Cu(I) catalyzed microwave assisted telescopic synthesis of 3,5-disubstituted isoxazoles in green media

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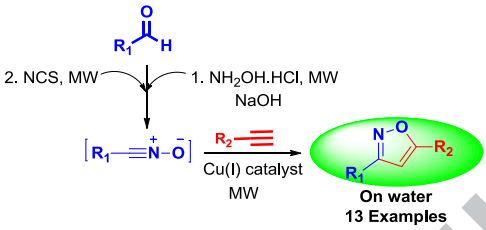

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ABSTRACT

A facile and efficient microwave assisted telescopic synthesis of diverse isoxazoles was reported in green reaction medium. Initially, N-hydroxyl imidoyl chlorides were reacted with substituted alkynes in aqueous medium using 2 mol% of $[Cu(phen)(PPh_3)_2]NO_3$ as catalyst to yield the 3,5-disubstituted isoxazoles. To improve the efficiency of the synthetic route for the regioselective synthesis of isoxazoles, commercially available aromatic aldehydes were converted to N-hydroxyl imidoyl chlorides followed by reaction with substituted alkynes in aqueous medium using Cu(I) as catalyst in telescopic manner. This telescopic new synthetic strategy facilitates the rapid generation of molecular frameworks in three-dimensional fashion leading to 3,5-disubstituted isoxazoles. This approach is visualized as an environmentally benign process and a simple operation to the privileged scaffolds. The present one-pot synthetic sequence allows the introduction of two points of structural diversity to expand chemical space with excellent purity and yields.

1. Introduction

Synthesis of highly functionalized heterocyclic small molecules are important in drug discovery programme due to their selective binding ability to the biological targets with respect to their chemical diversity.[1] With respect to that, diversity oriented synthesis (DOS) is proven a successful tool to swiftly synthesize novel bioactive compounds with skeletal diversity from simple starting materials.[2] Over the past two decades, multicomponent reactions (MCRs) have gained prominent importance as starting points for diversity oriented synthesis (DOS) owing to providing direct admittance to small molecule libraries.[3] MCRs provide high degree of chemical and structural diversity. In comparison to conventional multistep synthesis, MCRs has attracted special attention to organic chemists owing to its cost-effectiveness, time-efficiency and ecofriendly nature. Coupling of microwave irradiation with multicomponent reactions has become increasingly significant for both industry and academia on small scale to synthesize the chemical libraries with high degree of structural diversity.[4] Moreover, pharmaceutical industry supports the use of water as a solvent, rather than toxic organic solvents for the synthesis of drug entity. As a result, much effort has been directed towards using water as a solvent for organic reactions in recent years.[5]

Isoxazoles are well established as privileged scaffolds which are commonly encountered in many biologically active molecules.[6] Derivatives of isoxazoles were found to exhibit a wide variety of biological activities such as histone deacetylase (HADC) probes (**A**) antidepressant-like activity (**B**), β-lactamase-resistant antibiotics, (**C**), powerful neurotoxin as a brain-lesioning agent (**D**) along with synthetic androgenic steroid Danazol (**E**) to suppresses the production of gonadotrophins (Figure 1).[7] Moreover, isoxazole derivatives are useful as primary precursors for the synthesis of different organic compounds.[8]

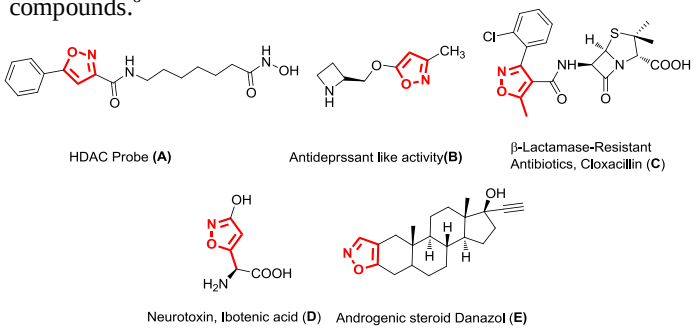

Figure 1. Biologicallly active isoxazole derivatives

Several synthetic methodologies are currently available for the synthesis of isoxazole skeleton. In 2005, Fokin *et al* synthesized the few isoxazole derivatives from N-hydroxyl imidoyl chlorides and alkynes using Cu(I) catalyst derived from $CuSO_4.5H_2O$ reduced by Na-ascorbate.[9] In particular the conventional approach towords the synthesis of isoxazole skeletons without metal catalyst can be summarized as the reaction of 2-alkyn-1-one *o*-methyl

