

### 3. EXPERIMENTAL

### 3 EXPERIMENTAL

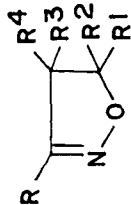
#### 3.1 SYNTHESIS OF ISOXAZOLINES

The isoxazolines were synthesised employing the nitrile oxide cycloaddition with alkenes. Acetonitrile oxide, propionitrile oxide, benzonitrile oxide, 4-chlorobenzonitrile oxide and 3-nitrobenzonitrile oxide are the five nitrile oxides used for cycloaddition with alkenes. The alkenes chosen for the present investigation are styrene,  $\alpha$ -methylstyrene, 2-methylstyrene, 1-hexene, allyl methyl sulphide, vinylcyclohexane, methyl acrylate, methyl methacrylate, cyclopentene, cyclohexene and norbornene. For the generation of nitrile oxides two general methods were used. Aliphatic nitrile oxides were generated by Mukaiyama's method<sup>17</sup> and aryl nitrile oxides by Torssell's method.<sup>16</sup>

##### 3.1.1 Mukaiyama's method<sup>17</sup>

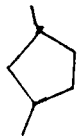
Acetonitrile oxide and propionitrile oxide were generated in situ by this method and the isoxazolines 1a-e to 11a-e are synthesised by the cycloaddition of these nitrile oxides with the alkenes. The physical constants of the isoxazolines are collected in Table 3.1, and the general procedure is given below.

Table 3.1  
Physical Constants of Isoxazolines



Isoxazoline	R	R <sup>1</sup>	R <sup>2</sup>	R <sup>3</sup>	R <sup>4</sup>	b.p.
1a	CH <sub>3</sub>	C <sub>6</sub> H <sub>5</sub>	H	H	H	163°C/50 mm Hg (Lit. b.p. 95-98°C/0.3 Torr) <sup>17</sup>
1b	CH <sub>3</sub> CH <sub>2</sub>	"	"	"	"	140°C/50 mm Hg (Lit. b.p. 90-92°C/ 0.15 Torr) <sup>17</sup>
2a	CH <sub>3</sub>	C <sub>6</sub> H <sub>5</sub>	CH <sub>3</sub>	H	H	Purified by column chromatography
2b	CH <sub>3</sub> CH <sub>2</sub>	"	"	"	"	"
3a	CH <sub>3</sub>	2CH <sub>3</sub> C <sub>6</sub> H <sub>4</sub>	H	H	H	105°C/45 mm Hg
3b	CH <sub>3</sub> CH <sub>2</sub>	"	"	"	"	145°C/45 mm Hg
4a	CH <sub>3</sub>	COOCH <sub>3</sub>	H	H	H	124°C/50 mm Hg (Lit. b.p. 50-60°C/ 0.1 mm Hg) <sup>164</sup>
4b	CH <sub>3</sub> CH <sub>2</sub>	"	"	"	"	145°C/50 mm Hg (Lit. b.p. 85°C/ 0.3 mm Hg) <sup>164</sup>

(contd.)

5a	CH <sub>3</sub>	COOCH <sub>3</sub>	CH <sub>3</sub>	H	H	Purified by column chromatography
5b	CH <sub>3</sub> CH <sub>2</sub>	"	"	"	"	"
6a	CH <sub>3</sub>	n-butyl	H	H	H	115°C/50 mm Hg
6b	CH <sub>3</sub> CH <sub>2</sub>	"	"	"	"	120°C/50 mm Hg (Lit. b.p. 46°C/ 0.2 mm Hg) <sup>165</sup>
7a	CH <sub>3</sub>	CH <sub>2</sub> SCH <sub>3</sub>	H	H	H	114°C/45 mm Hg
7b	CH <sub>3</sub> CH <sub>2</sub>	"	"	"	"	Purified by column chromatography
8a	CH <sub>3</sub>	Cyclohexyl	H	H	H	"
8b	CH <sub>3</sub> CH <sub>2</sub>	"	"	"	"	"
9a	CH <sub>3</sub>	H	-CH <sub>2</sub> -CH <sub>2</sub> -CH <sub>2</sub> -H	H	H	" (Lit. b.p. 61°C/2 Torr) <sup>166</sup>
9b	CH <sub>3</sub> CH <sub>2</sub>	"	"	"	"	" (Lit. b.p. 79°C/5 Torr) <sup>167</sup>
10a	CH <sub>3</sub>	H	-(CH <sub>2</sub> ) <sub>4</sub> -	H	H	"
10b	CH <sub>3</sub> CH <sub>2</sub>	H	"	H	H	" (Lit. 168)
11a	CH <sub>3</sub>	H		H	H	" (Lit. b.p. 88°C/1 mm Hg) <sup>169</sup>
11b	CH <sub>3</sub> CH <sub>2</sub>	H	"	H	H	" (Lit. 170)

