

## Preparation of trichloroacetoamidoxime in aqueous media and application in one pot synthesis of 1,2,4-oxadiazoles

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### Abstract

Oxadiazoles are heterocyclic compounds with a variety application in many pharmaceuticals and agrochemicals products. We reported here the convenient synthesis of 3-trichloromethyl-1,2,4-oxadiazoles from trichloroacetoamidoxime and RC(O)Cl (R= methyl ethyl, propyl, Ph, CH<sub>2</sub>Cl, CHCl<sub>2</sub>, CCl<sub>3</sub>) by one pot reaction.

**Keywords:** Azoles, 1,2,4-oxadiazoles, heterocycles, *O*-acylation

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### Introduction

Azoles and derivatives have a long history in medicinal chemistry. In particular, 1,2,4-oxadiazoles represent a class of heterocyclic with a wide variety of biological activities, especially as antiinflammatory, agrochemical and antifungal activities.<sup>1-3</sup> Biologically relevant compounds containing the 1,2,4-oxadiazole moiety also include HIV integrase inhibitors,<sup>4</sup> antituberculostatic agents<sup>5</sup> and antikinoplastid agents.<sup>6</sup> In particular, the introduction of halogens and halogenated groups into organic molecules often confers significant changes in their chemical, physical and pharmacological properties.<sup>7-10</sup>

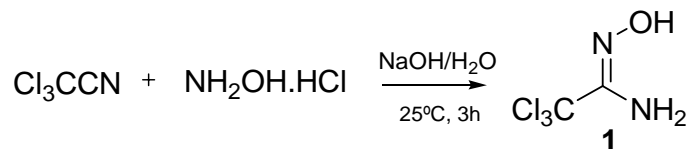
Several methods have been reported in the literature for the synthesis of oxadiazoles.<sup>11-15</sup> The major synthetic route to obtain oxadiazoles is the reaction of amidoximes and acyl chloride promoted by either heat or by bases, such NaH, NaOEt or pyridine. Usually this synthesis involve a two step procedure, the first one is the formation of *O*-acyl derivative and the second one and intramolecular cyclization with hard conditions (thionyl chloride, phosphorus oxychloride or acid sulfuric).

The common protocol for the preparation of precursor amidoximes includes reactions of hydroxylamines with nitriles, or thioamides.<sup>16</sup> In recent years, we have studied the preparation of halogen-containing building blocks<sup>17</sup> and have demonstrated their usefulness as precursor on synthesis of five<sup>18</sup> and six members rings.<sup>18-19</sup> In accordance with our program research in organic chemistry, in this work, we chose to explore the versatility of the trichloroacetoamidoxime **1** as halogen-precursor in a one-pot conversion with acyl chlorides **2a-g** to the corresponding 3-trichloromethyl-1,2,4-oxadiazoles **3a-g** with good yields.

## Results and Discussion

The use of water as a solvent in organic synthesis has been extensively studied, with application in the tetrahydropyranlation of alcohols, Diels-Alder reactions, Claisen Rearrangement, Michael additions, Barbier-Grignard reactions, Reformatsky reactions, enaminations and oxidation and reduction with the research of reaction in water.<sup>20-23</sup>

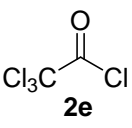
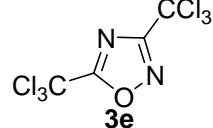
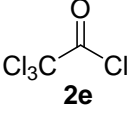
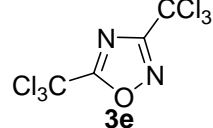
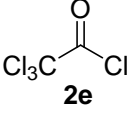
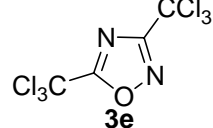
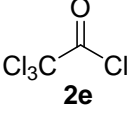
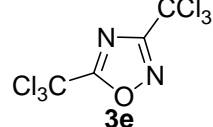
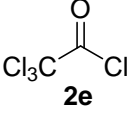
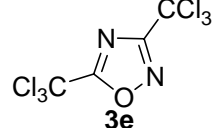
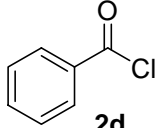
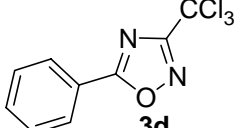
The precursor trichloroacetoamidoxime **1** could be easily synthesized by reaction of trichloroacetonitrile and hydroxylamine hydrochloride in water at room temperature for 3 hours in 90% yield (Scheme 1). This yield was better than the literature (64%).<sup>24</sup>



