first step of this experiment: "Preparation of benzaldehyde oxime", is a simple condensation reaction between an aldehyde (benzaldehyde) and hydroxylamine.

The benzaldehyde oxime prepared was clear oil with a relatively good % yield (73%).

The comparison between the infrared spectra of the benzaldehyde oxime in the literature and the one recorded for this experiment (attached in the end of this paper) clearly indicates the successful preparation of the same.

The Nujol[®] peaks are shown more strongly in the prepared spectra, but nevertheless it proves a clear way of identifying the functional groups of this compound.

M. p. ranges were not measured, and therefore even though the IR spectrum correlates to the actual oxime's, its purity should be treated as questionable.

1, 3-dipolar Cycloaddition Reaction

In this second step of the experiment, the syn-benzaldehyde oxime produced undergoes hypochlorite oxidation to form the 1, 3-dipolar benzonitrile oxide which then reacts with the dipolarophile styrene in a 1, 3-dipolar cycloaddition reaction.

The benzonitrile oxide is termed 1, 3-dipole because of one of the resonance forms in which the formal position of the positive and negative charges are 1, 3 with respect to one another. However, the term 1, 3 does not directly relate to the position of the charges themselves but to the position of the bonding atoms in the dipolar molecule.

In this cycloaddition reaction, the dipole atoms in position 1 and 3 of the benzonitrile oxime (LUMO) bind to the styrene (HOMO) to form diphenylisoxazoline. Benzonitrile oxime contributes four π electrons to the system: two π electrons from the π bond and two non-bonding electrons from the oxygen or nitrogen. On the other hand, the dipolarophile styrene

<https://assignbuster.com/preparation-of-diphenylisoxazoline-by-a-dipolar-cycloadditio/>

contributes further two π electrons. In total $[4 + 2]$: an electronically allowed cycloaddition in which all $4 + 2$ electrons are in the ground state (thermal).

Depending of the spacial orientation of the styrene in solution, there are two theoretical products possible:

3, 4 regioisomer

3, 5 regioisomer

The reaction therefore allows 5-membered rings synthesis, proceeding with high stereospecificity. The study of spectra data such as infrared and $^1\text{H-NMR}$ allows not only the confirmation of the final product but also helps to determine the regioselectivity of the reaction.

Infra-red Spectra

By evaluation of the spectrum of diphenylisoxazoline, one can confirm the product synthesised. The peaks mentioned in the results session of this paper are indeed in accordance to the 3, 5-diphenyl-2-isoxazoline structure.

By comparison to the previous oxime spectrum, it is obvious the absence of the OH- group and the formation of a C-O bond. The sp^2 hybridised C-H stretches are also seen in the diphenylisoxazoline spectrum.

Diastereostopic Systems and $^1\text{H-NMR}$ Spectra

Diastereostopic groups are not equivalent and have different chemical shifts in NMR.

A pair of hydrogens located in a carbon atom adjacent to a stereocenter is expected to be diastereostopic.

Diastereostopic protons

According to Pavia et al, in some compounds with diastereostopic hydrogens, the chemical shifts of H_a and H_b are different and the peaks split each other into doublet of doublets (2Jab).

In this case of 3, 5-diphenyl-2-isoxazoline, the adjacent proton H_c shows large differences between the vicinal couplings between a_c ($3J_{ac}$) and b_c ($3J_{bc}$).

Referring to NMR results in the results section, the geminal coupling constant between hydrogen 8 and 7 is large. Therefore, the presence of the diastereostopic hydrogens is confirmed as the geminal coupling depends upon the bond angle between both protons. In practice the smaller the angle the larger the coupling constant.

H_8 at CD: $2J_{8,7} = 16.4$ Hz and H_7 at CD: $2J_{7,8} = 16.4$ Hz

However, the question remains: Which is the final product: 3, 5-diphenyl-2-isoxazoline or 3, 4-diphenyl-2-isoxazoline?

By using an H-NMR predictor, one can estimate the difference in chemical shifts between the diastereostopic and adjacent protons in both compounds.

3, 5-diphenyl-2-isoxazoline or 3, 4-diphenyl-2-isoxazoline?

The use of an H-NMR predictor will help to understand the final product and its regioselectivity.

Spectrum – Prediction of H-NMR spectrum of 3, 5-diphenylisoxazoline. See references

Spectrum – Prediction of H-NMR spectrum of 3, 4-diphenylisoxazoline. See references

As one can see, the chemical shifts predicted for the 3, 5-diphenyl product in respect to diastereostopic hydrogens and the methine hydrogens are: δ 3ppm and δ 6ppm respectively. On the other hand, the chemical shifts for the 3, 4-diphenyl product in respect to diastereostopic hydrogens and the methine hydrogens are: δ 5ppm and δ 4.5ppm respectively.

The above values for the 3, 5-diphenyl product are in close relation to the ones in the results section and hence the final product is the 3, 5-diphenyl-2-isoxazoline.

For the 3, 5-diphenyl-2-isoxazoline, the vicinal coupling are in accordance to the structure of the this regio-isomer.

H8 at CD: $3J_{8,6} = 8.4 \text{ Hz}$

H7 at CD: $3J_{7,6} = 11.2 \text{ Hz}$

H6 at CE: $3J_{6,7} = 11.2 \text{ Hz}$, $3J_{6,8} = 8.4 \text{ Hz}$

The vicinal coupling constant depends upon the dihedral angle between the nuclei. As such, the 3, 4-diphenyl product would have very different values.

<https://assignbuster.com/preparation-of-diphenylisoxazoline-by-a-dipolar-cycloadditio/>

Furthermore, by looking at the structure of both compounds one could say that the 3, 4-diphenyl product allows more steric hindrance than the 3, 5-diphenyl product.

Diazomethane and Ozone

Ozone and diazomethane both behave as 1, 3-dipoles.

Their reactions with styrene also yields 5-membered rings.

Ozone with Styrene

Resonance forms of ozone as 1, 3-dipoles

Diazomethane with Styrene

Conclusion

Both reactions were successful and the products characterized. The regioselectivity of the isoxazoline was analysed by H-NMR spectrum and the product determined to be 3, 5-diphenylisoxazoline.

Melting point ranges could have helped to determine the purity of the samples.

In order to further understand the factors contributing to the regioselectivity product of the 1, 3-dipolar cycloaddition reaction, molecular modelling software could be used to determine energy differences between the products and transition states and whether the reaction is thermodynamically or kinetically favoured or both.

In conjunction with frontier orbital of both HOMO and LUMO and vice versa of the reagents, one could determine the reason for one product being more favoured than other.

Nevertheless, the reaction of styrene with 1, 3-dipolar benzaldehyde oxime yields 3, 5-diphenyl-2-isoxazoline