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## AN IMPROVED SYNTHESIS OF 3-METHYL-4-NITRO-5-HETEROARYLETHENYLISOXAZOLES

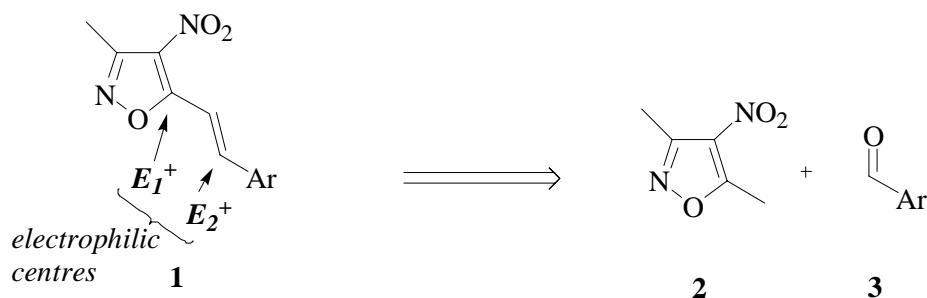
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**Abstract** – A high yielding synthesis of polyfunctional scaffold  
 3-methyl-4-nitro-5-heteroarylethenylisoxazole is described. The novel condition  
 allowed the preparation of reactive title compounds in high yield.

### INTRODUCTION

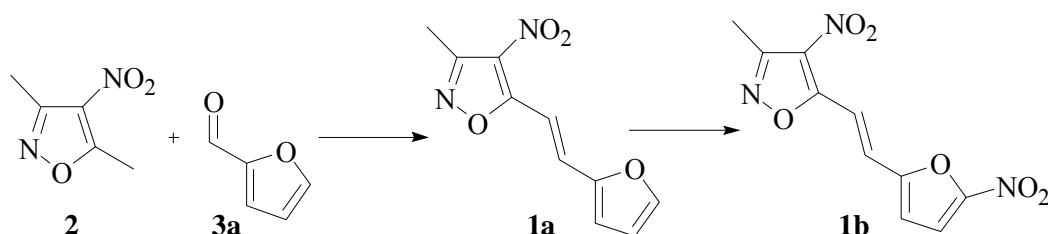
3-Methyl-4-nitro-5-styrylisoxazoles **1** represent a class of poly-functional scaffolds, which hold excellent potential for the generation of diversity.<sup>1-6</sup> Our approach to the development of multicomponent diversity oriented syntheses is based on the generation of building blocks containing several functionalities which can be selectively reacted.<sup>1-5</sup> For example, we have shown that **1** could be employed efficiently for the preparation of spiroisoxazolines,<sup>1,2</sup> heteroarylpropionic acids<sup>3-5</sup> or 3-indolepropionic acids.<sup>6</sup> In these syntheses, the two electrophilic centres present in **1**, were reacted selectively and independently.<sup>1-6</sup>



**Figure 1** Polyfunctional scaffold 5-styryl-4-nitroisoxazole **1**

Compounds **1** could be prepared from the condensation of commercially available 3,5-dimethyl-4-nitroisoxazole **2** and an aromatic aldehyde **3** (**Figure 1**).

While several compounds **1** have been reported in which Ar is represented by a substituted phenyl ring,<sup>7,8</sup> only a few examples have been described in which Ar is of heterocyclic nature.<sup>9,10</sup> In these syntheses, 5-styrylisoxazoles **1** were prepared by heating equimolar amounts of isoxazole **2** and an aromatic aldehyde in the presence of a large excess of amine bases.<sup>7-10</sup> This procedure failed at producing in particular compounds bearing additional electron-withdrawing groups. For example, while isoxazole **2** was efficiently reacted with furfural **3a** to give 5-styrylisoxazole **1a** in good yield, the reaction of **2** with 5-nitrofurfural gave a complex mixture of products. Therefore the synthesis of **1b**, which was found possessing antibacterial activity, required the condensation of **2** and **3a** and successive nitration of the resulting **1a** (Scheme 1).<sup>10</sup>