### Scheme 1

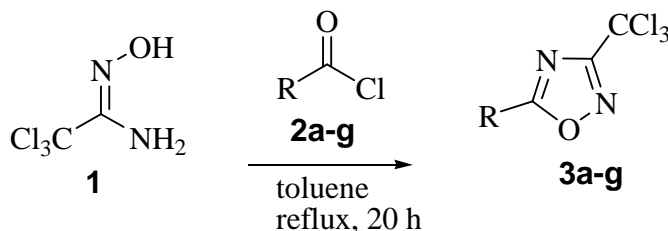
In preliminary experiments, we have observed that the reaction between amidoxime **1** with trichloroacetyl chloride **2e** was solvent and temperature dependent. When the reaction was carried out at low boiling point solvent such as ethyl ether, chloroform or dichloromethane, the starting materials were recovered and we did not observe the formation of the product (entry 1, 2 and 3 - Table 1). In our studies, we found that the toluene was the appropriated solvent for these reactions giving the best results. The increased of temperature raise the formation of 1,2,4-oxadiazoles in excellent yield (entry 5 and 6, Table 1). The reaction was monitored by TLC (thin layer chromatography). The important particularity of this reaction process is the work-up, in which we observed that the use of successive treatment with solution of Na<sub>2</sub>CO<sub>3</sub> gave the products without purifications.

**Table 1.** Study of conditions to synthesis of 1,2,4-oxadiazoles **3a-g**<sup>a</sup>

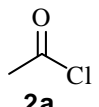
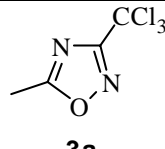
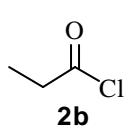
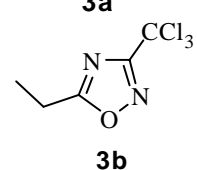
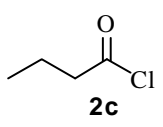
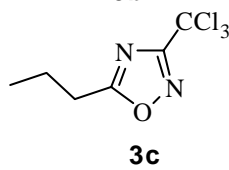
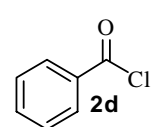
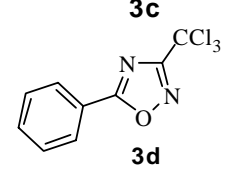
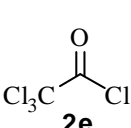
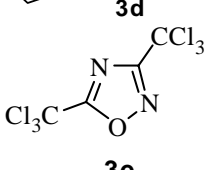
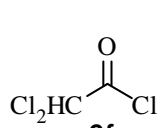
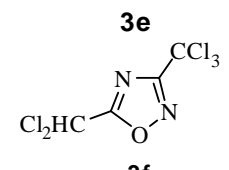
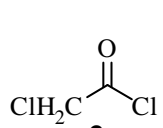
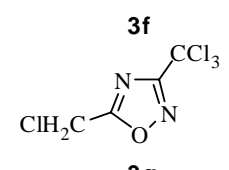
Entry	Acyl chloride	Solvent	Temp (°C)	Product	Yield (%)
1	 <b>2e</b>	Ethyl ether	34	 <b>3e</b>	-
2	 <b>2e</b>	CH <sub>2</sub> Cl <sub>2</sub>	40	 <b>3e</b>	-
3	 <b>2e</b>	CHCl <sub>3</sub>	61	 <b>3e</b>	-
4	 <b>2e</b>	Solvent free	100	 <b>3e</b>	-
5	 <b>2e</b>	Toluene	100	 <b>3e</b>	90
6	 <b>2d</b>	Toluene	100	 <b>3d</b>	88

<sup>a</sup>reaction time 20 h.

The 5-substituted-3-trichloromethyl-1,2,4-oxadiazoles **3a-g** were synthesized by treatment of trichloroacetamidoxime **1** with acyl chlorides **2a-g** using toluene for 20 hours at 100°C (Scheme 2). The compounds **3a-g** were obtained in good yields (60–90%). The scope and generality of this process is illustrated by a series of seven oxadiazoles and the results are presented in Table 2.

**Scheme 2**

**Table 2.** Synthesis of 3 trichloromethyl-1, 2, 4 oxadiazoles **3a-g**

Acyl chloride	Product	mp	bp	Yield (%) <sup>a</sup>
 <b>2a</b>	 <b>3a</b>	55	203	61
 <b>2b</b>	 <b>3b</b>		oil	60
 <b>2c</b>	 <b>3c</b>		oil	74
 <b>2d</b>	 <b>3d</b>	65	106	88
 <b>2e</b>	 <b>3e</b>	-	250	90
 <b>2f</b>	 <b>3f</b>	-	253	71
 <b>2g</b>	 <b>3g</b>	-	242	70

<sup>a</sup> yield of isolated compound

The products were identified concerning both analytical and spectral data (<sup>1</sup>H NMR and <sup>13</sup>C NMR) of all compounds are in full agreement with the proposed structure.

