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An efficient green protocol to access synthesis of 3,5-disubstitueted 1,2,4-oxadizoles and 2-substituted benzimidazoles using Spinach Juice.

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Abstract : An ecofriendly and facile approach for synthesis of 3,5-disubstituted 1,2,4-oxadizoles and 2-substituted benzimidazoles has been developed from Benzimidoximes and o-Phenylenediamines with aldehydes respectively through green solvent spinach juice and PTSA catalyst. Various functional groups were well endured and imparted corresponding 3,5-disubstituted 1,2,4-oxadizoles and 2-substituted benzimidazoles in moderate to good yields.

Keywords: Benzimidoximes, o-Phenylnediamine, 3,5-disubstituted 1,2,4-oxadizoles, 2-Substituted benzimidazoles, ecofriendly solvent and Spinach Juice.

INTRODUCTION

Oxadizoles and Benzimidazoles are privileged Heterocyclic structural scaffolds existed in numerous natural compounds, synthetic molecules which fabricate many medicinal and biological properties.[1] These Heterocyclic nuclei have found wide range of applications in material science, pharmaceuticals and dyes.[2-6]Among Oxadizoles, the 3,5-disubstituted-1,2,4-oxadiazoles play vital role in Medicinal Chemistry and has been used toreplace amide and Ester functionalities.[7] In addition, 1,2,4-oxadiazole ring found in various biologically active compound such as Butalamine which is a Coronary Vasodilator and Local anesthetic,[8] Libexin is a cough suppressant,[9] and Ataluren is used for the treatment of fibrosis[10]**(Fig. 1).** Besides, the compounds bearing benzimidazoles motifs also exhibit a broad spectrum of biological properties such as anti-viral,[11] anti-cancer,[12] anti-bacterial,[13] anti-fungal[14] and anti-HIV activities **(Fig. 1).** Therefore, their synthesis and studies of their bioactivity have more attractive attention in Chemistry, Biology and Medicine.

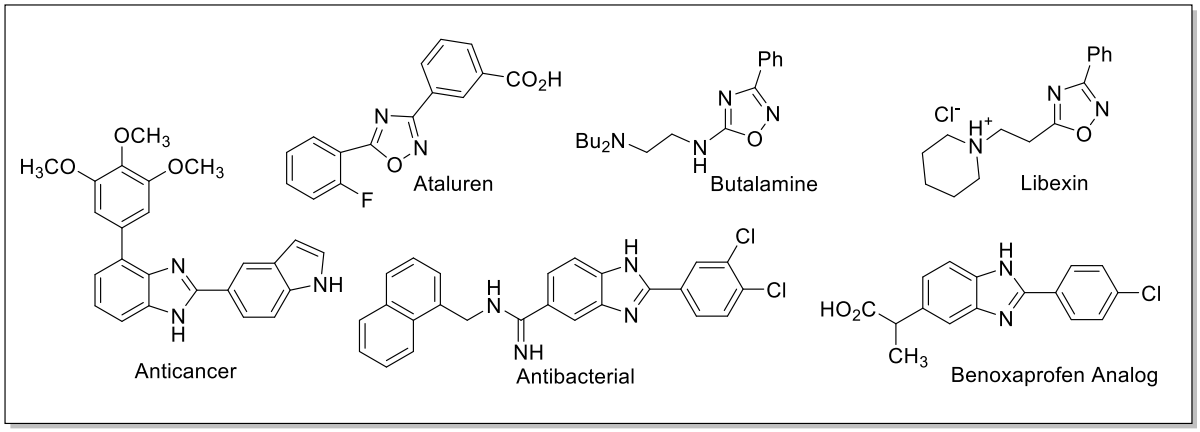
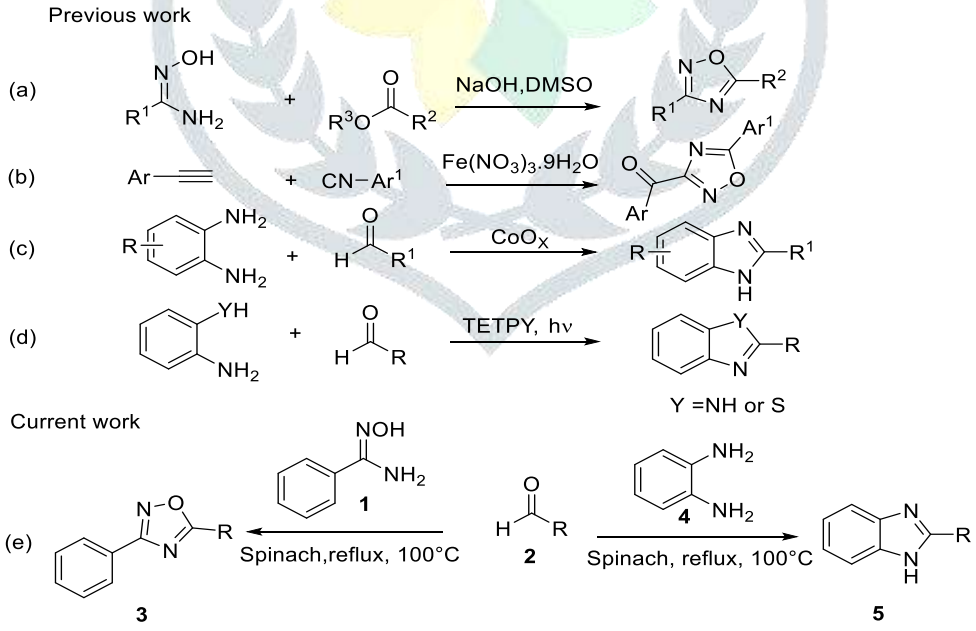