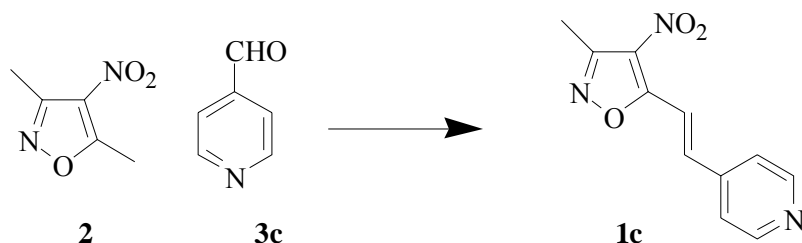


**Scheme 1** Synthesis of heterocyclic 5-styrylisoxazoles **1a** and **1b**.

During the development of some multicomponent reactions using isoxazole **2**,<sup>1-6</sup> we found that condensation of **2** with aromatic aldehydes proceeded in the presence of a catalytic amount of piperidine. Herein we report our studies on the condensation of **2** with different heterocyclic aldehydes, which proceeded in high yields using a limited amount of piperidine base.

## RESULTS AND DISCUSSION

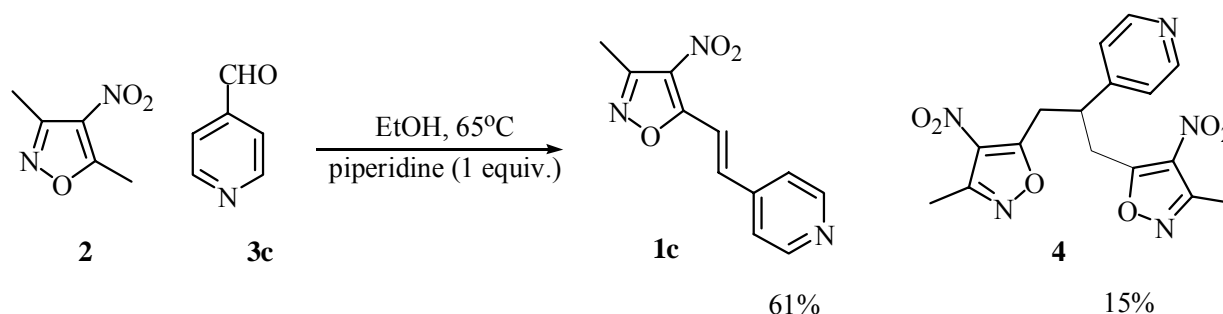
We began our studies from the condensation of **2** with pyridine-4-carbaldehyde **3c**, as this reaction constituted an ideal test given the high reactivity of the resulting **1c** (Scheme 2).



**Scheme 2** Optimisation of the synthesis of **1c**.

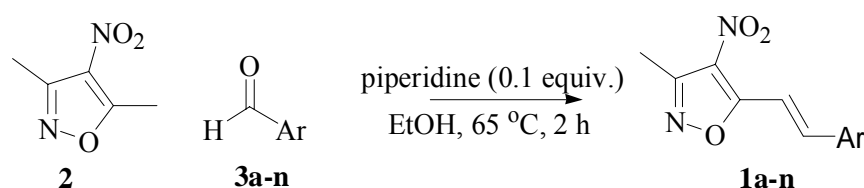
The following parameters were particularly studied: nature of the amine catalyst, catalyst loading, solvent, reactants concentrations, temperature and reaction time. It was found that the nature of the amine catalyst played a crucial role, where secondary amines proved to be superior catalysts compared to tertiary ones. In agreement with published reports, this reaction required at least 3 equivalents of triethylamine and

several hours in order to proceed to completion (**Scheme 1**).<sup>7-10</sup> Other tertiary amines like *N*-methylmorpholine and *N*-methylpyrrolidine gave similar results. However, when 1 equivalent of piperidine was used, the reaction of **2** and **3c** in ethanol required 35 min to convert the starting material **2** quantitatively. Significantly, this reaction proceeded equally well in the presence of substoichiometric amounts of base (0.5 eq., 0.2 eq. and 0.1 eq.). Similar results were obtained using morpholine and pyrrolidine, while a complete conversion of **2** was observed with diethylamine only when 0.2 eq. of amine was used. We also noticed that compound **1c** was obtained in an increased yield when piperidine was employed in catalytic amounts. This was due to a concomitant Michael reaction of isoxazole **2** and **1c**, which produced adduct **4** (**Scheme 3**).<sup>11</sup>



