

# A new one-pot synthesis of 1,2,4-oxadiazoles from aryl nitriles, hydroxylamine and crotonoyl chloride

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**Abstract.** The reaction of aryl nitriles with hydroxylamine using acetic acid as a catalyst followed by subsequent addition of crotonoyl chloride to the intermediate amidoxime represents a straightforward one-pot access to new 1,2,4-oxadiazole synthesis under mild conditions. The course of the reaction was found to be high yielding and all new compounds were well characterized by nuclear magnetic resonance (NMR), mass spectrometry (MS) and elemental analysis.

**Keywords.** 1,2,4-Oxadiazole; crotonoyl chloride; amidoxime; hydroxylamine.

## 1. Introduction

1,2,4-Oxadiazoles are well-known compounds with promising physiological activities.<sup>1–3</sup> Oxadiazoles have also shown activity as benzodiazepine receptor partial agonists,<sup>4</sup> dopamine receptor (D<sub>4</sub>) ligands, growth hormone secretagogues,<sup>5</sup> antispasmodics, anti-inflammatory agents and antithrombotic agents.<sup>6</sup> Thus, they have received considerable attention during the last two decades in the drug discovery programmes<sup>7</sup> and development of clean, safe, effective, economical and high-yielding synthesis routes is still desirable and is in demand.

The general synthesis of oxadiazoles involves the reaction of aryl nitriles with hydroxylamine and coupling of a prepared amidoxime with an activated carboxyl group, yielding an O-acyl amidoxime followed by its dehydrative cyclization.<sup>8–10</sup> Cyclization of the O-acyl amidoxime is generally the most difficult and time-consuming step and often requires multi-step procedures,<sup>11</sup> silica gel column,<sup>12</sup> exhaustive reflux conditions in dimethylformamide (DMF) or pyridine<sup>13</sup> and the use of a strong base such as alumina-supported ammonium fluoride,<sup>14</sup> MgO<sup>15</sup> and KF<sup>16</sup> as catalysts and solid supports. It has been reported that 1,2,4-oxadiazoles can be prepared from an amidoxime and carboxylic acids derivatives through a one-pot reaction.<sup>17</sup> However, ami-

doxime needs to be prepared from commercially available aryl nitriles in an additional step. Thus, it will take two steps (amidoxime preparation, and one-pot cyclization/dehydration) to prepare substituted 1,2,4-oxadiazoles. One-pot, three-component preparation of disubstituted 1,2,4-oxadiazoles was reported recently through two-step microwave-assisted reaction of nitriles, hydroxylamine and aldehydes.<sup>18</sup>

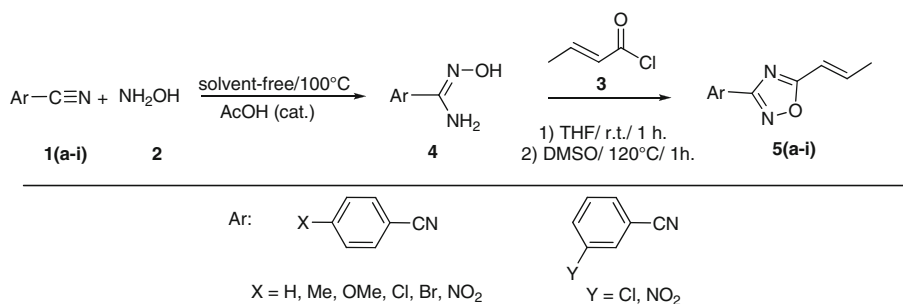
In the present study, we report an efficient and simple synthesis of new 1,2,4-oxadiazoles (**5a–i**) in high yield via an one-pot reaction of nitriles **1**, hydroxylamine **2**, and crotonoyl chloride **3** as reactants. A more concise synthesis would be the reaction of various aryl nitriles **1(a–i)** and a hydroxylamine **2** through a solvent-free condensation to give an aryl amidoxime **4**, followed by esterification in tetrahydrofuran (THF) and cyclization/dehydration in dimethyl sulphoxide (DMSO) to give 1,2,4-oxadiazole (scheme 1). In general, there is no need to remove THF after esterification and both cyclizations/dehydrations are facilitated in high temperatures by addition of DMSO, and therefore these three steps may proceed in one-pot.