Fig.1: Bioactive 3,5- disubstituted 1,2,4-oxadizoles and 2- substituted benzimidazoles

There are number of methods reported for synthesis of 1,2,4-oxadizoles and 2- substituted benzimidazoles. Previously, Baykov and his coworkers reported 3,5 disubstituted 1,2,4-oxadiazoles via condensation between amidoximes and carboxylic acid esters using superbase medium and DMSO.[15a] Recently, Bian et al. developed a protocol from alkynes and nitriles using Iron(III) nitrate mediates[15b]**(Scheme 1a and 1b)**. Furthermore, synthesis of benzimidazoles were also repored from Cobalt nanocomposite catalyzed the coupling of phenylenediamines and aldehydes[15c] and Supramolecular nanoassemblies of an AIEE-ICT-active pyrazine derivative (TETPY) catalyzed in strong absorption in the visible region[15d] **(Scheme 1c and 1d)**. However, these protocols have some drawbacks such as use of hazardous solvents such as DMSO, expensive metal catalysts, difficulty in solvent separation and require special equipments. These reaction conditions create non ecofriendly environment.[16] Therefore, Current challenge in Organic synthesis is development of ecofriendly methodologies particularly using greener solvents. In this aspect development of new methodology for synthesis of 1,2,4-oxadiazoles and Benzimidazoles using a ecofriendly solvent Spinach juice **(Scheme 1e)** is highly desirable. So, herein we report environmentally benign synthesis of 3,5-disubstituted1,2,4-oxadiazoles and 2-substituted benzimidazoles.

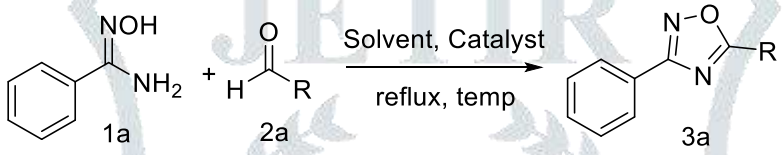


Scheme-1: Synthesis of 3,5- disubstituted 1,2,4- oxadiazoles and 2- substituted benzimidazoles

RESULTS AND DISCUSSIONS

We initiated our studies on 0the investigation of synthesis of 1, 2, 4 - Oxadiazoles from Amidoximes **(1a)** and aldehydes **(2a)** in Green solvent like Water at room temperature. Reaction was moved but product was obtained in trace with prolonged time **(Table 1, Entry1)**. We continued our studies with same starting materials for temperature screening in order to increase the yield of the Product. We enhanced the temperature, at 100°C reflux conditions yield was improved **(Table 1, entry 2)**. Next we examined the influence of catalytic amount of Organic acid on reaction time and yield of the product. We observed 50% yield with CH_3COOH **(Table 1, Entry3)** and we tested with different catalysts, the yield of **3a** enhanced to 55% when CF_3COOH catalyst and 60% and 70% when C_6H_5COOH and PTSA were performed respectively **(Table 1, Entries 4-6)**. Encouraged by these results, we focused on the introducing a greener solvent Spinach juice which contain variety of Organic acids and phenolic compounds[17] in order to enhance the yield and shortening the reaction time**(Table 1. Entry 7)**. In presence of Spinach juice at 100°C under reflux conditions, 82% yield obtained under short reaction time **(Table 1. Entry 8)**. In Continuation of our studies we examined the Scope of Organic acid catalyst, we observed decrease in the time of reaction and the yield increased when strong acid PTSA Catalyst is used **(Table 1. Entries 9-12)**.

