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Synthesis of 3,5-disubstitueted 1,2,4-oxadiazoles from Amidoximes and N-Hydroxyl Phthalimide Esters in Water

L. Rajeswari[1, 2], L. Chinnari[1], Y. Kumari[1]
[1]*Department of Organic chemistry and FDW, Andhra University, Visakhapatnam, Andhra Pradesh*
[2]*Department of Chemistry, Smt. NPS. Govt. College (W), Chittoor, Andhra Pradesh*
Corresponding Author: V. Siddaiah

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ABSTRACT: A simple and ecofriendly approach has been developed for synthesis of 3,5-disubstituted 1,2,4-oxadizoles from Benzimidoximes and N-hydroxyl phthalimide esters in green solvent under catalyst free conditions. Various functional groups were well tolerated and imparted corresponding 3,5-disubstituted 1,2,4-oxadizoles in moderate to good yields.

KEYWORDS: Benzimidoximes, N-Hydroxyl phthalimide ester,3,5-disubstituted 1,2,4-oxadizoles, ecofriendly solvent and Water

I. INTRODUCTION

Five membered heterocyclic oxadiazolemoiety is an important constituent in various biologically active compounds. Among oxadiazoles, recently,1,2,4- oxadiazoles have been studied with more interest because of their distinguished synthetic and pharmacological applications such as sphingosine-1-phosphate-1 (S1P1) receptor agonist,[1] muscarinic agonist,[2] serotoninergic antagonists,[3] monoamine oxidase inhibitor,[4] and dopamine transporters,[5]Antitussive, Anti-inflammatory, Anaesthetic, Vasodilator, anthelmintic, antiallergic, antiplatelet effects invitro, antithrombotic propertiesinvivo, etc.These bioactive moieties are stable bioisosters of amide and ester functionality. Hence, there is a need to design various 3,5- disubstituted 1,2,4-oxadiazoles. Therefore, in this regard different methodologies have been explored for synthesis of pharmacologically important 3,5-disubstituted 1,2,4-Oxadiazoles moieties.

Figure1. Some biological active 3,5-disubstituted 1,2,4-oxadiazoles.

Conventionally, 1,2,4- oxadiazoles have been synthesized from Aminoimidoximes and carboxylic acids in presence of DCC and dioxane as solvent.[6] Previously, B. Kaboudin and his co-worker L. Malekzadeh reported 3,5- disubstituted 1,2,4- oxadiazoles from amidoximes and anhydrides in water.[7]Recently, Baykov and his co-workers reported 3,5-disubstituted 1,2,4-oxadiazoles via condensation between amidoximes and carboxylic acid esters using super base medium and DMSO[8] **(Scheme-1a and 1b)**. But these methods are associated with disadvantages like usage of additives and harsh reaction conditions. Moreover, in the above mentioned methods, there is a difficulty to removal of solvent, required long time to complete the reaction and safety handling is required. These reaction conditions lead to non-environment benign conditions. Therefore, development of ecofriendly protocols in organic synthesis is challenging and alluring. In this context, we report a new methodology for synthesis of 1,2,4-oxadiazoles using ecofriendly solvent water **(Scheme-1c)**.

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Scheme -1. Synthesis of 3,5-disubstituted 1,2,4- oxadizoles.

Nowadays, there is demand to develop environmental friendly chemical methodologies. Therefore Green chemistry is the most attractive concept by which we reduce or eliminate the use or generation of hazardous substances in various processes. Particularly, the use of solvents leads to toxicity, Contamination and waste treatment issues. These are the main sources of unwanted mass in synthetic pathways.[9] One of the key principles of this sustainable chemistry is elimination or replacement of hazardous solvents with solvents which are benign to environment. However, reactions should run under suitable solvent to facilitate mass, heat transfer, allows the reaction rates and selectivity in chemical processes. Presently, water is one of the attractive green solvent. Since it is cheap,readily available, non-toxic solvent. So that water, being attractive from both an economical and environmental point of view. Water being a poor solvent for organic transformations, However it has been established due to its structural and physiochemical properties,develop polarity, hydrogen bonding and hydrophobic interactions which could influence the reaction.Herein, we report synthesis of bioactive 3,5-disubstituted 1,2,4-oxadizoles from amidoximes and esters of N-hydroxyl phthalimide using Water which is green solvent without use of any catalyst.

II. RESULTS AND DISCUSSION

We have initiated our studies on the investigation of reaction conditions for the synthesis of 3,5-disubstituted 1,2,4- oxadiazoles. We started Synthesis of 1,2,4- oxadiazoles from Amidoximes and N-Hydroxyl phthalimide ester at room temperature in presence of DCM. Reaction carried out and trace amount of product was obtained **(Table 1, Entry 1)**. Encouraged by this result, we focused on screening ofvarious solvents to increase the yield of 1,2,4-Oxadiazoles by increases the polarity of solvents at room temperature. In this screening, examination of our results showed in **Table 1** as only 16 % yield with DMF, 19 % yield with EtOAc **(Table 1, Entries 2&3)**. We observed reaction with EtOH solvent led to 22 % yield and with H_2O led to 30 % yield **(Table 1, Entries 4&5)**. This solvent screening showed, yield of product was increased with increasing polarity of solvent at r.t conditions. Next, we focused our studies for temperature screening to increase the yield of product. It was found that yields of **3a** was formed maximum when the temperature is at 100°C**(Table 1.Entry 10)**. On further increase in the temperature above 100°C lead to decrease in the yield.