## 2. Experimental

### 2.1 General remarks

<sup>1</sup>H and <sup>13</sup>C NMR spectra were measured on a Bruker DRX 500 AVANCE apparatus at 500 and 125 MHz frequencies, respectively. Infrared spectra were recorded

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**Scheme 1.** One-pot synthesis of 1,2,4-oxadiazole derivatives.

in potassium bromide pellets on a FT-IR Bruker Tensor 27 over the range 400–4000  $\text{cm}^{-1}$ . Elemental analysis performed by a Perkin Elmer 2004 (II) CHN Analyzer. Melting points were measured with an Electrothermal Engineering LTD 9200 apparatus. Gas chromatography–mass spectrometry (GC–MS) spectra were recorded on an Agilent Technologies 6890 Network GC System and an Agilent 5973 Network Mass Selective Detector. Also, all reported yields are referred to isolated compounds.

## 2.2 General procedure for the synthesis of 1,2,4-oxadiazoles

A mixture of 4-methoxybenzonitrile (0.23 g, 2 mmol), hydroxylamine 50% (0.20 g, 3 mmol) and a catalytic amount of AcOH (2–3 drops) was stirred at 100°C for 2 h. After nearly complete conversion into an intermediate presumed to be the corresponding amidoxime, as indicated by TLC monitoring, the reaction mixture was cooled to room temperature, then crotonoyl chloride (0.19 g, 2 mmol) was added to the cooled reaction mixture in the presence of 4–5 drops of THF and stirring continued for 1 h at room temperature. Next, the temperature was increased and DMSO (1 mL) was added to the reaction mixture, which was stirred at 120°C for a further 1 h. For the **5c–i**, after cooling to room temperature, the reaction mixture stayed overnight. The obtained crystalline products washed thrice with ethanol and dried at 40–50°C. 1,2,4-Oxadiazole derivatives were analytically pure without recrystallization. Oily products of the entries **5a** and **5b** were purified by column chromatography using petroleum ether–ethyl acetate (9:1).

The physical and spectral data of the products are as follows.

**2.2a** (*E*)-3-phenyl-5-(prop-1-enyl)-1,2,4-oxadiazole (**5a**): Oily;  $\nu_{\text{max}}$  IR (KBr): 3061, 2925, 1664, 1590,

1473, 1364  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta_{\text{H}}$ : 2.06–2.08 (dd,  $J = 6.9, 1.6$  Hz, 3H,  $\text{CH}_3$ ), 6.50–6.54 (dq,  $J = 16.0, 1.6$  Hz, 1H, CH), 7.16–7.24 (dq,  $J = 15.9, 6.9$  Hz, 1H, CH), 7.50–7.55 (m, 3H, ArH), 8.12–8.14 (m, 2H, ArH);  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ )  $\delta_{\text{C}}$ : 19.31, 115.43, 127.45, 127.82, 129.22, 131.47, 143.25, 168.89, 175.18; MS  $m/z$  186 ( $\text{M}^+$ ), 158, 144, 133, 116, 105, 90, 77, 64, 53, 41. Anal. Calcd. for  $\text{C}_{11}\text{H}_{10}\text{N}_2\text{O}$ ; C, 70.95; H, 5.41; N, 15.0. Found: C, 70.78; H, 5.55; N, 14.91.

**2.2b** (*Z*)-3-phenyl-5-(prop-1-enyl)-1,2,4-oxadiazole (**5b**): Oily;  $\nu_{\text{max}}$  IR (KBr): 3061, 2955, 1666, 1578, 1473, 1369  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta_{\text{H}}$ : 2.37–2.39 (dd,  $J = 6.7, 1.5$  Hz, 3H,  $\text{CH}_3$ ), 5.02–5.04 (dq,  $J = 11.0, 1.3$  Hz, 1H, CH), 6.50–6.56 (m, 1H, CH), 7.52–7.57 (m, 3H, ArH), 8.15–8.17 (dd,  $J = 8.0, 2.5$  Hz, 2H, ArH);  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ )  $\delta_{\text{C}}$ : 14.35, 116.02, 124.55, 127.68, 129.25, 131.55, 141.25, 169.08, 175.12; MS  $m/z$  186 ( $\text{M}^+$ ), 158, 133, 118, 105, 93, 77, 64. Anal. Calcd. for  $\text{C}_{11}\text{H}_{10}\text{N}_2\text{O}$ ; C, 70.95; H, 5.41; N, 15.04. Found: C, 70.75; H, 5.58; N, 14.96.