Table-1: Optimization conditions[a]



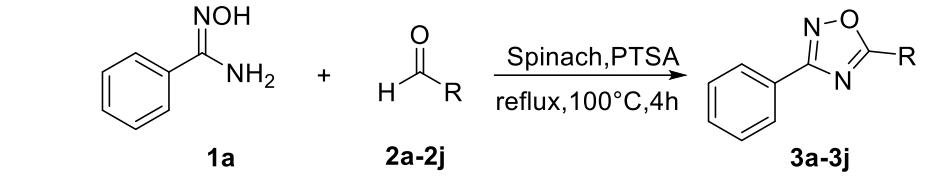
Entry	Solvent	Catalyst	Temp(°C)	Time (hrs)	Yield[b] (%)
1.	Water	-	rt	24	trace
2.	Water	-	100	10	40
3.	Water	CH_3COOH	100	9	50
4.	Water	CF_3COOH	100	9	55
5.	Water	C_6H_5COOH	100	8	60
6.	Water	PTSA	100	8	70
7.	Spinach	-	rt	24	30
8.	Spinach	-	100	9	80
9.	Spinach	CH_3COOH	100	9	78
10.	Spinach	CF_3COOH	100	5	80
11.	Spinach	C_6H_5COOH	100	6	79
12.	**Spinach**	**PTSA**	**100**	**4**	**86**

[a]Reaction conditions: **1a** (2.2 mmol), **1b** (2.6 mmol), Spinach juice (4 mL), PTSA Catalyst (0. 2 mmol), 100 °C, 4h. [b]Isolated yield.

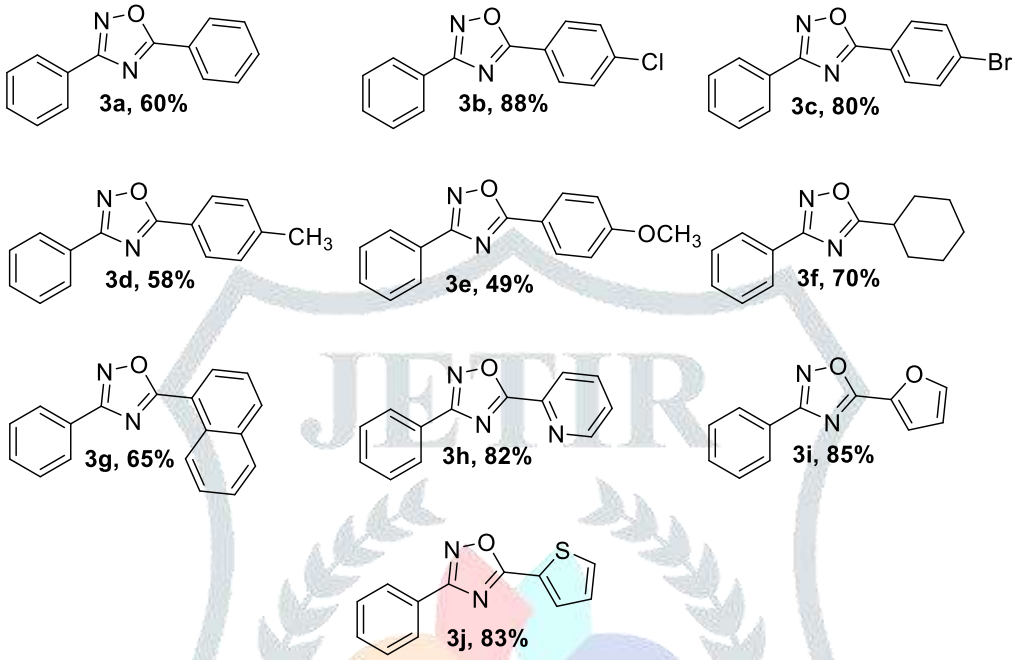
With the Optimized conditions in our hand, we explored substrate scope towards this simplest methodology. In this context, we employed wide range of Aromatic aldehydes bearing electron withdrawing, electron donating groups including alicyclic aldehyde and Heterocyclic aldehydes for the scope of this transformation gave moderate to good yield. Under this examination, we found aromatic aldehydes having electron withdrawing groups -Cl, -Br increases the yield about 80-88% (**Scheme-2, Entry 3b and 3c**), whereas electron donating groups such as $-CH_3$, $-OCH_3$ decreased the yield nearly 49- 58% (**Scheme-2, Entry 3d and 3e**). We also extended substrate scope with Cyclohexane carbaldehyde gave good yield (**Scheme-2, Entry 3f**) and 1- Naphthaldehyde

gave moderate yield (**Scheme-2, Entry 3g**). We obtained good yields with heterocyclic aldehydes Piconiladehyde, Furan-2-Carbaldehyde and Thiophene- 2- Carbaldehyde (**Scheme-2, entries 3h, 3i, 3j**).

