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Synthesis of 1,3-Oxazoles via Van Leusen Reaction in a Pressure Reactor and Preliminary Studies of Cations Recognition †

Verónica G. García-Ramírez [1], Claudia Contreras-Celedón [1], Gabriela Rodriguez-García [2], Luis Chacón-García [1] and Carlos J. Cortes-García [1,*]

[1] Laboratorio de Diseño Molecular, Instituto de Investigaciones Químico Biológicas, Universidad Michoacana de San Nicolás de Hidalgo, Ciudad Universitaria C.P., 58033 Morelia, Michoacán, Mexico; guadalupe_vero_12_13@hotmail.com (V.G.G.-R.); celedon@umich.mx (C.C.-C.); lchacon@umich.mx (L.C.-G.)

[2] Laboratorio de Productos Naturales, Instituto de Investigaciones Químico Biológicas, Universidad Michoacana de San Nicolás de Hidalgo, Ciudad Universitaria C.P., 58033 Morelia, Michoacán, Mexico; dragabyroga@gmail.com

* Correspondence: ccortes@umich.mx

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Abstract: Six 1,3-oxazoles were synthetized in moderate to good yields by Van Leusen reaction in a pressure reactor. The methodology allowed to decrease the reaction times reported in the literature from hours to 20 min. In addition, preliminary qualitative recognition of cations with some synthetized oxazoles such as Hg^{2+}, Ni^{2+}, $Zn^{2+,}$ Ag^{+}, Cu^{2+}, Pb^{2+} was done and a "turn off" effect was observed with Ni^{2+}. Finally, the 1,3-oxazoles could be of biological relevance because they are considered privileged nucleus in medicinal chemistry and therefore will be useful to obtain pharmacophoric hybrid molecules.

Keywords: 1,3-oxazoles; Van Leusen; cation recognition

1. Introduction

1,3-oxazoles based molecules are of biological and pharmacological relevance, and other potential applications have been described, including those as fluorescent dyes, pH probes, laser dyes and scintillators (Figure 1) [1–6]. Given the importance of this privileged heteroaromatic fragment, several synthetic strategies have been developed in the last decade. To date, Van Leusen reaction is undoubtedly the most attractive and efficient among them, despite the reported methodologies for this reaction require hours for adequate reaction yields [7–9]. Thus, alternative protocols are in continuous demand. In this work the synthesis of six 1,3-oxazoles derivates via Van Leusen reaction is described, allowing moderate to good yields at 20 min in reaction time by using a pressure reactor as simplistic strategy, thereby, compatibility of the employed reaction conditions with Van Leusen reaction. The best of knowledge, there is no literature reports about the use of pressure reactor in this kind of reaction, consequently, an improvement of the methodology is herein described. Finally, preliminary assays of cation recognition of oxazole **9b** by naked-eye was done and a "turn off" effect was observed with Ni^{2+}. Also, fluorescent changes by naked-eye by variating pH was done and increasing of fluorescence was observed in acid medium.