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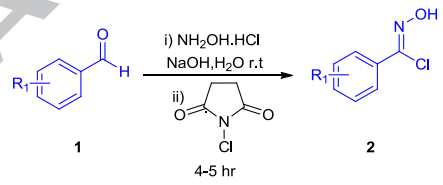
oximes with ICl, I_2, Br_2, reaction of N-hydroxyl-4-toluenesulfonamide with α,β-unsaturated carbonyl compounds, cycloaddition between alkynyliodides and nitrile oxide, dehydration of nitro alkanes with dipolarophiles in the presence DABCO, and cascade reaction of α-azido acrylates and aromatic oximes.[10] However, the homogeneous metal catalyzed synthesis of isoxazole derivatives involve the Pd catalyzed four-component coupling of a terminal alkyne, hydrazine (hydroxylamine), carbon monoxide and an aryl iodide, Pd catalysed Sonogashira coupling of acid chlorides with terminal alkynes, followed by 1,3-dipolar cycloaddition, $AuCl_3$-catalyzed cycloisomerization of α,β-acetylenic oximes, sequential Fe and Pd catalyzed four-step sequence from propargylic alcohols, and the reaction of terminal alkynes with n-BuLi, followed by aldehydes, I_2 and hydroxylamine.[11] In 2013, Huang group studied the facet dependent properties of Cu_2O nanocrystals for the regioselective synthesis of 3,5-disubstituted isoxazoles using EtOH as solvent for 2 h.[12] Recently Ramón *et al* have synthesized 3,5-disubstituted isoxazoles in deep eutectic solvents.[13] However, all these reactions suffered from drawbacks such as low yields, multistep synthetic sequence, harsh reaction conditions, use of expensive Pd or Au catalyst, use of toxic reagents, and difficult work up procedure. We therefore wished to develop a convenient, microwave assisted Cu(I) catalyzed telescopic method for the disubstituted isoxazoles in green medium. Compared to earlier methods, the major advantages associated with the present methodology for the synthesis of isoxazoles are the use of microwave irradiation, which reduces the reaction time to minutes for the faster delivery of compounds, water as green and ecofriendly solvent and excellent yields with high purity.

As part of our ongoing programme on the diversity oriented synthesis of bioactive heterocycles,[14] we report a novel Cu(I) catalyzed telescopic synthesis of 3,5-disubstituted isoxazoles from readily available aromatic aldehydes and substituted alkynes on water under microwave irradiation. The synthetic strategy commences with the synthesis of N-hydroxyl imidoyl chlorides from aromatic aldehydes, hydroxylamine hydrochloride and N-chloro succinimide followed by 1,3-dipolar cycloaddition of substituted alkynes to obtain the 3,5-disubstituted isoxazoles in one-pot manner.

2. Results and Discussion

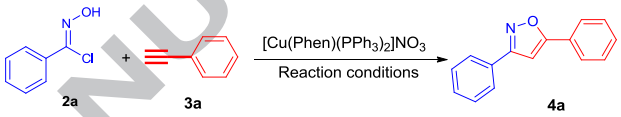
Our exploration starts with the synthesis of N-hydroxyl imidoyl chlorides **2** as the primary precursors. To obtain the substituted N-hydroxyl imidoyl chlorides **2**, we reacted various aromatic aldehydes **1** with hydroxylamine hydrochloride using NaOH as base and water as solvent followed by chlorination with N-chlorosuccinimide at room temperature for 4 h (Scheme 1).