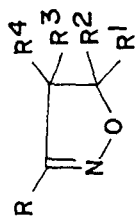
**Mukaiyama's procedure :**

Into a two-necked round bottomed flask provided with a magnetic stirrer and a reflux condenser, was added benzene (75mL) *containing 0.1 mol of phenyl isocyanate.* nitroethane (7.5g, 0.1mol) or 1-nitropropane (9g, 0.1mol). To the stirred solution was added the alkene (0.1mol) and catalytic amounts of triethylamine (2 drops in 1mL benzene). After allowing the reaction mixture to stir for 2 hours, the precipitated diphenylurea was removed by filtration. The filtrate was heated under reflux for 1 hour and allowed to cool. The solvent was removed by evaporation under reduced pressure. Distillation under reduced pressure afforded the isoxazolines in pure form. In certain cases the isoxazolines were obtained by separation using column chromatography. The yield generally ranges from 75% to 80%.

**3.1.2 Torssell's method**

Benzonitrile oxide, 4-chlorobenzonitrile oxide and 3-nitrobenzonitrile oxide have been generated in situ by Torssell's method. The isoxazolines 1c-e to 11c-e have been prepared by this method and the general procedure is given below. The physical constants of the isoxazolines are given in Table 3.2.

Table 3.2  
Physical Constants of Isoxazolines



Isoxazoline	R	R <sup>1</sup>	R <sup>2</sup>	R <sup>3</sup>	R <sup>4</sup>	m. p.
1c	C <sub>6</sub> H <sub>5</sub>	C <sub>6</sub> H <sub>5</sub>	H	H	H	75°C/EtOH(Lit. m. p. 76°C/EtOH) 171
1d	4ClC <sub>6</sub> H <sub>4</sub>	"	"	"	"	137°C/EtOH
1e	3NO <sub>2</sub> C <sub>6</sub> H <sub>4</sub>	"	"	"	"	--
2c	C <sub>6</sub> H <sub>5</sub>	C <sub>6</sub> H <sub>5</sub>	CH <sub>3</sub>	H	H	74°C/Petroleum ether 60-80° (Lit. m. p. 76°C/EtOH) 172
2d	4ClC <sub>6</sub> H <sub>4</sub>	"	"	"	"	70°C
2e	3NO <sub>2</sub> C <sub>6</sub> H <sub>4</sub>	"	"	"	"	71°C/EtOH
3c	C <sub>6</sub> H <sub>5</sub>	2CH <sub>3</sub> C <sub>6</sub> H <sub>4</sub>	"	"	"	77°C
3d	4ClC <sub>6</sub> H <sub>4</sub>	"	"	"	"	--
3e	3NO <sub>2</sub> C <sub>6</sub> H <sub>4</sub>	"	"	"	"	--
6c	C <sub>6</sub> H <sub>5</sub>	n-butyl	H	H	H	40°C/Petroleum ether 60-80° (Lit. m. p. 41°C/EtOH) 174
6d	4ClC <sub>6</sub> H <sub>4</sub>	"	"	"	"	184°C/Petroleum ether 60-80°
6e	3NO <sub>2</sub> C <sub>6</sub> H <sub>4</sub>	"	"	"	"	56°C/EtOH

(contd)



