



MINI-REVIEW ON THE SYNTHESIS OF OXAZOLE DERIVATIVES USING NON-CONVENTIONAL METHODS.

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ABSTRACT

In the literature there are several methods for the synthesis of oxazole derivatives using different reagents as catalysts. However, some of these reagents are hazardous and require special conditions, such as either pH differences or higher temperatures. Analyzing these data, the aim of this study was to carry out an analysis on the synthesis of some oxazole derivatives through non-conventional methods. The results showed that non-conventional methods can have some advantages over conventional methods such as; *i*) catalyst-free reactions; *ii*) reaction times are shorter; *iii*) some reactions are more selective. In conclusion, the use of unconventional methods is a chemical tool to synthesize new oxazole derivatives.

KEYWORDS. Oxazole, derivatives, non-conventional methods.

INTRODUCTION

For several years there has been interest in the development of new oxazole derivatives in organic chemistry field and pharmaceutical industry using some conventional methods^{i-x}, which involve some catalyst agents such as sulfuric acid^{xi}, iodide^{xii}, palladium chloride^{xiii}, CopperIII^{xiv}, bromide acid^{xv}, rhodium^{xvi}, zinc trifluoromethanesulfonate^{xvii}, dichlorobis(triphenylphosphine)nickel(II)^{xviii}; however, some of these reagents are expensive and difficult to handle, requiring specific conditions. In the search for new chemical alternatives, some methods have been used to synthesize oxazole derivatives; for example, a study showed the synthesis of a two oxazole derivatives using two methods. The first stage (Method A), the *N*-hydroxybenzimidoyl chloride reacted with an alkyne derivative to produce 3,4-Diphenyl-5-(phenylsulfonyl)isoxazole using tris(acetonitrile)cyclopenta-dienylrutheniumhexafluoro-

phosphate ($\text{CpRu}(\text{MeCN})_3\text{PF}_6$) as catalyst (Figure 1). In the second stage (Method B) the reaction was carried out without catalyst to produce 3,5-Diphenyl-4-(phenylsulfonyl)isoxazole; it is noteworthy that method B is stereoselective to binding phenyl groups in the position 3,5 to isoxazole.^{xix}

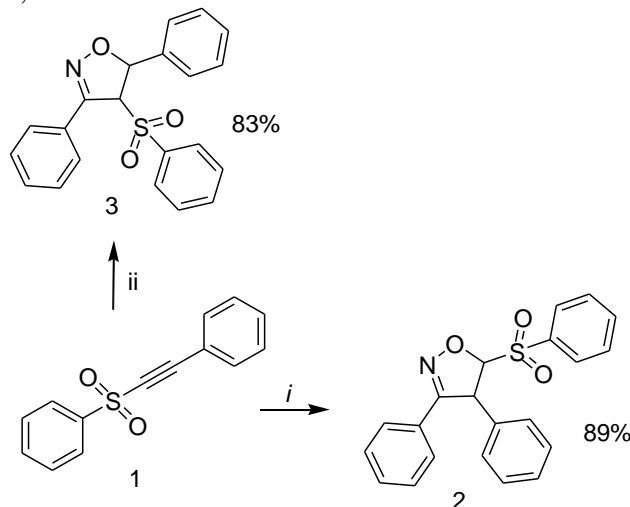


Figure 1. Synthesis of 5-(benzenesulfonyl)-3,4-diphenyl-isoxazole (**3**). Conditions and reagents;

i = ($\text{CpRu}(\text{MeCN})_3\text{PF}_6$), trimethylamine, diethyl ether anhydrous, room temperature; ii = acetonitrile, trimethylamine, tetrahydrofuran, room temperature. Other data showed that both thermal and ultrasonic methods can be used to synthesis of an oxazole derivative using a deep eutectic solvent (choline chloride) as a reaction medium (Figure 2). It is noteworthy that applying ultrasound method improved yields and reduced reaction times compared to thermal method.^{xx}