Scheme 1. Synthesis of substituted N-hydroxyl imidoyl chlorides **2**

The model study for the Cu(I) catalyzed 1,3-dipolar cycloaddition was performed on N-hydroxy benzimidoyl chlorides **2a** with phenylacetylene **3a** under room temperature condition for 12 h using EtOH as solvent (Table 1, entry 1). The reaction using 2 mol% of the $[Cu(phen)(PPh_3)_2]NO_3$ as catalyst yielded the 3,5-diphenylisoxazole **4a** in 50% yield. Analysis of the reaction mixtures indicated the presence of starting materials. Increasing the reaction temperature to 65°C using EtOH as solvent for 6 h slightly increase the yield upto 60% (Table 1, entry 2). The yield of the 1,3-dipolar cycloaddition reaction gradually increased upto 70% when the reaction was performed using binary mixture of H_2O-tBuOH (1:1) as solvent (Table 1, entry 3). In order to obtain the 3,5-diphenylisoxazole **4a** in high yield, and under green synthetic condition, the same set of reaction was carried out in H_2O as solvent at 65 °C for 6 h to obtain the product **4a** (80%) yield (Table 1, entry 4). However, the same cycloaddition reaction carried out under neat conditions with slight excess of phenyl acetylene, the yield of the product **4a** (75%) was obtained (Table 1, entry 5). The reason behind the decreased yield was probably due to the decomposition of the reactants under the neat condition. However to enrich the synthetic efficiency, the same set of reaction was performed under microwave irradiation for 5 min using H_2O as solvent to obtain the desired product **4a** in 95% yield (Table 1, entry 6). The table 1 provides the complete optimization study for the 1,3-dipolar cycloaddtion reaction to obtain the 3,5-diphenylisoxazole **4a**.

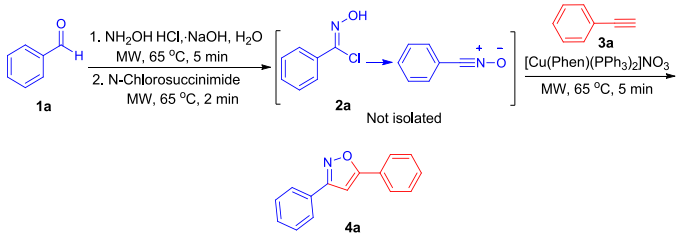
Table 1. Optimization of 1,3-dipolar cycloaddition reaction[a]



Entry	Solvent	Temperature	Time	Yield %[c]
1	EtOH	rt	12 h	50
2	EtOH	65 °C	6 h	60
3	EtOH-^{t}BuOH	65 °C	6 h	70
4	H_2O	65 °C	6 h	80
5	Neat	65 °C	3 h	75
6	H_2O	MW[b], 65 °C	5 min	95

[a]The reaction was performed using **2a** (1 mmol), **3a** (2 mmol), catalyst (2 mol%). [b]Microwave reactions were carried out in Microwave Model No. CATA R (Catalyst systems, Pune).[c] Yield of the isolated product.

In multicomponent reaction, sequential addition of reagent, one at a time without any post- synthetic work up is known as telescoped reaction approach.[15] Advantage of telescoped reaction approach involves the reduction of number of purification steps, use of toxic solvents, operational simplicity which boosts the reaction result. We performed our multicomponent reaction by a telescoped approach. Condensation of benzaldehyde **1a** with hydroxylamine hydrochloride under microwave heating in the presence of NaOH using H_2O as solvent at 65 °C for 5 min followed by subsequent addition of N-chloro succinimide for further 2 min heating at the same temperature yielded N-hydroxybenzimidoyl chloride **2a**.

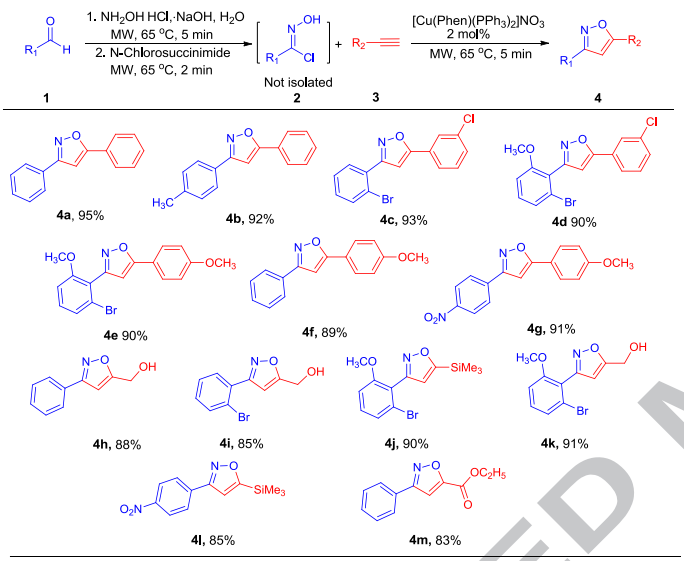


Scheme 2. Telescoped approach to 3,5-diphenylisoxazole **4a**

The *in-situ* generated N-hydroxybenzimidoyl chloride **2a** underwent 1,3-dipolar cycloaddition reaction with phenyl