Table-1. Optimization conditions[a]

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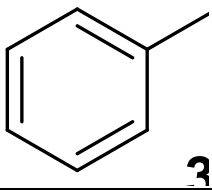
Entry	Solvent	Temp (^oC)	Time (h)	Yiel[b] (%)
1.	DCM	r.t	24	trace
2.	DMF	r.t	18	16
3.	EtOAc	r.t	14	19
4.	EtOH	r.t	12	22
5.	H_2O	r.t	20	30
6.	H_2O	50	20	50
7.	H_2O	60	14	56
8.	H_2O	70	10	60
9.	H_2O	80	10	65
10.	**H_2O**	**100**	**3**	**80**

[a]Rection conditions: **1a**(2.2 mmol), **2a**(4.4 mmol), Water (5 mL) and 100 ^oC.

With the established optimized reaction conditions, we examined the substrate scope for the synthesis of 3,5-disubstituted 1,2,4-oxadizoles by structurally divergent amidoximes and N-hydroxyl Phthalimide esters bearing electron donating groups, strong donating and withdrawing groups in moderate to good yields. In this examination, we found that electron donating groups such as -CH_3 on N- Hydroxyl phthalimide ester decrease the yields 56-60% **(Scheme-2, entries 3b&3g)**, Strong electron donating groups such as –OCH_3 further decrease the yield of desired Oxadizoles about 52-55% **(Scheme -2, entries 3d&3i)**, whereas electron withdrawing groups like -Cl significantly increase the amount of product up to 90% **(Scheme-2,, entries 3c&3h)**. Further, effect of two strong electron donating groups (-OCH_3) on yields shows decreases more about 50% **(Scheme-2, entries 3e&3j)**. We also observed effect of electron withdrawing group such as –Cl on Benzimidoximes led to increase the yields 50- 90% **(Scheme-2, entries 3f- 3j)** compared to simple H atom.

Scheme-2: Substrate scope for the synthesis of 3,5-disubstituted 1,2,4- oxadiazoles in water



3

[a]Reaction conditions: **1a**(2.2 mmol), **2a**(4.4 mmol), Water (5 mL),100 ^oC.

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III. ANTI-FUNGAL ACTIVITY

The newly synthesized compounds were evaluated for activity against Aspergillus flavus as pathogen and Fluconazole (25mg) was used as standards for antifungal activity.

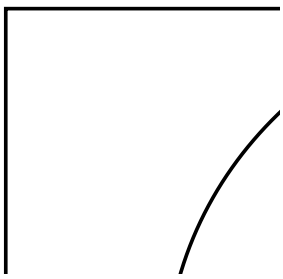
For the anti-fungal examination, 20ml of Potato dextrose agar was poured into each of the sterile petridishes. With the help of sterile cork borer the cups were punched and scooped off the set agar. The agar plates so prepared are divided into different sites and each of the plates was inoculated with suspension of particular organism by spread plate technique. The cups of the inoculated plates were then filled with 0.1 mL of the test solution. The test solution of the synthesized compounds and the standard drug Fluconazole were prepared in DMSO at 1mg/mL. All the inoculated plates were incubated at 38^{o}C and results were evaluated after 48h. Then the zone of inhibition was measured. The results are represented in **Table 2**.

Table 2: Anti-fungal activities compounds

Compound code	Aspergillus flavus (Zone of inhibition in nm)
	1mg
3a	7
3c	8
3d	4
3e	10
3f	11
3g	13
3h	0
3i	10
Fluconazole	15

IV. PLAUSIBLE MECHANISM

On the basis of controlled experiments and earlier studies, we believed that the reaction proceeds via nucleophillic attack of Amidoximes**(1)** on N-Hydroxyl phthalimide ester**(2)** leads to corresponding adduct **(A)**. Adduct **(A)** which involved in cyclisation by the loss of N- Hydroxy phthalimide as a byproduct results compound **(B)**. Further, compound **(B)** undergoes dehydration followed by intranucleophillic attack produce Oxadizoles **(3)**.



Scheme-3: Plausible mechanism

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V. EXPERIMENTAL SECTION

To an oven dried RB flask, Amidoxime (2.2 mmol) was dissolved in 5mL of water and then N-Hydroxyl phthalimide ester (4.4 mmol) was added and placed under stirring at room temperature. After some time resulting mixture was stirred with help of mechanical stirrer under reflux condition at 100℃. Progress of the reaction was monitored with help of TLC. After completion of the reaction, reaction mixture was cooled to room temperature and extracted with ethyl acetate. The organic layer was dried over anhy. Na_2SO_4 and removed under vacuum to get crude product. The crude was purified by column chromatography on silica gel (100-200 mesh) using EtOAc/hexane as eluents to afford the corresponding product.

VI. CONCLUSION

In conclusion, we developed a green synthetic route for synthesis of pharmacologically interesting 3,5-disubstituted 1,2,4-oxadizoles. Our main interest on this ecofriendly synthetic methodology is to replace the hazardous solvent by greener solvent without use of catalyst. This methodology was efficient, rapid and ecofriendly to environment. Finally, this methodology was highly efficient sustainable process compared with reported methodologies in literature.

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