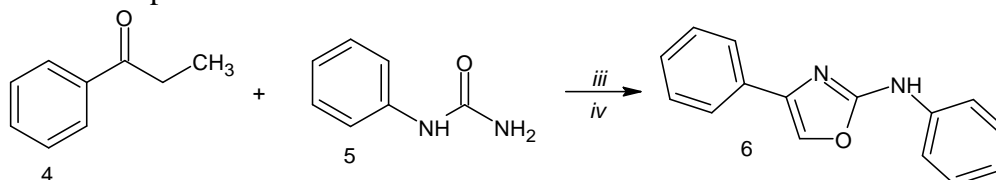


Figure 2. Synthesis of N,4-diphenyl-1,3-oxazol-2-amine (**6**). Conditions and reagents; iii = thermal method (65 °C); phenacyl bromide (**4**), phenylurea (**5**), choline chloride, 5 h, yield 60%; iii = ultrasound method; compound **4** and **5**, choline chloride, 17 min, room temperature. On the other hand, a study showed the synthesis of a substituted oxazole from a β -diketone analog and benzylamine using an electrochemical method. The authors indicate that this method not need hazardous oxidants and catalysts.^{xxi}

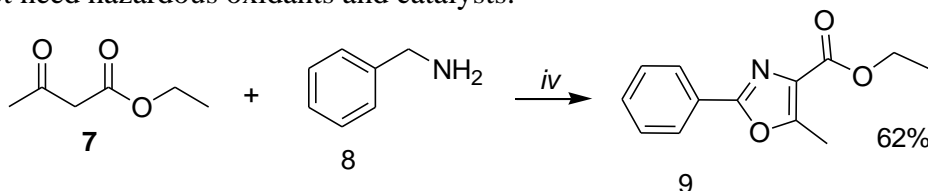


Figure 3. Preparation of 5-Methyl-2-phenyl-oxazole-4-carboxylic acid ethyl ester (**9**). Conditions and reagents; iv = electrolyte (NaI), dimethylformamide, room temperature.

In addition, a report display the synthesis of 3-(4,5-dihydro-3-methyl-5-oxopyrazol-1-yl)-3-oxopropanenitrile (**12**). The first stage involved the reaction of ethyl cyanoacetate with hydrazine hydrate to produce the compound 2-Cyano aceto hydrazide (**11**). Then, **11** was condensed with ethylacetoacetate to form the compound **12** (Figure 4). It is noteworthy that the reaction was carried out without a catalyst and does not require special conditions.^{xxii}

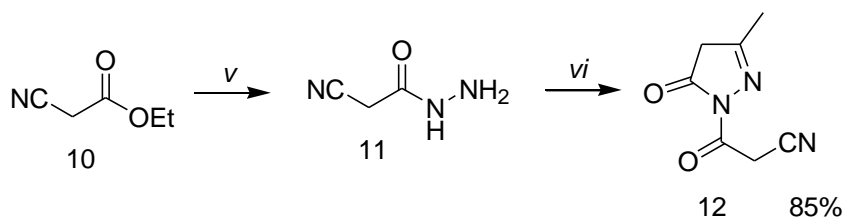


Figure 4. Preparation of 3-(4,5-dihydro-3-methyl-5-oxopyrazol-1-yl)-3-oxopropanenitrile (12). Conditions and reagents; *v* = ethanol, 0 °C (10 min), 3-4 hs, room temperature; *vi* = ethanol, 80-82 °C 8 hs, reflux.