**2.2c** (*E*)-5-(prop-1-enyl)-3-*p*-tolyl-1,2,4-oxadiazole (**5c**): White crystals; mp 68–70°C;  $\nu_{\text{max}}$  IR (KBr): 3060, 2965, 1660, 1445, 1367  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta_{\text{H}}$ : 2.06–2.08 (dd,  $J = 6.9, 1.7$  Hz, 3H,  $\text{CH}_3$ ), 2.33 (s, 3H,  $\text{CH}_3$ ), 6.50–6.54 (dq,  $J = 17.0, 1.7$  Hz, 1H, CH), 7.03–7.06 (m, 1H, CH), 7.25–7.27 (d,  $J = 8.5$  Hz, 2H, ArH), 8.12–8.14 (d,  $J = 8.8$  Hz, 2H, ArH);  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ )  $\delta_{\text{C}}$ : 19.31, 55.85, 114.60, 115.51, 119.99, 129.42, 143.00, 162.35, 168.68, 174.94; MS  $m/z$  200 ( $\text{M}^+$ ), 130, 116, 105, 91, 77, 69, 41. Anal. Calcd. for  $\text{C}_{12}\text{H}_{12}\text{N}_2\text{O}$ ; C, 71.98; H, 6.04; N, 13.99. Found: C, 71.78; H, 6.11; N, 13.91.

**2.2d** (*E*)-3-(4-methoxyphenyl)-5-(prop-1-enyl)-1,2,4-oxadiazole (**5d**): White crystals; mp 84–86°C;  $\nu_{\text{max}}$  IR (KBr): 3032, 2929, 1664, 1611, 1584, 1543, 1442,

1363  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta_{\text{H}}$ : 2.06–2.08 (dd,  $J = 7.0, 1.7$  Hz, 3H,  $\text{CH}_3$ ), 3.90 (s, 3H,  $\text{CH}_3$ ), 6.48–6.52 (dq,  $J = 17.0, 1.5$  Hz, 1H, CH), 7.01–7.03 (d,  $J = 8.8$  Hz, 2H, ArH), 7.14–7.20 (m, 1H, CH), 8.05–8.07 (d,  $J = 8.8$  Hz, 2H, ArH);  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ )  $\delta_{\text{C}}$ : 19.30, 55.79, 114.62, 115.48, 119.90, 129.41, 143.03, 162.26, 168.57, 174.91; MS  $m/z$  216 ( $\text{M}^+$ ), 149, 134, 120, 106, 90, 69, 55, 41. Anal. Calcd. for  $\text{C}_{12}\text{H}_{12}\text{N}_2\text{O}_2$ ; C, 66.65; H, 5.59; N, 12.96. Found: C, 66.50; H, 5.75; N, 12.80.

2.2e (*E*)-3-(4-chlorophenyl)-5-(prop-1-enyl)-1,2,4-oxadiazole (**5e**): White crystals; mp 72–73°C;  $\nu_{\text{max}}$  IR (KBr): 3057, 2921, 1657, 1583, 1468, 1408, 1358  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta_{\text{H}}$ : 2.07–2.09 (dd,  $J = 7.0, 1.5$  Hz, 3H,  $\text{CH}_3$ ), 6.49–6.53 (dq,  $J = 16.0, 1.6$  Hz, 1H, CH), 7.18–7.23 (m, 1H, CH), 7.48–7.50 (d,  $J = 8.5$  Hz, 2H, ArH), 8.06–8.07 (d,  $J = 8.5$  Hz, 2H, ArH);  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ )  $\delta_{\text{C}}$ : 19.34, 115.29, 125.95, 129.13, 129.55, 137.61, 143.59, 168.08, 175.35; MS  $m/z$  220 ( $\text{M}^+$ ), 137, 125, 111, 102, 90, 75, 63, 50. Anal. Calcd. for  $\text{C}_{11}\text{H}_9\text{ClN}_2\text{O}$ ; C, 59.88; H, 4.11; N, 12.70. Found: C, 59.80; H, 4.32; N, 12.64.

