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Green and Efficient Synthesis of New Imidazoles Derivatives †

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Abstract: Imidazole, an organic compound with a five-membered ring structure composed of three carbon atoms and two nitrogen atoms at non-adjacent positions, is renowned for its basicity and nucleophilicity. These properties make imidazole a useful ligand in coordination chemistry and a participant in various organic reactions, including alkylation, acylation, and nucleophilic substitution. As a key building block in many biologically active molecules, imidazole is found in essential biomolecules such as histidine and histamine. Imidazoles represent the largest class of heterocyclic compounds. These versatile molecules are amphoteric, meaning they can react as both acids and bases. Imidazole derivatives, long recognized for their significance, have recently garnered significant interest due to their applications in diverse fields. These compounds exhibit a wide range of biological properties, including antitubercular, antifungal, antibacterial, antiviral, antioxidant, anticancer, and anti-inflammatory activities. The extensive biological significance of imidazole derivatives has driven organic chemists to develop numerous synthetic techniques to produce these compounds efficiently. In this context, we present an efficient and straightforward method for synthesizing a variety of tetra-substituted imidazoles under solvent-free conditions. This innovative approach not only simplifies the synthetic process but also aligns with green chemistry principles by minimizing the use of hazardous solvents and reducing environmental impact.

Keywords: N-heterocyclic; imidazole; solvent-free conditions

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1. Introduction

The term "multicomponent reactions" (MCRs) refers to synthetic methods that efficiently generate complex organic molecules by combining three or more reactants in a single reaction vessel to produce new compounds [1]. Multicomponent reactions (MCRs) have garnered significant attention from the scientific research community over time due to their high efficiency in organic transformations, excellent atom economy, eco-friendly processes, lower energy requirements, minimal by-product formation, and straightforward procedures. Additionally, MCRs are versatile tools for constructing biologically and pharmaceutically active heterocyclic structures [2].

Imidazole (1,3-diaza-2,4-cyclopentadiene) is an N-heterocyclic aromatic organic compound, first identified in 1840. Its molecular formula is C3H4N2, consisting of a five-membered nitrogen-containing ring with two nitrogen atoms in the aromatic system. The imidazole unit forms a fundamental and essential building block for various medicinal scaffolds [3]. Imidazole derivatives are widely utilized in numerous commercial drugs [4].

such as anti-high pressure drugs like Losartan and Eprosartan, and Omeprazole. There are four conventional methods for synthesizing polyfunctionalized imidazole derivatives: the Van Leusen synthesis, Wallach synthesis, Marckwald synthesis, and Debus-Radziszewski synthesis [5].

In this work, we present a simple, efficient, and environmentally friendly method for the synthesis of new 1,2,4,5-tetrasubstituted imidazoles (Figure 1) through a one-pot multicomponent catalyst-free and solvent free reaction of benzil, aromatic aldehydes, ethanolamine, and ammonium acetate, in good yields.

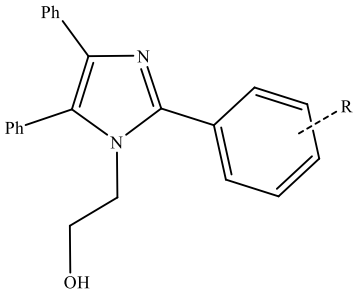
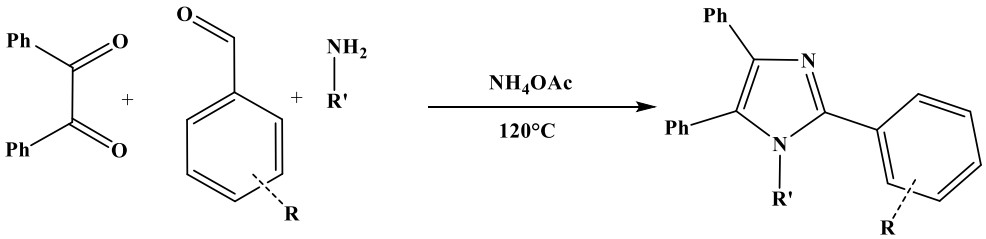


Figure 1. structure of 1,2,4,5 tetrasubtituted imidazoles.

2. Results and Discussion

In this work, an efficient new method for the synthesis of new 1,2,4,5-tetrasubstituted imidazoles derivatives has been presented. Related to our recent work on the synthesis of nitrogen heterocycles under solvent-free conditions, we report here a single reaction in stoichiometric quantities for the synthesis of 1,2,4,5-tetrasubstituted imidazoles derivatives. This method is a process in which four easily accessible components are combined in a single reaction to produce the desired product. Initially, a model reaction was conducted using Benzil, Ethanolamine, and Aromatic aldehyde in the presence of ammonium acetate at 120 °C for one hour under solvent-free conditions (Table 1). The product is confirmed by NMR, IR, and MS analyses.

Table 1. Optimization of conditions.



R	R′	Yield%
H	HO-(CH2)2-	54

In order to evaluate the generality of this model reaction, we were encouraged to extend this reaction to a variety of aromatic aldehyeds, so we have examined this reaction employing the optimized conditions. As a result, we found that using the temperature at 120 °C method gives good yields (Table 2).

Table 2. synthesis of new imidazoles derivatives.

R′	R	Yield
HO-(CH2)2-	H	54
	Cl	83
	F	67

HO-(CH2)2-	Me	59
	2,3-diOMe	71

3. Experimental Procedure

Here, we describe a simple and efficient synthesis of tetrasubstituted imidazoles derivatives under solvent-free conditions.

General procedure for the synthesis of 1,2,4,5-tetrasubstituted imidazoles derivatives: A mixture of Benzil (0.1 mol), Aromatic aldehydes derivatives (0.1 mol), Ethanolamine (0.1 mol) in the presence of ammonium acetate (0.4 mol) was stirred at 120 °C under solvent-free conditions. After cooling, the solid obtained was washed several times with diethyl ether to give tetrasubtituted imidazoles derivatives.

4. Conclusions

We have developed an efficient synthesis of new tetrasubstituted imidazoles derivatives with good yields via a reaction between Benzil, Aromatic aldehydes derivatives, Ethanolamine and ammonium acetate. The compounds structure is confirmed by spectral analysis. This approach includes some advantages such as mild reaction conditions and environmentally benign conditions. The simplicity of this synthetic route provides an attractive alternative to traditional methods.

Author Contributions:

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