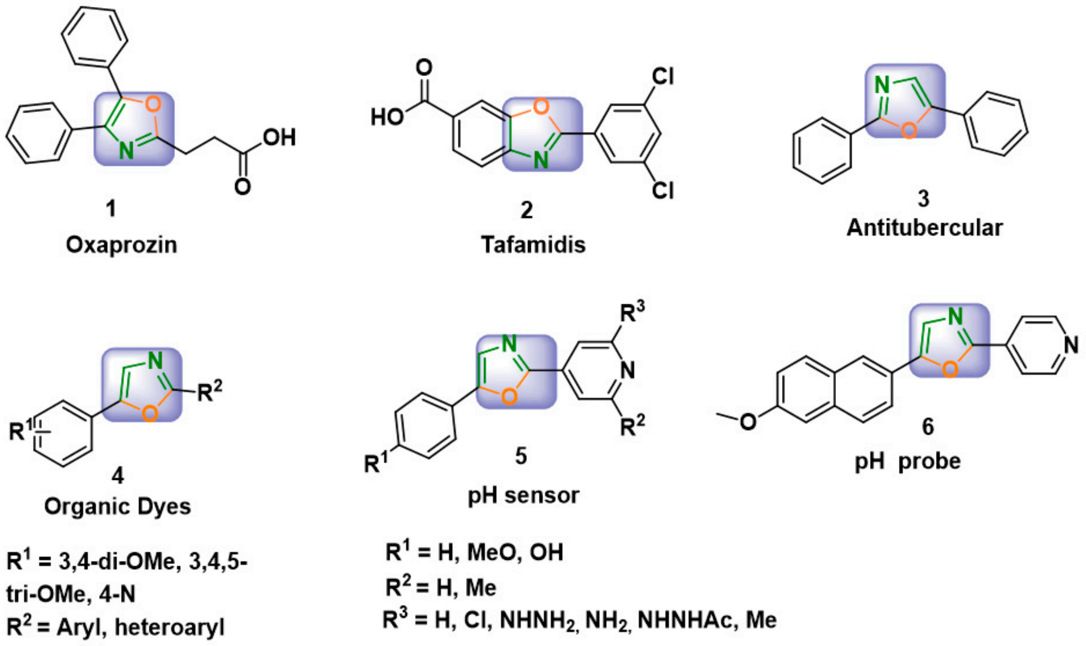


Figure 1. Several examples of bioactive, medicines and fluorescent compounds containing 1,3-oxazole motif.

2. Materials and Methods

2.1. Experimental Section

All reagents, reactants and solvents were purchased from Merck (before Sigma-Aldrich Co.) without further purification. Melting points (uncorrected) were determined on a Fischer apparatus. Thin-layer chromatography (TLC) was performed with silica gel plates from Merck (silica gel 60 F_{254}) and by using as eluent a mixture of heptane-AcOEt. NMR spectra were recorded at 400 MHz for ^{1}H and 100 MHz for ^{13}C on a Varian Mercury 400 NMR spectrometer, using $CDCl_3$ as the solvent, and TMS as the internal standard. Chemical Shift (δ) are reported in ppm, and *J* values are given in Hertz. High-resolution mass spectrometry (HRMS) was performed using a Micro TOF-II spectrometer and the samples were ionized by electrospray ionization on positive mode (ESI$^+$).

2.2. General Procedure for 1,3-Oxazoles **9a–f**

Aldehyde (0.6 mmol, 1 eq), TosMIC (1.1 eq) and K_2CO_3 (2.5 eq) were suspended in MeOH (0.1 M) for chemical reaction under pressure, using a stainless-steel reactor. The reaction mixture was stirred and heated at 105 °C for 20 min. After the reactor was cooled to room temperature, the reaction mixture was dried under vacuum. Then, the evaporated reaction crude was purified by flash column chromatographic (6:4 Hex:AcoEt *v*/*v*) to afford the 1,3-oxazoles **9a–f**.

5-(4-(pyridin-2-yl)phenyl)oxazole (**9a**): White solid, mp = 144–147 °C; R_F = 0.28 (Hex-AcOEt 6:4 *v*/*v*); FT-IR (ATR)ν_{max}/cm^{-1} 3090, 3057, 2956, 2914, 1584, 1471, 1431.; ^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.23–7.28 (m, 1H), 7.42 (s, 1H), 7.73–7.78 (m, 4H), 7.94 (1H), 8.07 (d, *J* = 8.6 Hz, 1H), 8.71 (dt, *J* = 4.8, 1.4 Hz, 1H). ^{13}C-NMR (100 MHz, $CDCl_3$): δ 120.4, 121.9, 122.4, 124.6, 127.3, 128.0, 136.8, 139.3, 149.7, 150.5, 151.1, 156.3. HRMS (ESI+) *m*/*z* calcd. for $C_{14}H_{10}N_2NaO$ [M + Na]$^+$ 245.0685; found 245.0630.

5-(4-(pyridin-4-yl)phenyl)oxazole (**9b**): White solid, mp = 141–143 °C; R_F = 0.10 (Hex-AcOEt 6:4 *v*/*v*); FT-IR (ATR)ν_{max}/cm^{-1} 3108, 2925, 1595, 1477, 1403; ^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.44 (s, 1H), 7.52–7.54 (m, 2H), 7.71 (d, *J* = 8.5 Hz, 2H), 7.78 (d, *J* = 8.5 Hz, 2H), 7.96 (s, 1H), 8.68–8.69 (m, 1H). ^{13}C-NMR (100 MHz, $CDCl_3$): δ 121.3, 122.3, 125.0, 127.5, 128.3, 138.1, 147.2, 150.3, 150.7, 150.8. HRMS (ESI+) *m*/*z* calcd. for $C_{14}H_{10}N_2NaO$ [M + Na]$^+$ 245.0685; found 245.0664.