7c	C <sub>6</sub> H <sub>5</sub>	Cyclohexyl	H	H	H	36°C/Petroleum ether 60-80°
7d	4ClC <sub>6</sub> H <sub>4</sub>	"	"	"	"	112°C/Petroleum ether 60-80°
7e	3NO <sub>2</sub> C <sub>6</sub> H <sub>4</sub>	"	"	"	"	88°C/Petroleum ether 60-80°
8c	C <sub>6</sub> H <sub>5</sub>	CH <sub>2</sub> SCH <sub>3</sub>	H	H	H	--
8d	4ClC <sub>6</sub> H <sub>4</sub>	"	"	"	"	176°C/EtOH
8e	3NO <sub>2</sub> C <sub>6</sub> H <sub>4</sub>	"	"	"	"	84°C/EtOH
9c	C <sub>6</sub> H <sub>5</sub>	H	-(CH <sub>2</sub> ) <sub>3</sub> -	H	H	49°C/EtOH(Lit.m.p. 38.5°C/ petroleum ether-ether) <sup>175</sup>
9d	4ClC <sub>6</sub> H <sub>4</sub>	"	"	"	"	--
9e	3NO <sub>2</sub> C <sub>6</sub> H <sub>4</sub>	"	"	"	"	--
10c	C <sub>6</sub> H <sub>5</sub>	"	-(CH <sub>2</sub> ) <sub>4</sub> -	H	H	(Lit. 51)
11c	C <sub>6</sub> H <sub>5</sub>	H		H	H	109°C/EtOH (Lit. 177)
11d	4ClC <sub>6</sub> H <sub>4</sub>	H		"	"	88°C/EtOH
11e	3NO <sub>2</sub> C <sub>6</sub> H <sub>4</sub>	"	"	"	"	90°C/EtOH
14c	C <sub>6</sub> H <sub>5</sub>	COOCH <sub>3</sub>	H	H	H	140°C/Petroleum ether 60-80°(Lit. 173)
4d	4ClC <sub>6</sub> H <sub>4</sub>	"	"	"	"	73°C/EtOH
4e	3NO <sub>2</sub> C <sub>6</sub> H <sub>4</sub>	"	"	"	"	85°C/EtOH
5c	C <sub>6</sub> H <sub>5</sub>	COOCH <sub>3</sub>	CH <sub>3</sub>	H	H	46°C/EtOH
5d	4ClC <sub>6</sub> H <sub>4</sub>	"	"	"	"	48°C/EtOH
5e	3NO <sub>2</sub> C <sub>6</sub> H <sub>4</sub>	"	"	"	"	105°C/EtOH

Table 3.3

## Microanalytical Data of Some Isoxazolines

Isoxazoline	% Calculated			% Observed		
	C	H	N	C	H	N
2d	70.8	5.2	5.2	70.3	5.0	4.9
4c	64.4	5.4	6.8	63.4	4.9	6.6
4d	55.2	4.2	5.9	55.2	4.2	6.1
4e	52.8	4.0	11.2	52.4	3.9	11.0
7d	54.8	5.0	5.8	56.3	5.0	6.0
7e	54.6	5.0	11.6	53.3	5.1	10.8
11c	78.9	7.0	6.6	78.3	6.8	5.0
11d	68.0	5.7	5.7	68.2	5.7	5.1
11e	65.1	5.4	10.9	65.2	5.4	10.2



Torssell's procedure :

To a round-bottomed flask provided with a reflux condenser was added N-chlorosuccinimide (2.66g, 0.02 mol) and dichloromethane (75 mL). To the suspension was added pyridine (1mL) and araldoxime (0.02 mol).. The mixture was heated under reflux for 1 hour and then allowed to cool. A solution of alkene (0.02 mol in 10mL CH<sub>2</sub>Cl<sub>2</sub>) and then triethylamine (2mL in 5mL CH<sub>2</sub>Cl<sub>2</sub>) were added and heated under reflux for 1 hour. After allowing the reaction mixture to cool, it was washed with water (to remove succinimide, pyridine.HCl) and dried (anhydrous Na<sub>2</sub>SO<sub>4</sub>). Concentration in vacuo yielded the isoxazolines which were purified by recrystallization or by column chromatography. The yield generally ranges from 60% to 70%.

### 3.2 CHROMATOGRAPHY

Analytical thin-layer chromatography was performed using silica gel G (Sisco-Chem). A slurry of silica gel was prepared by mixing silica gel G(30g) with 3:l(v/v)mixture of chloroform and methanol. The slurry was made homogeneous and the glass plates were coated by dipping them in the slurry and then allowing to dry.

Preparative column chromatography was done using silica-gel for column chromatography (Sisco-Chem). The eluent used was dichloromethane for the separation of the isoxazolines.

### 3.3. NMR SPECTRAL MEASUREMENTS

#### 3.3.1 Proton nmr spectra

Proton nmr spectra at 270 MHz were recorded principally on a Bruker WH-270 NMR spectrometer. Samples were prepared by dissolving the isoxazolines (10-20mg) in 1mL of chloroform-d containing 1% TMS.

#### 3.3.2 CARBON-13 nmr spectra

Proton decoupled  $^{13}\text{C}$  nmr spectra were recorded on a Bruker WH-270 NMR spectrometer using 10mm sample tubes. The samples were prepared by dissolving the isoxazolines in chloroform-d and the spectra recorded with TMS as internal standard.

### 3.4. MASS SPECTRAL MEASUREMENTS

Mass spectra of the isoxazolines have been recorded under electron-impact with mass spectrometer at 70eV ionizing voltage.