2.2f (*E*)-3-(3-chlorophenyl)-5-(prop-1-enyl)-1,2,4-oxadiazole (**5f**): White crystals; mp 69–70°C;  $\nu_{\text{max}}$  IR (KBr): 3046, 2940, 1651, 1586, 1537, 1448, 1400, 1379  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta_{\text{H}}$ : 2.05–2.07 (dd,  $J = 7.1, 1.5$  Hz, 3H,  $\text{CH}_3$ ), 6.46–6.50 (dq,  $J = 15.9, 1.6$  Hz, 1H, CH), 7.10–7.13 (m, 1H, CH), 7.44–7.47 (m, 2H, ArH), 8.00 (s, 1H, ArH), 8.15–8.17 (d,  $J = 8.0$  Hz, 1H, ArH);  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ )  $\delta_{\text{C}}$ : 19.35, 115.33, 125.07, 125.91, 129.32, 129.86, 130.55, 137.62, 142.60, 168.11, 175.38; MS  $m/z$  220 ( $\text{M}^+$ ), 137, 125, 111, 103, 90, 76, 61. Anal. Calcd. for  $\text{C}_{11}\text{H}_9\text{ClN}_2\text{O}$ ; C, 59.88; H, 4.11; N, 12.70. Found: C, 59.94; H, 4.28; N, 12.58.

2.2g (*E*)-3-(4-nitrophenyl)-5-(prop-1-enyl)-1,2,4-oxadiazole (**5g**): White crystals; mp 69–70°C;  $\nu_{\text{max}}$  IR (KBr) 3046, 2925, 1653, 1604, 1536, 1467, 1408, 1347  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta_{\text{H}}$ : 2.10–2.12 (dd,  $J = 7.1, 1.5$  Hz, 3H,  $\text{CH}_3$ ), 6.53–6.56 (dq,  $J = 15.6, 1.6$  Hz, 1H, CH), 7.24–7.29 (m, 1H, CH), 8.32–8.34 (d,  $J = 8.0$  Hz, 2H, ArH), 8.38–8.40 (d,  $J = 8.0$  Hz, 2H, ArH);  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ )  $\delta_{\text{C}}$ : 19.32, 115.35, 125.0, 125.95, 129.24, 129.59, 137.68, 143.64, 168.18, 175.38; MS  $m/z$  231 ( $\text{M}^+$ ), 201, 185, 164, 134, 106, 88, 68, 54, 41. Anal. Calcd. for  $\text{C}_{11}\text{H}_9\text{N}_3\text{O}_3$ ; C, 57.14; H, 3.92; N, 18.17. Found: C, 57.10; H, 4.01; N, 18.21.

2.2h (*E*)-3-(3-nitrophenyl)-5-(prop-1-enyl)-1,2,4-oxadiazole (**5h**): White crystals; mp 73–76°C;  $\nu_{\text{max}}$  IR (KBr): 3045, 2920, 1659, 1600, 1535, 1463, 1408, 1337  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta_{\text{H}}$ : 2.05–2.07 (dd,  $J = 6.8, 1.7$  Hz, 3H,  $\text{CH}_3$ ), 6.54–6.57 (dq,  $J = 16.0, 1.7$  Hz, 1H, CH), 7.24–7.29 (m, 1H, CH), 7.72–7.74 (t,  $J = 8.5$  Hz, 1H, ArH), 8.23–8.25 (d,  $J = 8.0$  Hz, 1H, ArH), 8.58–8.61 (m, 2H, ArH);  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ )  $\delta_{\text{C}}$ : 19.20, 115.22, 125.13, 125.98, 129.29, 129.80, 130.55, 137.64, 142.66, 168.10, 175.35; MS  $m/z$  231 ( $\text{M}^+$ ), 201, 185, 164, 134, 106, 89, 68, 53, 41. Anal. Calcd. for  $\text{C}_{11}\text{H}_9\text{N}_3\text{O}_3$ ; C, 57.14; H, 3.92; N, 18.17. Found: C, 57.09; H, 3.98; N, 18.29.