5-(9H-fluoren-2-yl)oxazole (**9c**): White solid, mp = 155–158 °C; R_F = 0.62 (Hex-AcOEt 6:4 *v*/*v*); FT-IR (ATR)ν_{max}/cm^{-1} 3103, 2922, 2851, 1717, 1449; ^{1}H-NMR (400 MHz, CDCl$_3$): δ 3.92 (s, 2H), 7.30–7.34 (m, 1H), 7.37–7.41 (m, 2H), 7.55 (d, *J* = 7.4 Hz, 1H), 7.66 (d, *J* = 8.1 Hz, 1H), 7.78 (d, *J* = 5.6 Hz, 2H), 7.81 (s, 1H), 7.91 (s, 1H). ^{13}C-NMR (100 MHz, CDCl$_3$): δ 29.7, 36.9, 120.1, 120.2, 120.9, 121.1, 123.3, 125.1, 126.1, 126.9, 127.2, 140.9, 142.2, 143.4, 143.8, 150.2, 152.0.

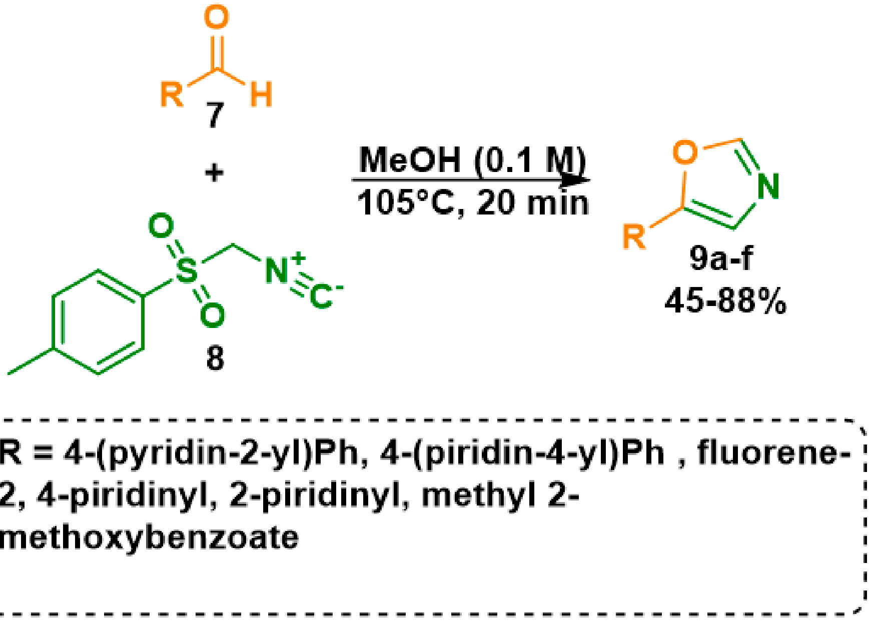
5-(pyridin-4-yl)oxazole (**9d**): White solid, mp = 88–91 °C; R_F = 0.18 (Hex-AcOEt 6:4 *v*/*v*); FT-IR (ATR)ν_{max}/cm^{-1} 3090, 2951, 1616, 1584, 1481, 1423, 1220; ^{1}H-NMR (400 MHz, CDCl$_3$): δ 7.52–7.54 (m, 1H), 7.58 (s, 1H), 8.02 (s, 1H), 8.68–8.69 (m, 2H). ^{13}C-NMR (100 MHz, CDCl$_3$): δ 118.1, 124.8, 134.5, 149.0, 150.5, 151.6.

5-(pyridin-2-yl)oxazole (**9e**): White solid, mp = 80–83 °C; R_F = 0.23 (Hex-AcOEt 6:4 *v*/*v*); ^{1}H-NMR (400 MHz, CDCl$_3$): δ 7.18–7.22 (m, 1H), 7.61–7.64 (m, 1H), 7.66–7.67 (m, 1H), 7.94–7.95 (m, 2H). ^{13}C-NMR (100 MHz, CDCl$_3$): δ 119.3, 123.0, 124.7, 136.9, 146.9, 149.8, 150.9, 151.1.

methyl 2-methoxy-5-(oxazol-5-yl)benzoate (**9f**): White solid, mp = 48–51 °C; R_F = 0.31 (Hex-AcOEt 6:4 *v*/*v*); FT-IR (ATR)ν_{max}/cm^{-1} 3121, 2957, 2922, 2852, 1686, 1623, 1564, 1437, 1249, 1218; ^{1}H-NMR (400 MHz, CDCl$_3$): δ 3.93 (s, 3H), 3.95 (s, 3H), 7.05 (d, *J* = 8.7 Hz, 1H), 7.30 (s, 1H), 7.75 (dd, *J* = 8.7, 2.4 Hz, 1H), 7.91 (s, 1H), 8.09 (d, *J* = 7.4 Hz, 1H). ^{13}C-NMR (100 MHz, CDCl$_3$): δ 52.2, 56.1, 112.5, 120.2, 120.5, 120.7, 127.9, 129.3, 150.2, 150.5, 159.1, 166.0.