## Conclusions

In conclusion, we have described the facile preparation of trichloroacetoamidoxime **1** in aqueous media, and its application in an one-pot approach to the synthesis of 1,2,4-oxadiazoles in good yields. This method works well with a variety of acyl chlorides.

## Experimental Section

**General.** Starting trichloroacetoamidoxime **1** was prepared from of our procedure. All solvents and reagents were obtained from Aldrich and used without further purification. The data of NMR spectra were recorded on a Bruker DPX 400 ( $^1\text{H}$  at 400.13 MHz and for  $^{13}\text{C}$  at 100.63 MHz) spectrometer, 5 mm sample tubs, 298 K, digital resolution of  $\pm 0.01$  ppm, 0,5 M in  $\text{CDCl}_3$ , containing TMS as internal standard. Mass spectra were registered in HP 6890 GC connected to HP 5973 MSD and interfaced by a Pentium PC. The CG was equipped with a split-splitless injector, autosampler, cross-linked HP-5 capillary column (30m, 0,32 mm of internal diameter), and helium was used as the carrier gas.

### General procedures. Trichloroacetoamidoxime (1)

A mixture of hydroxylamine hydrochloride 2.36g (3.5 mmol) and NaOH 1.36g (3.5mmol) in water was added trichloroacetonitrile 1.7 mL (1.7 mmol). The mixture was stirred at room temperature for 3 h. For the compound **1** a solid was observed. The product was isolated by filtered, dried in a vacuum and recrystallized in gradient hexane/acetate (3:1).

### Synthesis of 1,2,4-oxadiazoles 3a-g

A mixture of acyl chloride **2a-g** (6 mmol) in toluene was added dropwise in a solution of the trichloroacetoamidoxime **1** (3 mmol) in toluene at 0 °C. The reaction mixture was stirred for 20 h at reflux. After the time the solvent was remove and  $\text{CH}_2\text{Cl}_2$  was added, the organic solution was washed (twice in water), (twice in solution  $\text{Na}_2\text{CO}_3$ ), and (once in water). The organic layer was dried ( $\text{Na}_2\text{SO}_4$ ) and the solvent removed under pressure. Finally, the 1, 2, 4-oxadiazoles **3a-g** were obtained in good yields.

**3-Trichloromethyl-5-methyl-1,2,4-oxadiazole (3a).**  $\text{C}_4\text{H}_3\text{Cl}_3\text{N}_2\text{O}$ ; 201.5; mp 54°C; bp 203.7°C; yield (61%);  $^1\text{H}$  NMR (400 MHz;  $\text{CDCl}_3$ ):  $\delta$  (ppm) 2.70 (3H, s,  $\text{CH}_3$ );  $^{13}\text{C}$  NMR (100 MHz;  $\text{CDCl}_3$ ):  $\delta$  (ppm) 179.2, 170.9; 99.96 ( $\text{CCl}_3$ ); 12.4 ( $\text{CH}_3$ ); MS CG-MS (EI, 70 eV):  $m/z$  200 ( $\text{M}^+-1$ , 1), 169 (11.4), 167(61.9) 165(100), 131(9.5), 129(9.5), 126(15.2), 124(19);

**3-Trichloromethyl-5-ethyl-1,2,4-oxadiazole (3b).**  $\text{C}_5\text{H}_5\text{Cl}_3\text{N}_2\text{O}$ ; 215.5; oil; yield (60%);  $^1\text{H}$  NMR (400 MHz;  $\text{CDCl}_3$ ):  $\delta$  (ppm) 3.03 (2H, q,  $\text{CH}_2$ ); 1.50 (3H, t,  $\text{CH}_3$ );  $^{13}\text{C}$  NMR (100 MHz;  $\text{CDCl}_3$ ):  $\delta$ (ppm) 170.8, 183.3; 109.5 ( $\text{CCl}_3$ ); 20.5 ( $\text{CH}_2$ ); 10.4 ( $\text{CH}_3$ ); MS CG-MS (EI 70 eV):  $m/z$  214 ( $\text{M}^+-1$ , 1), 182.9(10), 180.9(60.7), 179.9(6), 178.9(100),126(24), 124(38);