**Scheme 3** Reaction of **2** and **3c** run in the presence of 1 equivalent of piperidine.

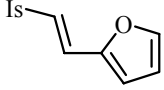
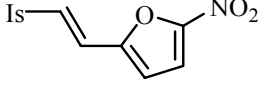
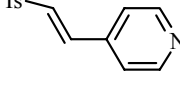
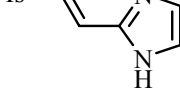
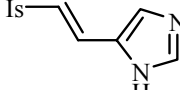
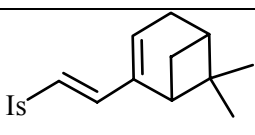
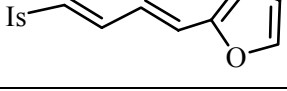
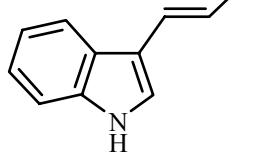
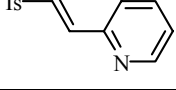
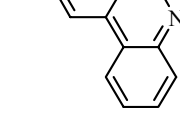
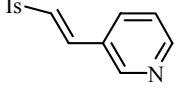
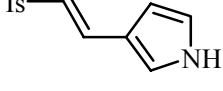
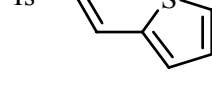
Indeed, the extent of formation of **4** was minimised by using only catalytic amount of a secondary amine. Additionally, the results obtained using secondary and tertiary amines indicated that when secondary amines are used, the condensation of **1** and aldehydes **3** must proceed via a fast Mannich reaction. Even at low catalyst loading the secondary amines condensed with **3c** to give an iminium ion which rapidly consumed starting material **2**. Typically with 0.1 eq. of piperidine present, **1a** was obtained in 85% yield along with only 3% of **4**. The reaction of **2** and **3c** was then studied in different solvents including methanol, ethanol, tetrahydrofuran, dioxane and dichloromethane. Ethanol and methanol ensured the best results furnishing high yields of **1c** in 2-3 h. The reaction proceeded in tetrahydrofuran and dichloromethane equally well, although it required longer reaction times (6-8 h).



**Scheme 4** Synthesis of 5-heteroaromatic 5-styrylisoxazoles **1a-n**.

These studies identified a standard procedure which was used to prepare compounds **1a-n** in high yield (**Scheme 4**, **Table 1**). Using this procedure it was possible to obtain a vast number of

**Table 1** Yields of 5-styrylisoxazoles **1a-n**.

Entry	Compound	Aldehyde	Product <sup>a</sup>	Yield%
1	<b>1a</b>	furan-2-carbaldehyde		89
2	<b>1b</b>	5-nitro-furan-2-carbaldehyde		69
4	<b>1c</b>	pyridine-4-carbaldehyde		89
5	<b>1d</b>	1 <i>H</i> -imidazole-2-carbaldehyde		84
6	<b>1e</b>	1 <i>H</i> -imidazole-5-carbaldehyde		81
7	<b>1f</b>	6,6-dimethylbicyclo [3.1.1]-hept-2-ene-2-carbaldehyde		81
8	<b>1g</b>	3-furan-2-ylpropenal		77
9	<b>1h</b>	1 <i>H</i> -indole-3-carbaldehyde		85
10	<b>1i</b>	pyridine-2-carbaldehyde		76
11	<b>1k</b>	quinolin-4-carbaldehyde		71
12	<b>1l</b>	pyridine-3-carbaldehyde		85
13	<b>1m</b>	1 <i>H</i> -pyrrole-3-carbaldehyde		83
14	<b>1n</b>	thiophene-3-carbaldehyde		91

<sup>a</sup> Is = 3-methyl-4-nitroisoxazol-5-yl

5-heteroarylstyrylisoxazoles including those bearing electron-withdrawing groups. We also briefly explored the scope of aldehyde and it was found that only aromatic, heteroaromatic or  $\alpha,\beta$ -unsaturated aldehydes were good substrates. This data substantiates the proposal of a Mannich mechanism operating in the condensation of compound **2** with aldehydes.

In conclusion, we have developed a mild and efficient procedure for the formation of 5-styrylisoxazoles **1a-n**. The optimised conditions allowed obtaining the known 5-styrylisoxazoles in increased yield and expanded the range of compounds **1** that could be prepared.