3. Results and Discussion

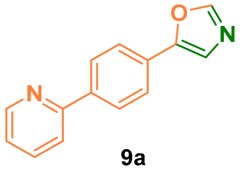
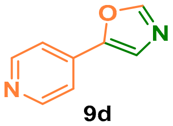
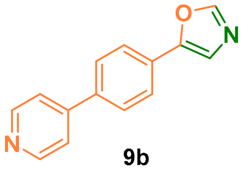
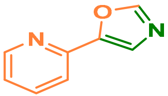
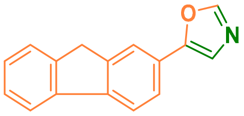
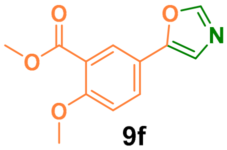
The 1,3-oxazoles **9a–f** were synthetized in moderate to good yields via Van Leusen reaction according to the Scheme 1 by using *p*-Toluenesulfonylmethyl isocyanide **8** (TosMIC) and different complex aldehydes **7** such as 4-(2-pyridyl)benzaldehyde which is a principal fragment of HIV drug Atazanavir or fluorene-2-carboxaldehyde which is present in drugs such as Indecainide, Lumefantrine and Lomitapide, useful as antiarrhythmic, antimalarial and inhibitor of the microsomal triglyceride transfer protein (MTP) agents, respectively.



Scheme 1. General synthetic route for the synthesis of 1,3-oxazoles **9a–f**.

The strength of this work relies on using a pressure reactor to accelerate Van Leusen reaction since this reaction take hours to complete and by using our methodology take only 20 min. the 1,3-oxazoles synthetized are shown in the Table 1. In addition, oxazoles **9a**, **9b**, **9d** and **9e** represent a contribution to the synthesis of hybrids molecules because they are considered pharmacophoric-chromophoric hybrids compounds which these kinds of molecules are scarcely explored.

Table 1. 1,3-oxazoles synthetized via Van Leusen reaction under a reactor pressure.

1,3-Oxazoles	Yield	1,3-Oxazoles	Yield
 **9a**	85%	 **9d**	65%
 **9b**	88%	 **9e**	45%
 **9c**	50%	 **9f**	70%

As preliminary assay directed to explore applicability of the oxazole derivatives herein synthesized, oxazole **9b** was undergone preliminary cation recognition and as fluorescent pH sensor studies. First, an individual preliminary study of fluoresence changes by naked-eye were conducted in DMSO solvent with several metal ions, including Hg^{2+}, Ni^{2+}, $Zn^{2+,}$ Ag^{+}, Cu^{2+} and Pb^{2+}. The oxazole showed a “turn-off” effect in the presence of Ni^{2+} and apparently a coordination complex was formed with Cu^{2+} due to the observed precipitate in reaction medium (Figure 2). This result is interesting because complexes with Cu^{2+} could be done, since these complexes are of biological relevance.

To evaluate qualitatively as possible fluorescent pH sensor the oxazole **9b** by naked-eye, it was dissolved on methanol and normal fluorescence is observed, but when pH decreases a strong fluorescence emission is presented. Conversely, increasing pH of the same solution exhibits similar fluorescence pattern before acid addition, therefore the changes are completely reversible (Figure 3). This preliminary result is interesting because novel fluorescents sensors for monitoring the change of various pH ranges can be developed by variating the functionality around the pyridine ring. To our delight, few reports about the use of 1,3-oxazoles as pH sensor have been published and this work contributes no-biological application of this azoles.