acetylene **3a** using 2 mol % of $[Cu(phen)(PPh_3)_2]NO_3$ as catalyst under microwave heating for 5 min to obtain the 3,5-diphenylisoxazole **4a** in 95 % yield as depicted in (Scheme 2).[16] Upon completion of the reaction, the ^{1}H NMR spectrum of the synthesized compound indicated the formation of pure 3,5-disubstituted isoxazoles without forming any 3,4-disubstituted isoxazoles. The ^{1}H NMR spectrum of 3,5-disubstituted isoxazole contains a singlet at 6.88 which corresponds to the diagnostic chemical shift of the 4H proton as compared to the chemical shift of the 5H-isoxazole congener between 8 and 9 ppm. Encouraged with this observation, we further investigated this telescopic transformation with substituted aldehydes and alkynes. The results are summarized in (Table 2).

Table 2. One-pot telescoped synthesis of 3,5-disubstituted isoxazoles.[a,b]



[a]Reaction conditions: aldehydes (1 mmol), $NH_2OH.HCl$ (1 mmol), NaOH (1.5 mmol), NCS (1 mmol), alkyne (1 mmol), Cu(I) catalyst (2 mol%). [b]Isolated yield

The overall reaction time is typically 12-20 min. The corresponding highly regioselective 3,5-disubstituted isoxazoles were obtained with excellent yields after a simple work-up involving filtration of the catalyst, washing, and solvent evaporation. Finally the crude products were purified by column chromatography followed by spectroscopic characterization using ^{1}HNMR, ^{13}C NMR, and mass spectroscopy (MS). We have observed the substituent effects of both aldehydes and alkynes. Aromatic aldehydes containing electron-withdrawing groups reacted efficiently to obtain the corresponding isoxazoles in excellent yields as compared to the electron-donating substituents. The aromatic terminal alkynes containing electron-withdrawing groups or electron-donating substituents have no effect on the outcome of the reaction followed by hydroxy-, silyl-,and ester-substituted alkynes to obtain the corresponding isoxazoles as single regioisomers in good to high yields.

3. Conclusions

In summary, we have developed an efficient one-pot, telescoped approach for the synthesis of biologically interesting disubstituted isoxazoles. The synergistic effect of microwave irradiation and water as green solvent effectively accelerates the reaction to proceed in short reaction times with excellent yields. To the best of our knowledge, this procedure is the first example for the synthesis of 3,5-disubstituted isoxazoles via microwave assisted multicomponent coupling procedure in green media. Further studies on the Cu(I) catalyzed synthesis of bioactive heterocycles for biological applications are current pursuing in our laboratory.

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16. **General Procedure for the one-pot multistep synthesis of 3,5-diphenyl isoxazoles (4a).** In a round bottomed flask, a mixture of benzaldehyde **1a** (0.027 g, 0.25 mmol, 1.0 equiv) and NaOH (0.020 g, 0.50 mmol, 2.0 equiv) was added to a solution of hydroxylamine hydrochloride (0.0177 g, 0.25 mmol, 1.0 equiv) containing 5 mL of H_2O. The reaction mixture was irradiated under microwave heating at 210 watt for 5 min at 65 ºC. The progress of the reaction was monitored by TLC. After completion, N-chlorosuccinimide (0.034 g, 0.25 mmol, 1.0 equiv) was added in small proportions for over 2 min, followed by microwave irradiation at same power for 2 min. After completion, phenylacetylene **3a** (0.0255 g, 0.25 mmol, 1.0 equiv) and $[Cu(phen)(PPh_3)_2]NO_3$ catalysts (0.0042 g, 2 mol%) was immediately added to the reaction mixture. Subsequently, the reaction mixture was irradiated under microwave for 5 min. The reaction progress was monitored by TLC. After completion, the reaction mixture was cooled to room temperature and extracted with ethyl acetate (10 mL, twice). The combined organic layer was dried over anhydrous $MgSO_4$. The combined filtrate was subjected to evaporation to obtain the crude compound, which was purified over silica gel column (60–120 mesh) using 1% ethyl acetate in hexane as eluent to obtain the corresponding 3,5-diphenylisoxazoles **4a** as the product.

Supplementary Material

Experimental procedures, compound characterization data and copies of NMR spectra for all products are included in Supplementary data. Supplementary data associated with this article can be found in the online version.

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Highlights

- Microwave assisted one-pot telescopic synthesis of isoxazoles in green media
- Readily accessible starting materials and short reaction times.
- Using $[Cu(phen)(PPh_3)_2]NO_3$ as an efficient catalyst in green media.
- Broad substrate scope and good functional group tolerance