## EXPERIMENTAL

$^1\text{H}$  and  $^{13}\text{C}$  spectra were recorded on a 200 or 400 MHz spectrometers at ambient temperatures.  $^1\text{H}$  NMR spectral assignments are supported by  $^1\text{H}$ - $^1\text{H}$  COSY and  $^{13}\text{C}$ - $^1\text{H}$  COSY where necessary. For  $^1\text{H}$  NMR recorded in  $\text{CDCl}_3$  chemical shifts ( $\delta_{\text{H}}$ ) are quoted in parts per million (ppm) and are referenced to the residual solvent peak. The following abbreviations are used: s, singlet, d, doublet, t, triplet, dd, doublet of doublets, dt, doublet of triplets, tt, triplet of triplets, m, multiplet and br, broad. Coupling constants ( $J$ ) were measured in Hertz (Hz) to the nearest 0.5 Hz. Carbon spectra are supported by DEPT analysis where necessary. Infrared (IR) spectra were recorded as thin films between NaCl plates. Absorption maximum ( $\nu_{\text{max}}$ ) was reported in wave numbers ( $\text{cm}^{-1}$ ) and only selected peaks are reported. The following abbreviations are used: w, weak, m, medium, s, strong and br, broad. Flash chromatography was carried out using *silica gel 60* (0.040-0.063mm, 230-400 mesh) as the stationary phase. Thin layer chromatography was carried out on aluminium backed plates pre-coated with *silica gel 60*, which were visualized by quenching of u.v. fluorescence ( $\lambda_{\text{max}} = 254 \text{ nm}$ ) or by staining with either 10% w/v ammonium molybdate in 2M sulphuric acid or basic potassium permanganate solution (followed by heat) as appropriate. Retention factors ( $R_f$ ) are reported to  $\pm 0.5$ .

### General procedure for the preparation of 5-styrylisoxazoles **1a-n**

In a round-bottom flask was put 3,5-dimethyl-4-nitroisoxazole **2** (0.142 g, 1 mmol), an aldehyde **3a-n** (1 mmol), piperidine (10  $\mu\text{L}$ , 0.10 eq.) and EtOH (2 mL). The reactants were stirred at 65°C for 2 h. The reaction mixture was then allowed to reach rt, the solid obtained collected by filtration and crystallised from EtOH to give pure **1a-n**. Compounds **1a-n** are photoreactive and should be stored in the absence of light.

**5-(2-Furan-2-ylvinyl)-3-methyl-4-nitroisoxazole 1a<sup>10</sup>**

Yellow solid (196 mg, 89% yield);  $R_f = 0.62$  (EtOAc : acetone : petroleum spirits as 1 : 1 : 8); mp 162-164°C (EtOH);  $\nu_{max}$  (film)/ $\text{cm}^{-1}$ : 1608m (Is), 1571s (NO<sub>2</sub>);  $\delta_H$  (200 MHz, CD<sub>3</sub>COCD<sub>3</sub>) 7.49 (1H, m), 7.42 (2H, m), 6.67 (1H, d,  $J = 3$ ), 6.43-6.47 (1H, m), 2.48 (3H, s);  $\delta_C$  (80MHz, CD<sub>3</sub>COCD<sub>3</sub>) 166.6, 155.7, 150.6, 145.5, 131.3, 128.2, 116.3, 112.6, 108.1, 11.5. *Anal.* Calcd for C<sub>10</sub>H<sub>8</sub>N<sub>2</sub>O<sub>4</sub>: C, 54.55; H, 3.66; N, 12.72. Found C 54.38, H 3.78, N 12.82. MS (EI):  $m/z$  220 (100%, M<sup>+</sup>).