**3-Trichloromethyl-5-propyl-1,2,4-oxadiazole (3c).**  $\text{C}_6\text{H}_7\text{Cl}_3\text{N}_2\text{O}$ ; 229.5; oil; yield (74%);  $^1\text{H}$  NMR (400 MHz;  $\text{CDCl}_3$ ):  $\delta$  (ppm) 2.48 (2H, t,  $\text{CH}_2$ ); 1.59 (2H, m,  $\text{CH}_2$ ); 0.85 (3H, t,  $\text{CH}_3$ );  $^{13}\text{C}$  NMR (100 MHz;  $\text{CDCl}_3$ ):  $\delta$  (ppm) 171.1, 178.8; 104.8 ( $\text{CCl}_3$ ); 29.7 ( $\text{CH}_2$ ); 20.6 ( $\text{CH}_2$ ); 13.3 ( $\text{CH}_3$ ); 227 ( $\text{M}^+-2$ , 11); 213 (1.2); 199(5.7); 185(6); 171(6); 143(17); 129(8.7); 101(8); 97(9.4); 88(6.8); 87(70); 84(5); 83(12); 81(5); 75(17); 74(100); 71(7); 69(17); 67(5); 59(8); 57(16); 43(27)

**3-Trichloromethyl-5-phenyl-1,2,4-oxadiazole (3d)**  $\text{C}_9\text{H}_5\text{Cl}_3\text{N}_2\text{O}$ ; 263.5; mp 65 and bp 106 °C ; yield (88%);  $^1\text{H}$  NMR (400 MHz;  $\text{CDCl}_3$ ):  $\delta$  (ppm) 8.2 and 7.5 (m, Ph); MS CG-MS (EI 70 eV):

*m/z* (%) 263, 262, 264 (9)[M<sup>+</sup>] 229(63), 228(9.5), 227(100), 126(22), 124(33), 105(25), 103(35), 77(74), 76(21), 50(21), 51(43)

**3,5-Bis-trichloromethyl-1,2,4-oxadiazole (3e).** C<sub>4</sub>Cl<sub>6</sub>N<sub>2</sub>O; 305; bp 250 °C; yield (90%); <sup>13</sup>C NMR (100 MHz; CDCl<sub>3</sub>): δ (ppm) 190.5, 195.5; 103.8 (CCl<sub>3</sub>); 101.6 (CCl<sub>3</sub>); MS CG-MS (EI 70 eV): *m/z* (%) 304 (M<sup>+</sup>-1, 1), 274.5(4), 273(20), 271(62.8), 268.9(100), 267(64.8), 206(3.8), 203.9(7.6), 202(4.8), 128.9(2.9), 126(4.8), 124(4.8), 119(11.4), 116.9(13.3), 100(4.8), 98(6.7), 94(2.8), 84(6.7), 82(9.5), 73(1.9), 47(4.8).

**5-Dichloromethyl-3-trichloromethyl-1,2,4-oxadiazole (3f).** C<sub>4</sub>HCl<sub>5</sub>N<sub>2</sub>O; 270.5; bp 253 °C; yield (71%); <sup>1</sup>H NMR (400 MHz; CDCl<sub>3</sub>): δ (ppm) 6.8 (H, s, CH); MS CG-MS (EI 70 eV): *m/z* (%) 270 (M<sup>+</sup>, 10), 272.8(21), 271.8(5), 269.9(5), 268.8(100), 266.9(65), 236.9(5), 234.9(8), 232.9(6), 205.8(4), 203.85(8.5), 201.8(6.5), 126(7), 124(11), 121(6), 119(19), 117(23), 110(11), 108(14), 83(15), 81.9(24), 49(6), 47(17);

**5-Chloromethyl-3-trichloromethyl-1,2,4-oxadiazole (3g).** C<sub>4</sub>H<sub>2</sub>Cl<sub>4</sub>N<sub>2</sub>O; 235; bp 242; yield (70%); <sup>1</sup>H NMR (400 MHz; CDCl<sub>3</sub>): δ (ppm) 4,7 (2H, s, CH<sub>2</sub>); <sup>13</sup>C NMR (100 MHz; CDCl<sub>3</sub>): δ (ppm) 176.8, 171.3; 109.5 (CCl<sub>3</sub>); 33.06 (CH<sub>2</sub>); MS CG-MS (EI 70 eV): *m/z* (%) 237 (M<sup>+</sup>+2, 45), 235(100), 233.9(5), 232.9(89), 126(8), 124(13), 118(4), 116.9(5), 82.9(12), 81.9(5);

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