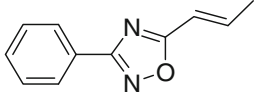
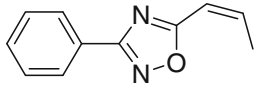
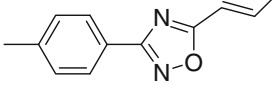
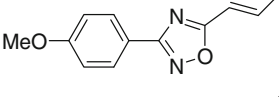
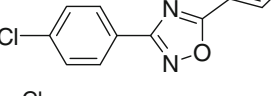
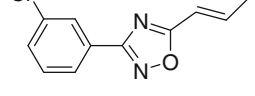
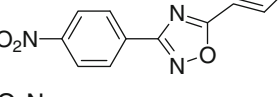
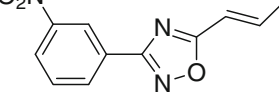
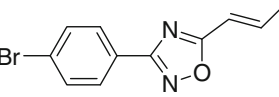
2.2i (*E*)-3-(4-bromophenyl)-5-(prop-1-enyl)-1,2,4-oxadiazole (**5i**): White crystals; mp 92–94°C;  $\nu_{\text{max}}$  IR (KBr) 3056, 2908, 1657, 1598, 1537, 1401, 1355  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta_{\text{H}}$ : 2.07–2.09 (dd,  $J = 7.0, 1.8$  Hz, 3H,  $\text{CH}_3$ ), 6.49–6.53 (dq,  $J = 15.9, 1.8$  Hz, 1H, CH), 7.16–7.24 (m, 1H, CH), 7.64–7.66 (d,  $J = 8.6$  Hz, 2H, ArH), 7.98–8.00 (d,  $J = 8.5$  Hz, 2H, ArH);  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ )  $\delta_{\text{C}}$ : 19.35, 115.27, 126.03, 126.40, 129.33, 132.51, 143.62, 168.17, 175.37; MS  $m/z$  264 ( $\text{M}^+$ ), 197, 181, 155, 132, 117, 90, 69, 54, 39. Anal. Calcd. for  $\text{C}_{11}\text{H}_9\text{BrN}_2\text{O}$ ; C, 49.84; H, 3.42; N, 10.57. Found: C, 49.65; H, 3.70; N, 10.45.

### 3. Results and discussion

As a part of our continuing efforts to develop efficient methods for the preparation of widely used organic compounds from readily available building blocks,<sup>19</sup> this study deals with the introduction of a new and very simple method for the synthesis of 3-aryl-5-(prop-1-enyl)-1,2,4-oxadiazoles. For this reason, a mixture of the aryl nitriles **1** and hydroxylamine **2** was converted *in situ* into amidoximes **4**. Next, the intermediate amidoxime compounds (**4**) were converted into corresponding 3-aryl-5-(prop-1-enyl)-1,2,4-oxadiazoles with crotonoyl chloride (**3**) in the presence of THF at room temperature followed by the addition of higher boiling point solvent (DMSO) and stirring for 1 h at 120°C. The synthetic procedure is outlined in scheme 1 and as shown in table 1, isolated yields of the prepared compounds were in the range of 60–75%.

To establish the generality of the method, a variety of available substrates were employed (table 1). The structure of these synthesized compounds was confirmed by IR and  $^1\text{H}$ , and  $^{13}\text{C}$  NMR spectroscopy as well as MS

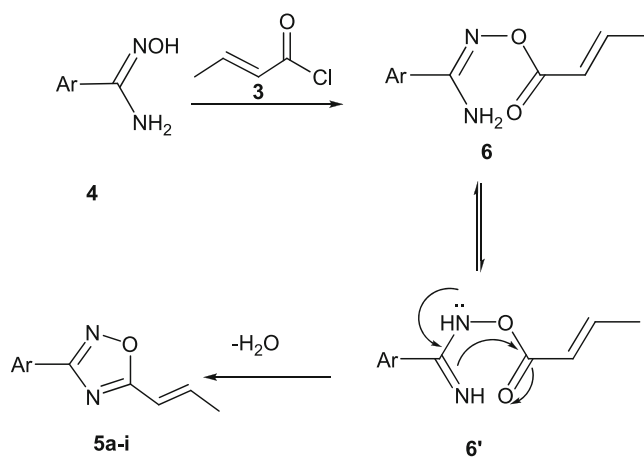
**Table 1.** Synthesis 1,2,4-oxadiazole derivatives **5a-i**.