**3-Methyl-4-nitro-5-[2-(5-nitrofuran-2-yl)vinyl]isoxazole 1b<sup>10</sup>**

Pale yellow solid (188 mg, 69% yield);  $R_f = 0.3$  (EtOAc : acetone : petroleum spirits as 2 : 1 : 8); mp 174-176°C (EtOH);  $\nu_{max}$  (film)/ $\text{cm}^{-1}$ : 1605m (Is), 1570s (NO<sub>2</sub>);  $\delta_H$  (400 MHz, CD<sub>3</sub>COCD<sub>3</sub>) 7.80 (1H, d,  $J = 16$ ), 7.73 (1H, d,  $J = 16$ ), 7.68-7.47 (2H, m), 2.62 (3H, s);  $\delta_C$  (100MHz, CD<sub>3</sub>COCD<sub>3</sub>) 166.7, 155.7, 142.6, 133.9, 130.8, 130.6, 127.9, 126.7, 110.4, 11.4. *Anal.* Calcd for C<sub>10</sub>H<sub>7</sub>N<sub>3</sub>O<sub>6</sub>: C, 45.29; H, 2.66; N, 15.85. Found C 45.17, H 2.79, N 15.99. MS (EI):  $m/z$  265 (100%, M<sup>+</sup>).

**4-[2-(3-Methyl-4-nitroisoxazol-5-yl)vinyl]pyridine 1c<sup>9</sup>**

Yellow solid (180 mg, 78% yield);  $R_f = 0.3$  (EtOH : benzene as 1 : 9); mp 154-156°C (ethanol);  $\nu_{max}$  (film)/ $\text{cm}^{-1}$ : 1601m (Is), 1580s (NO<sub>2</sub>);  $\delta_H$  (400 MHz, CD<sub>3</sub>COCD<sub>3</sub>) 8.80-8.70 (2H, m), 7.85 (1H, d,  $J = 18$ ), 7.60-7.49 (2H, m), 7.42 (1H, d,  $J = 18$ ), 2.60 (3H, s);  $\delta_C$  (100MHz, CD<sub>3</sub>COCD<sub>3</sub>) 165.6, 155.7, 142.6, 133.9, 130.7, 128.7, 127.9, 110.5, 11.5. *Anal.* Calcd for C<sub>11</sub>H<sub>9</sub>N<sub>3</sub>O<sub>3</sub>: C, 57.14; H, 3.92; N, 18.17. Found C 57.28, H 4.11, N 18.04. MS (EI):  $m/z$  231 (100%, M<sup>+</sup>).

**5-[2-(1H-Imidazol-2-yl)vinyl]-3-methyl-4-nitroisoxazole 1d**

Orange solid (185 mg, 84% yield);  $R_f = 0.5$  (EtOH : benzene as 2 : 9); mp 186-188°C (EtOH);  $\nu_{max}$  (film)/ $\text{cm}^{-1}$ : 1603m (Is), 1575s (NO<sub>2</sub>);  $\delta_H$  (400 MHz, CD<sub>3</sub>COCD<sub>3</sub>): 8.30 (1H, d,  $J = 16$ ), 7.98 (1H, d,  $J = 16$ ), 7.37 (1H, s), 7.29 (1H, s), 2.64 (3H, s, CH<sub>3</sub>);  $\delta_C$  (100MHz, CD<sub>3</sub>COCD<sub>3</sub>) 166.7, 155.7, 142.6, 131.2, 130.7, 127.6, 124.5, 110.5, 11.5. *Anal.* Calcd for C<sub>9</sub>H<sub>8</sub>N<sub>4</sub>O<sub>3</sub>: C, 49.09; H, 3.66; N, 25.45. Found C 48.99, H 3.71, N 25.35. MS (EI):  $m/z$  220 (100%, M<sup>+</sup>).

**5-[2-(3H-Imidazol-4-yl)vinyl]-3-methyl-4-nitroisoxazole 1e**

Yellow solid (178 mg, 81% yield);  $R_f = 0.6$  (EtOH : benzene as 2 : 9); mp 178-180°C (EtOH);  $\nu_{max}$  (film)/ $\text{cm}^{-1}$ : 1601m (Is), 1578s (NO<sub>2</sub>);  $\delta_H$  (400 MHz, CD<sub>3</sub>COCD<sub>3</sub>): 8.29 (1H, s), 8.00 (1H, d,  $J = 16$ ), 7.78 (1H, s), 7.65 (1H, d,  $J = 16$ ), 2.63 (3H, s, CH<sub>3</sub>);  $\delta_C$  (100MHz, CD<sub>3</sub>COCD<sub>3</sub>): 166.7, 155.7, 140.6, 133.9,

131.2, 129.1, 126.0, 110.5, 11.5. *Anal.* Calcd for  $C_9H_8N_4O_3$ : C, 49.09; H, 3.66; N, 25.45. Found C 49.15, H 3.58, N 25.6. MS (EI):  $m/z$  220 (100%,  $M^+$ ).