Scheme-2: Scope of substrate on the Synthesis of 3,5-disubstituted 1,2,4- oxadizoles[a]



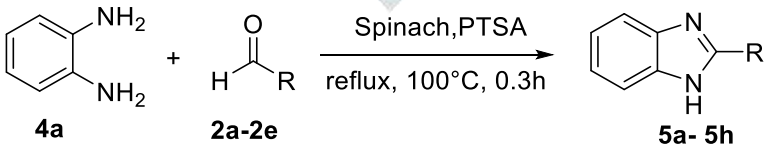
1a 2a-2j 3a-3j



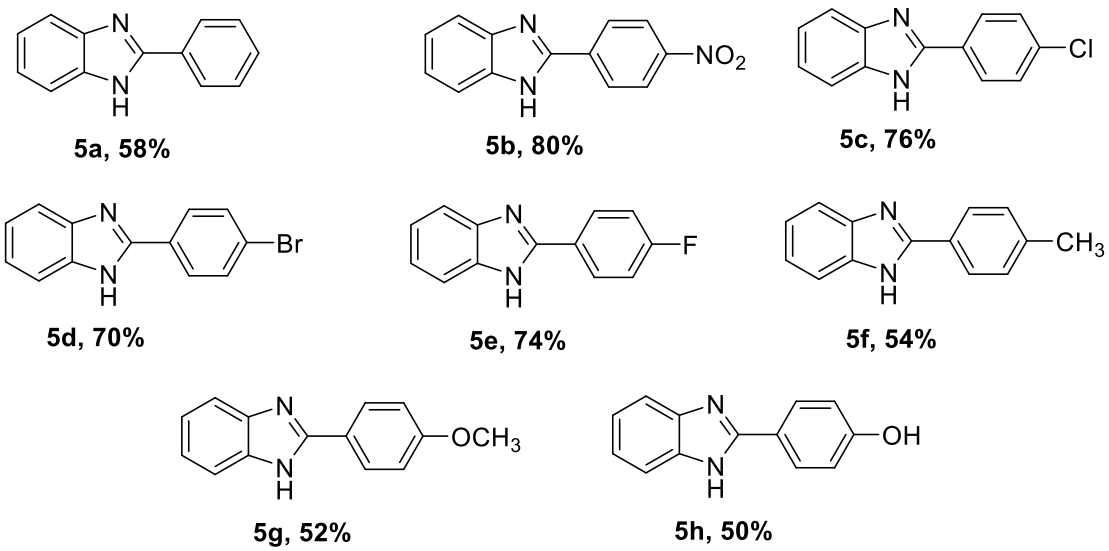
[a]Reaction conditions: **1a** (2.2 mmol), **2a** (2.6 mmol), Spinach juice (4 mL), PTSA Catalyst (0. 2 mmol),100 °C.

The above results motivated us to look for a simple and environmentally sustainable method for the synthesis of 2-substituted Benzimidazoles. Fortunately, following the above protocol, we synthesized 2- substituted Benzimidazoles from o-Phenylnediamine and Aromatic aldehydes. This methodology was performed from o-Phenylnediamine**(4a)** (2.7 mmol), aldehydes **(2a)**(2.7 mmol), Spinach juice (5mL), PTSA Catalyst (0.2 mmol), 100 °C. We obtained the corresponding product (**5a**) in excellent yield. Then we examined with various substituted aldehydes. All the functional groups are well tolerated and gave good to excellent yields. (**Scheme-3**).

Scheme-3: Scope of substrate on the Synthesis of 2-Phenylenebenzimidazoles[a]



4a 2a-2e 5a- 5h



[a]Reaction conditions: **4a** (2.7 mmol), **2a** (2.7 mmol), Spinach juice (5mL), PTSA Catalyst (0.2 mmol), 100 °C.

EXPERIMENTAL SECTION

3,5-disubstituted 1,2,4-oxadizoles / 2-substituted benzimidazoles have been synthesized by taking Benzaldehyde (**2.6 mmol**) dissolved in 4mL of Spinach juice and Catalyst, Amidoximes (**2.2 mmol**)/ o-Phynelenediamine (**2.7 mmol**) are added to a oven dried RB flask respectively and placed under stirring at room temperature. After some time resulting mixture was stirred with help of mechanical stirrer under reflux condition at 100 °C. Progress of the reaction was monitored with help of TLC. After completion of the reaction the reaction mixture was cooled to room temperature and separated with ethyl acetate and water. The organic layer is dried over anhy. Na_2SO_4 and the solvent is 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 products **3a - 3j** and **5a-5h.**

CONCLUSION

In conclusion we report an environmentally sustainable protocol for the synthesis of 3,5-di substituted 1,2,4-oxadizoles and 2-substituted benzimidazoles from easily available starting materials like benzimidazoles, aldehydes and o-Phenyldiamine using PTSA as catalyst in spinach solvent at 100 °C. In this method, we efficiently replaced hazardous solvents by green solvents to Control the environment pollution is one of the cause to develop ecofriendly methodologies for design of bioactive Oxadizoles and Benzimidazoles. In this Context, We avoided formation of byproduct by direct use of aldehydes instead of activated carboxylic acid derivatives.

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