Other report indicate the preparation of 4-(4-bromophenyl)-5-methyl-2-[4-(trifluoromethyl)phenyl]oxazole through *O,N*-acylation-cyclodehydration of an oxime with acid chloride under irradiation conditions; this method indicate that microwave irradiation method can produce good yield of product.^{xxiii}

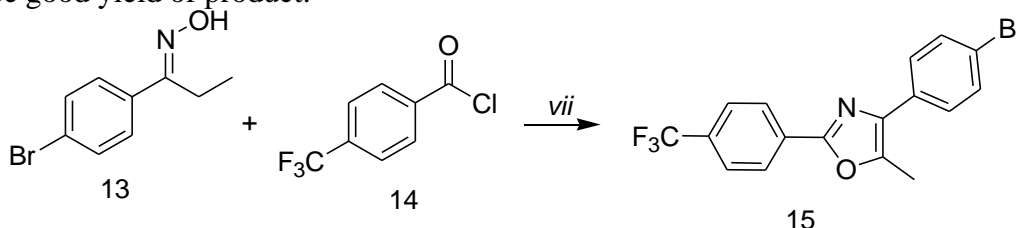


Figure 5. Synthesis of 4-(4-bromophenyl)-5-methyl-2-[4-(trifluoromethyl)phenyl]oxazole (15). Conditions and reagents; *vii* = 1-(4-bromo-phenyl)-propan-1-one oxime (13), 4-trifluoromethyl-benzoyl chloride (14), 1,2-dichlorobenzene, 4-dimethylaminopyridin, MW, 220 °C, 5min .

Besides a oxazole derivative was prepared from 2-acylamino carbonyl derivative and *N*-(triethylammoniumsulfonyl)carbamate under microwave conditions. The authors suggest an alternative method for synthesis of oxazole derivatives compared with Robinson-Gabriel reaction which involves an intramolecular reaction of 2-acylamino-ketone followed by a dehydration with sulfuric acid to give an oxazole derivative.^{xxiv}

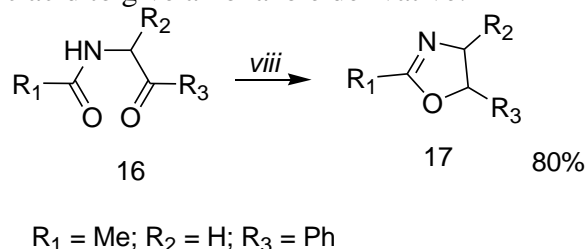


Figure 6. Preparation of an oxazole analog (17). Conditions and reagents; *viii* = *N*-(triethylammoniumsulfonyl) carbamate, MW 100 W, 2 min.

Another study showed a [3+2] cycloaddition reaction of the substituted benzaldehyde (18) to 4-toluenesulfonylmethyl isocyanide (19) in the presence of potassium phosphate (K_3PO_4) and isopropanol to form the oxazole derivative (20) under microwave irradiation. The reaction mechanism proposed indicates that K_3PO_4 base can extract a proton from methylene of 4-toluenesulfonylmethyl isocyanide, resulting in the formation of an intermediary ion, which subsequently reacts with the arylaldehyde. Next, there is a [3 + 2] cycloaddition reaction and then a protonation of 4,5-disubstituted oxazoline. Furthermore, the authors suggest that in the presence of another equivalent of K_3PO_4 and under heating conditions, the 5-substituted oxazole is produced.^{xxv}

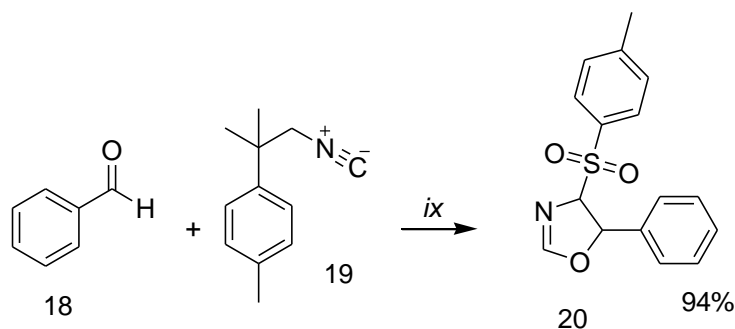


Figure 7. Synthesis of 5-Phenyl-4-(toluene-4-sulfonyl)-4,5-dihydro-oxazole. Conditions and reagents; ix = K_2PO_3 , isopropanol medium, MW 280 w, 60 °C, 6-8 min.