### 5-[2-(6,6-Dimethylbicyclo[3.1.1]hept-2-en-2-yl)vinyl]-3-methyl-4-nitroisoxazole 1f

Colourless solid (222 mg, 81% yield);  $R_f = 0.6$  (EtOAc: acetone: petroleum spirits as 5 : 5 : 90); mp 135-136°C (EtOH);  $\nu_{max}$  (film)/ $cm^{-1}$ : 1609m (Is), 1586s ( $NO_2$ );  $\delta_H$  (400 MHz,  $CD_3COCD_3$ ): 7.45 (1H, d,  $J = 16$ ), 7.00 (1H, d,  $J = 16$ ), 6.25 (1H, m), 2.76 (1H, t,  $J = 5$ ), 2.58 (3H, s), 2.48-2.55 (3H, m), 2.2 (1H, m), 1.41 (3H, s), 1.19 (1H, d,  $J = 8$ ), 0.82 (3H, s);  $\delta_C$  (100MHz,  $CD_3COCD_3$ ): 167.7, 155.6, 146.3, 143.5, 137.3, 132.5, 107.1, 40.2, 40.1, 33.0, 32.6, 30.7, 25.6, 20.4, 11.5. *Anal.* Calcd for  $C_{15}H_{18}N_2O_4$ : C, 65.68; H, 6.61; N, 10.21. Found C 65.54, H 6.73, N 10.18. MS (EI):  $m/z$  274 (100%,  $M^+$ ).

### 5-(4-Furan-2-yl-buta-1,3-dienyl)-3-methyl-4-nitroisoxazole 1g

Orange-red solid (189 mg, 77% yield);  $R_f = 0.7$  (EtOAc: acetone: petroleum spirits as 5 : 5 : 90); mp 186-188°C (EtOH);  $\nu_{max}$  (film)/ $cm^{-1}$ : 1589m (Is), 1569s ( $NO_2$ );  $\delta_H$  (400 MHz,  $CD_3COCD_3$ ): 7.53 (1H, dd,  $J = 15, J = 11$ ), 7.51 (1H, d,  $J = 2$ ), 7.22 (1H, d,  $J = 15$ ), 6.97 (1H, dd,  $J = 15, J = 11$ ), 6.81 (1H, d,  $J = 16$ ), 6.58 (1H, d,  $J = 4$ ), 6.50 (1H, dd,  $J = 4, J = 2$ ), 2.43 (3H, s);  $\delta_C$  (100MHz,  $CD_3COCD_3$ ): 166.7, 155.6, 151.7, 144.0, 142.4, 131.2, 127.9, 125.0, 113.3, 112.8, 112.1, 11.5. *Anal.* Calcd for  $C_{12}H_{10}N_2O_4$ : C, 58.54; H, 4.09; N, 11.38. Found C 58.40, H 4.19, N 11.45. MS (EI):  $m/z$  246 (100%,  $M^+$ ).

### 3-[2-(3-Methyl-4-nitroisoxazol-5-yl)vinyl]-1H-indole 1h

Red solid (232 mg, 85% yield);  $R_f = 0.4$  (EtOH : benzene 1 : 9); mp 168-171 °C (EtOH);  $\nu_{max}$  (film)/ $cm^{-1}$ : 1601m (Is), 1576s ( $NO_2$ );  $\delta_H$  (400 MHz,  $CD_3COCD_3$ ): 8.80 (1H, s, br), 8.07 (1H, d,  $J = 7$ ), 8.06 (1H, d,  $J = 16$ ), 7.72 (1H, d,  $J = 16$ ), 7.69 (1H, s), 7.48 (1H, dd,  $J = 8, J = 3$ ), 7.38-7.36 (2H, m), 2.62 (3H, s);  $\delta_C$  (80MHz,  $CD_3COCD_3$ ): 168.4, 155.5, 138.1, 137.9, 133.2, 125.6, 124.8, 123.1, 121.6, 119.8, 113.5, 112.7, 104.4, 11.7. *Anal.* Calcd for  $C_{14}H_{11}N_3O_3$ : C 62.45, H 4.12, N 15.61. Found C 62.38, H 4.22, N 15.58. MS (EI):  $m/z$  269 (100%,  $M^+$ ).

