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ORIGINAL ARTICLE

Potassium phthalimide as efficient basic organocatalyst for the synthesis of 3,4-disubstituted isoxazol-5(4*H*)-ones in aqueous medium

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Aryl aldehydes;
Three-component;
Water

Abstract Potassium phthalimide (PPI) is employed as an efficient and effective basic organocatalyst for the one-pot three-component reaction of β-oxoesters with hydroxylamine hydrochloride and various aromatic aldehydes. This cyclocondensation reaction was performed in water as an environmentally benign solvent at room temperature giving 3,4-disubstituted isoxazol-5(4*H*)-ones in good to excellent yields. PPI was found to be an effective organocatalyst for the synthesis of isoxazol-5(4*H*)-one system. The advantages of this method are efficiency, clean, easy work-up, high yields, shorter reaction times, inexpensive, and readily available catalyst.

1. Introduction

Since the first multicomponent process (MCP) was described by Strecker in 1850 [67] multicomponent processes (MCPs) have been demonstrated to be highly valuable tools for the expedient creation of the numerous chemical compounds including natural products and biologically active compounds [55,71,32,46,63]. Recently, considerable attention has been focused on MCPs owing to their high efficiency, mild conditions, simplistic completing, environmentally friendly, and minimizing time-consumption [4,33,34,61,20,6]. In addition to this, the other features of MCPs are the following: (i) simple procedures for the formation of final products in a one-pot process from at least three starting materials, (ii) green of bond-forming, (iii) atom and structural economy, (iv) minimization of waste produced, (v) easy construction of complex organic molecules, as well as (vi) avoiding complicated purification processes [72,73,16,17]. Carrying out MCPs in water as the reaction medium will be one of the most suitable methods, which will be a significant component of green chemistry [9,31,60,7,19].

On the other hand, isoxazol scaffold represents an important class of heterocycles which have a wide range of pharmacological properties. A variety of biological activities have been reported for isoxazol derivatives such as protein-tyrosine phosphatase 1B (PTP1B) inhibitory [21] anticonvulsant [3] antifungal [59] HDAC inhibitory [12] analgesic [22] antitumor [52] antioxidant [50,49] antimicrobial [54] COX-2 inhibitory

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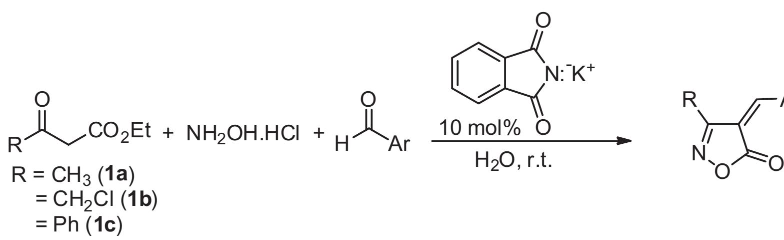
[69] nematicidal [65] antinociceptive [18] anti-inflammatory [23] anticancer [24] antiviral [35] antituberculosis [43] and antimycobacterial [10]. Furthermore, some of compounds containing the isoxazol ring in their structure were used for the treatment of leishmaniasis [68], as well as treatment of patients with active arthritis [30]. Due to the importance of isoxazol derivatives, recently, organic chemists are interested in the synthesis of such compounds [1,39,40,2,41,44,57]. Also, we synthesized arylmethylene-isoxazole-5(4*H*)-ones in water at room temperature in the presence of various catalysts [25–29].

Water is one of the best solvents due to its features such as being environmentally friendly, safe, non-toxic, non-flammable, clean, green, inexpensive, and readily available in organic transformations has received considerable attention. Also, use of water not only diminishes the risk of organic solvents, but also improves the rate of many chemical reactions [53,38,37,36,7,11]. Development of solid basic catalytic systems utilizing inexpensive, clean, environmentally benign, and commercially available catalysts has been a challenge in organic synthesis [70,13,47]. Potassium phthalimide (PPI) is a mild, green, inexpensive, commercially available, efficient basic recyclable catalyst, and a stable reagent. This reagent has been used in several reactions including synthesis of primary amines by the Gabriel method [58,64] the synthesis of phthalimide derivatives [66,8,45,51,62,42,74] and the preparation of cyanohydrin trimethylsilyl ethers [14,15]. Our literature survey revealed that there is no report on the use of PPI as a catalyst in the synthesis of isoxazol-5(4*H*)-one derivatives. Herein, we report the applicability of PPI as a readily available, efficient, and solid basic catalyst for the synthesis of a wide variety of isoxazol-5(4*H*)-one derivatives *via* the one-pot three-component process (Scheme 1).

2. Experimental

2.1. General

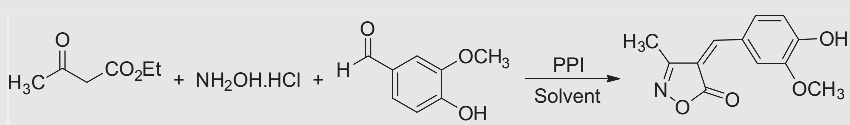
All chemicals, unless otherwise specified, were purchased from commercial sources and were used without further purification, with the exception of furan-2-carbaldehyde and benzaldehyde, which were distilled before using. 4-Hydroxy-3-nitrobenzaldehyde (**3m**) [5] and chromone-3-carbaldehyde (**3n**) [48] were synthesized according to the procedures reported in the literature.



1 **2** **3a-n** **4a-y**

Scheme 1 Synthesis of 3,4-disubstituted isoxazol-5(4*H*)-ones catalyzed by PPI.

Table 1 Solvent effect in the reaction of ethyl acetoacetate (**1a**) with hydroxylamine hydrochloride (**2**) and vanillin (**3d**).[a]



1a **2** **3d** **4d**

Entry	Solvent	PPI amount (mol%)	Time (min)	Yield (%)[b]
1	H_2O	5	80	89
2	H_2O	10	70	95
3	H_2O	15	70	96
4	H_2O	20	70	95
5	C_2H_5OH	10	120	55
6	Acetone	10	120	10
7	Hexane	10	120	21
8	H_2O/C_2H_5OH (1:1)	10	120	70
9	H_2O/acetone (1:1)	10	120	15
10	H_2O/dioxane (1:1)	10	120	10
11	1,4-Dioxane	10	120	Trace
12	Cyclohexane	10	120	Trace
13	Solvent-free	10	120	20

[a] Reaction conditions: ethyl acetoacetate (1 mmol), hydroxylamine hydrochloride (1 mmol), vanillin (1 mmol), water (4 mL), room temperature.
[b] Isolated yield of product.