Furthermore, a report shows the synthesis of 4-phenyl-oxazol-2-ylamine (**23**) using two methods. In the first method phenacyl bromide reacted with thiourea and basic alumina under microwave irradiation to form **23**. The second method involves a thermal method without microwave irradiation for this same reaction. The results showed higher yield and lower reaction time with microwave irradiation compared with conventional method.^{xxvi}

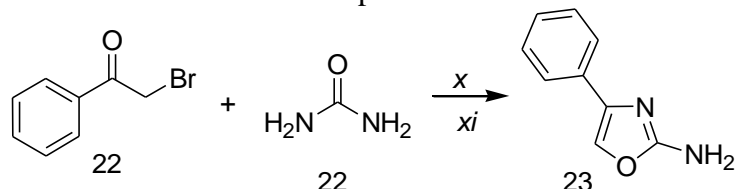


Figure 8. Synthesis of 4-Phenyl-oxazol-2-ylamine. Conditions and reagents; x = basic alumina, MW (0.5 min intervals, 140 °C), 2-3 min; xi = basic alumina, 140 °C, 33 h.

Other data indicate the preparation of an oxazole derivative (**26**) from an aryl diazoester (**24**) and acetonitrile (**25**) in the presence of a blue light-emitting diode (blue LED) with a constant current of 50 μA , using RVC electrode. The reaction involves an electro-photochemical reaction of the aryl diazoester to generate an anion which subsequently react with acetonitrile to produce a substituted oxazole.^{xxvii}

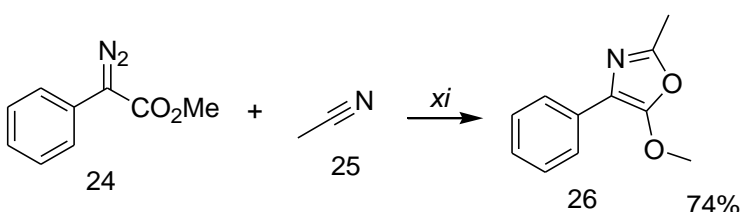


Figure 9. Synthesis of 5-Methoxy-2-methyl-4-phenyl-oxazole (**26**). Conditions and reagents; xi = blue LED, RVC(-)Pt(+), N_2 , 4.5 hs.

Furthermore, another report showed the preparation of a 2,5-substituted oxazole by intramolecular oxidative cyclization of N-allylbenzamides (**27**) using N-bromosuccinimide (NBS). The authors indicate that reaction gives an efficient synthetic strategy to form an oxazole nucleus directly from easily accessible substrates under temperate conditions.^{xxviii}

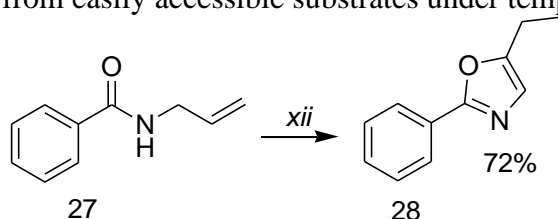


Figure 10. Synthesis of 5-Ethyl-2-phenyl-oxazole (**26**). Conditions and reagents; xii = NBS, 1,2-dichloroethane 80 °C, 24 hs.

new oxazole derivatives, some non-conventional methods have been developed. Analyzing these data, the objective of this study was to carry out a mini-review on the preparation of some oxazole derivatives by non-conventional methods. The results showed that non-conventional methods can have some advantages over conventional methods such as; *i*) some reactions are catalyst-free; *ii*) Reaction times are shorter; and *iii*) Some reactions present regioselectivity. Therefore, the use of microwave irradiation is a valuable tool for the field of organic chemistry. In addition, microwave-assisted reactions have a positive relationship with the environment by reducing some toxic products.

Acknowledgement

None

Conflict of Interest

Authors declare that there is no conflict of interests regarding the publication of the paper.

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