### 2-[2-(3-Methyl-5-nitroisoxazol-5-yl)vinyl]pyridine 1i

Green solid (176 mg, 76% yield);  $R_f = 0.3$  (EtOAc : acetone : petroleum spirits as 1 : 1 : 8); mp 149-150°C (EtOH);  $\nu_{max}$  (film)/ $cm^{-1}$ : 1608m (Is), 1570s ( $NO_2$ );  $\delta_H$  (400 MHz,  $CD_3COCD_3$ ): 8.75-8.68 (1H, m), 8.19 (1H, d,  $J = 16$ ), 7.75 (1H, d,  $J = 16$ ), 7.80-7.21 (3H, m), 2.60 (3H, s);  $\delta_C$  (100MHz,  $CD_3COCD_3$ ): 166.4, 155.7, 149.6, 142.6, 133.9, 131.3, 130.7, 128.7, 127.9, 110.5, 11.5. *Anal.* Calcd for  $C_{11}H_9N_3O_3$ : C, 57.14; H, 3.92; N, 18.17. Found C 57.28, H 3.77, N 18.37. MS (EI):  $m/z$  231 (100%,  $M^+$ ).

**4-[2-(3-Methyl-4-nitro-isoxazol-5-yl)vinyl]quinoline 1k**

Yellow solid (251 mg, 89% yield),  $R_f = 0.5$  (EtOH : benzene as 1 : 9); mp 166-168°C (EtOH);  $\nu_{max}$  (film)/ $\text{cm}^{-1}$ : 1606m (Is), 1581s (NO<sub>2</sub>);  $\delta_H$  (400 MHz, CD<sub>3</sub>COCD<sub>3</sub>): 9.03 (1H, d,  $J = 2$ ), 8.55 (1H, d,  $J = 16$ ), 8.21 (2H, m), 7.94 (1H, d,  $J = 16$ ), 7.83 (1H, t,  $J = 7$ ), 7.76 (1H, d,  $J = 4$ ), 7.71 (1H, t,  $J = 8$ ), 2.67 (3H, s, CH<sub>3</sub>);  $\delta_C$  (100MHz, CD<sub>3</sub>COCD<sub>3</sub>): 165.5, 155.9, 149.7, 148.4, 138.9, 136.5, 130.0, 129.9, 129.0, 127.3, 125.8, 122.8, 117.9, 116.7, 11.4 (CH<sub>3</sub>). *Anal.* Calcd for C<sub>15</sub>H<sub>11</sub>N<sub>3</sub>O<sub>3</sub>: C 60.05, H 3.94, N 14.94. Found C 59.91, H 3.98, N 11.90. MS (EI):  $m/z$  281 (100%, M<sup>+</sup>).

**3-[2-(3-Methyl-4-nitroisoxazol-5-yl)vinyl]pyridine 1l**

Pale yellow solid (164 mg, 71% yield);  $R_f = 0.3$  (EtOAc : acetone : petroleum spirits as 1 : 1 : 8); mp 147-148°C (EtOH);  $\nu_{max}$  (film)/ $\text{cm}^{-1}$ : 1600m (Is), 1575s (NO<sub>2</sub>);  $\delta_H$  (400 MHz, CD<sub>3</sub>COCD<sub>3</sub>) 7.85 (1H, d,  $J = 16$ ), 7.80-7.35 (4H, m), 7.25 (1H, d,  $J = 16$ ), 2.60 (3H, s);  $\delta_C$  (100MHz, CD<sub>3</sub>COCD<sub>3</sub>) 166.1, 155.7, 146.1, 142.6, 133.9, 131.7, 130.7, 128.7, 127.9, 110.5, 11.5. *Anal.* Calcd for C<sub>11</sub>H<sub>9</sub>N<sub>3</sub>O<sub>3</sub>: C, 57.14; H, 3.92; N, 18.17. Found C 57.31, H 3.80, N 18.34. MS (EI):  $m/z$  231 (100%, M<sup>+</sup>).