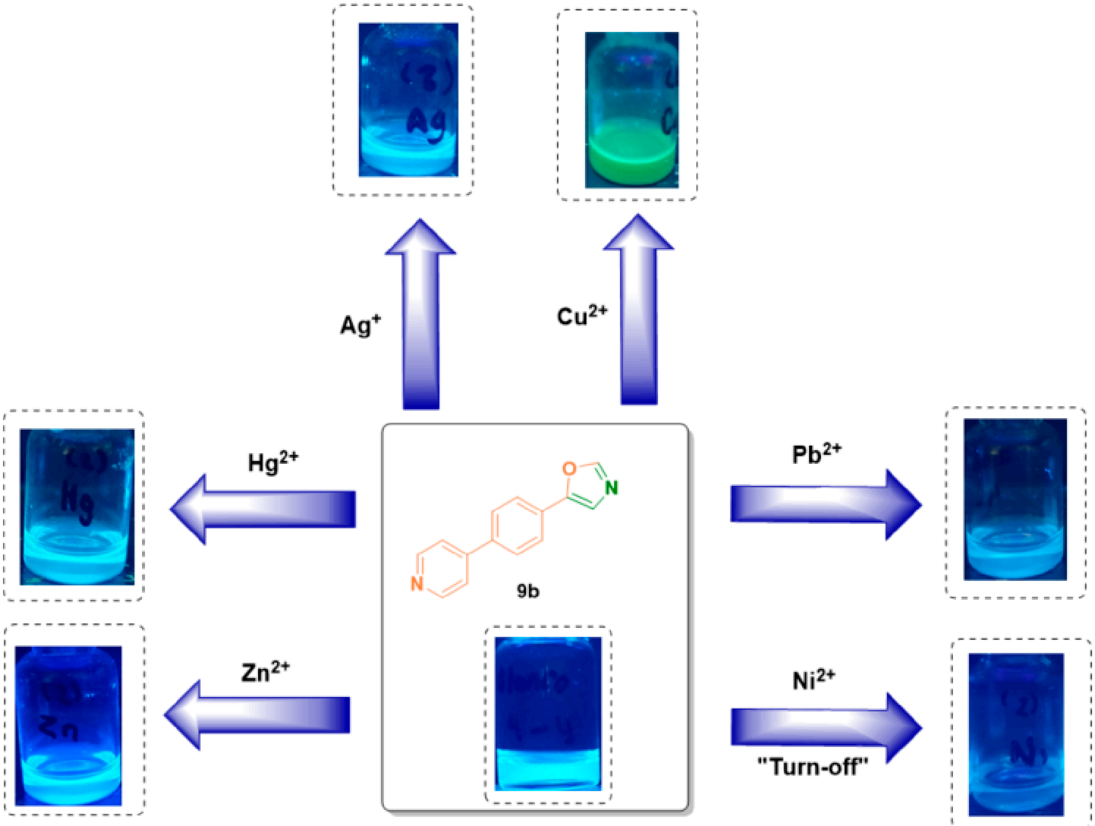


Figure 2. Fluorescence changes studies by naked-eye of oxazole **9b** of various cations.

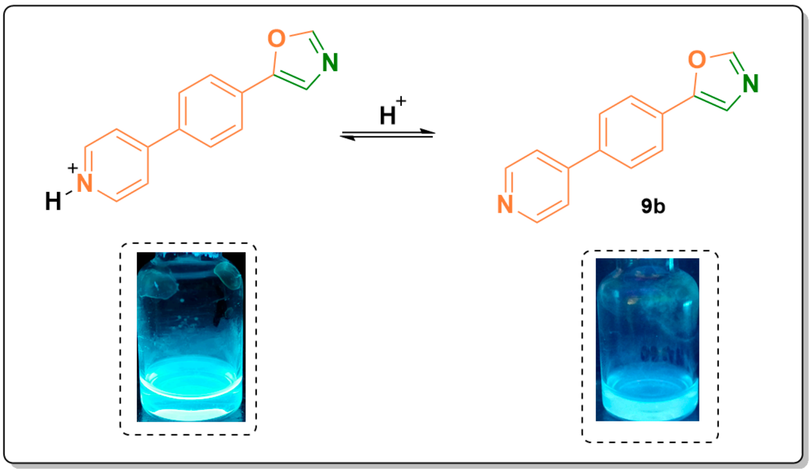


Figure 3. Fluorescence changes studies by naked-eye of oxazole **9b** in medium acid.

4. Conclusions

A new protocol for the synthesis of 1,3-oxazoles via Van Leusen reaction was presented by using a pressure reactor, which complex oxazoles can be synthetized on minutes. The protocol described offers operational simplicity, general applicability and it provides a practical procedure better than the existing methods. The preliminary fluorescent cation recognition studies by naked-eyed for the oxazole **9b** shows a "turn-off" fluorescent effect when Ni^{2+} is added, which mean it could be a promising optical sensor for this cation. Nevertheless, the same compound shows a marked fluorescence change in medium acid. Therefore, deeply studies by using fluorescence technique and titration by ^{1}H-NMR is ongoing in our laboratory.

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Conflicts of Interest: The authors declare no conflicts of interest or state.

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