Compound	Nitrile	Product	Yield <sup>a</sup> (%)
<b>5a</b>	C <sub>6</sub> H <sub>4</sub> CN		75
<b>5b</b>	C <sub>6</sub> H <sub>4</sub> CN		10
<b>5c</b>	4-Me-C <sub>6</sub> H <sub>4</sub> CN		70
<b>5d</b>	4-OMe-C <sub>6</sub> H <sub>4</sub> CN		75
<b>5e</b>	4-Cl-C <sub>6</sub> H <sub>4</sub> CN		75
<b>5f</b>	3-Cl-C <sub>6</sub> H <sub>4</sub> CN		70
<b>5g</b>	4-NO <sub>2</sub> -C <sub>6</sub> H <sub>4</sub> CN		75
<b>5h</b>	3-NO <sub>2</sub> -C <sub>6</sub> H <sub>4</sub> CN		65
<b>5i</b>	4-Br-C <sub>6</sub> H <sub>4</sub> CN		65

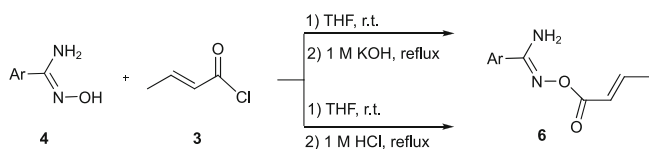
<sup>a</sup>Isolated yield.

and elemental analyses. For instance, in the IR spectrum of **5a**, the characteristic bands of amidoxime primary amine (3455 and 3360 cm<sup>-1</sup>) and ester groups of a crotonoyl chloride (1720 cm<sup>-1</sup>) in the reactant were completely disappeared. In the <sup>1</sup>H NMR spectrum, resonance signals at downfield regions 8.12–8.14 ppm are ascribed to the two *ortho*-proton of aromatic ring and two doublet of quarted around 6.50–6.54 and 7.16–7.24 with the same vicinal coupling constant around 1.6 Hz are ascribed to the allylic protons. Also, the area of integration for the protons is in accordance with the assignment. <sup>13</sup>C NMR spectrum of **5a** reveals that two carbons of the heterocycle ring resonate in the downfield at 168.89 and 175.18 ppm. The chemical shift in the upfield region (19.31 ppm) is ascribed to the resonance of aliphatic methyl group. In addition to IR and NMR spectra, the elemental analysis and mass spectra results of **5a** also generally agreed with the proposed structures.

The most probable mechanism for this reaction is illustrated in scheme 2.

**Scheme 2.** Plausible mechanism for the formation of **5a-i**.





**Scheme 3.** Reaction between amidoximes and crotonoyl chloride in different conditions.

Initially in the presence of THF, estrification reaction occurred between amidoxime and crotonoyl chloride. Owing to better nucleophilicity of the oxygen atom compared to amidic nitrogen atom,<sup>20</sup> oxygen atom attacks the crotonoyl chloride carbonyl group. Then, DMSO was added and this intermediate is cyclized to the 3-aryl-5-(prop-1-enyl)-1,2,4-oxadiazoles derivatives (**5a–i**) after stirring for 1 h at 120°C. A variety of different conditions to obtain cyclic products were examined, including basic and acidic conditions (scheme 3). However, both conditions resulted in the corresponding O-acylamidoxime **6** as a major product.

When benzonitrile was used as a reactant, the products were a mixture of compounds **5a** and **5b** with yields of 75% and 10%, respectively (table 1). The GC–MS analysis revealed the same pattern for both compounds and analysis of <sup>1</sup>H NMR spectroscopy indicated that there is a mixture of *cis* and *trans* isomers. The isomers were separated by column chromatographic techniques, and the differences in the magnitude of the vicinal coupling constant (<sup>3</sup>*J*<sub>HH</sub>) of the double bond hydrogens in the <sup>1</sup>H NMR spectra was used to evaluate structural identification. Since the vicinal coupling constants are larger for *trans* isomers than for *cis* isomers,<sup>21</sup> the 16 Hz coupling constant value measured for major isomer, was attributed to the *trans* isomer.

#### 4. Conclusion

In summary, we have introduced a simple and one-pot procedure for the synthesis of 1,2,4-oxadiazoles without using any dehydrating agent or support. Reaction occurred in a short time without any work-up process and this method was applicable for aryl nitriles substituted with both electron donor or acceptor groups, demonstrating proof-of-concept for the rapid synthesis of focused libraries of small molecule heterocycles based on this scaffold.

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