**3-Methyl-4-nitro-5-[2-(1H-pyrrol-2-yl)vinyl]isoxazole 1m**

Yellow solid (182 mg, 83% yield);  $R_f = 0.6$  (EtOH : benzene as 2 : 9); mp 221-222°C (EtOH);  $\nu_{max}$  (film)/ $\text{cm}^{-1}$ : 1609m (Is), 1586s (NO<sub>2</sub>);  $\delta_H$  (400 MHz, CD<sub>3</sub>COCD<sub>3</sub>) 12.0 (1H, br), 7.78 (1H, d,  $J = 16$ ), 7.23 (1H, d,  $J = 16$ ), 7.21-7.18 (1H, m), 6.73-6.81 (1H, m), 6.28-6.21 (1H, m), 2.43 (3H, s);  $\delta_C$  (100MHz, CD<sub>3</sub>COCD<sub>3</sub>) 167.7, 155.7, 142.6, 133.9, 131.7, 130.7, 128.7, 127.9, 110.5, 11.5. *Anal.* Calcd for C<sub>10</sub>H<sub>9</sub>N<sub>3</sub>O<sub>3</sub>: C, 54.79; H, 4.14; N, 19.17. Found C 54.95, H 4.28, N 19.11. MS (EI):  $m/z$  219 (100%, M<sup>+</sup>).

**3-Methyl-4-nitro-5-(2-thiophen-2-ylvinyl)isoxazole 1n<sup>9</sup>**

Yellow solid (215 mg, 91% yield),  $R_f = 0.9$  (EtOH : benzene as 1 : 9); mp 141-142°C (EtOH);  $\nu_{max}$  (film)/ $\text{cm}^{-1}$ : 1589m (Is), 1565s (NO<sub>2</sub>);  $\delta_H$  (400 MHz, CD<sub>3</sub>COCD<sub>3</sub>): 7.91 (1H, d,  $J = 16$ ), 7.53 (1H, d,  $J = 5$ ), 7.45 (1H, d,  $J = 16$ ), 7.42 (1H, d,  $J = 4$ ), 7.14 (1H, dd,  $J = 5$ ,  $J = 4$ ), 2.60 (3H, s, CH<sub>3</sub>);  $\delta_C$  (80MHz, CD<sub>3</sub>COCD<sub>3</sub>) 166.9, 156.1, 140.0, 135.4, 132.0, 130.3, 130.2, 128.6, 109.6, 11.8. *Anal.* Calcd for C<sub>10</sub>H<sub>8</sub>N<sub>2</sub>O<sub>3</sub>S: C 50.84, H 3.41, N 11.86. Found C 50.72, H 3.51, N 11.68. MS (EI):  $m/z$  236 (100%, M<sup>+</sup>).

**4-[2-(3-Methyl-4-nitro-isoxazol-5-yl)-1-(3-methyl-4-nitro-isoxazol-5-ylmethyl)ethyl]pyridine 4**

Colourless solid (52 mg, 14% yield);  $R_f = 0.4$  (EtOAc : petroleum spirits as 2 : 8); mp 142-144°C (EtOH);  $\nu_{max}$  (film)/ $\text{cm}^{-1}$ : 1601m (Is), 1573s (NO<sub>2</sub>);  $\delta_H$  (400 MHz, CD<sub>3</sub>COCD<sub>3</sub>) 8.55 (2H, d,  $J = 7$ ), 7.03 (2H, d,  $J = 7$ ), 3.90 (1H, quintet,  $J = 8$ , CHPh), 3.74 (2H, dd,  $J = 14$ ,  $J = 8$ , CH<sub>2</sub>CH), 3.57 (2H, dd,  $J = 14$ ,  $J = 8$ , CH<sub>2</sub>CH), 2.50 (6H, s, 2CH<sub>3</sub>);  $\delta_C$  (100MHz, CD<sub>3</sub>COCD<sub>3</sub>) 171.5, 156.8, 155.2, 145.2, 139.0, 130.0, 41.0,



33.3, 11.1. *Anal.* Calcd for C<sub>16</sub>H<sub>15</sub>N<sub>5</sub>O<sub>6</sub>: C, 51.48; H, 4.05; N, 18.76. Found C 51.69, H 4.16, N 18.51. MS (EI): *m/z* 373 (100%, M<sup>+</sup>).

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