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ORIGINAL PAPER

Phthalimide-*N*-oxyl salts: efficient organocatalysts for facile synthesis of (*Z*)-3-methyl-4-(arylmethylene)-isoxazole-5(4*H*)-one derivatives in water

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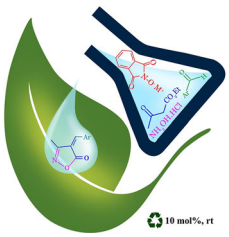
Abstract Green and simple protocols have been developed for the synthesis of (*Z*)-3-methyl-4-(arylmethylene)-isoxazole-5(4*H*)-one derivatives in the presence of tetrabutylammonium or potassium salts of phthalimide-*N*-oxyl, as transition metal-free catalysts, through the multicomponent reaction strategy in aqueous medium at ambient temperature. These procedures offer many advantages including clean reaction profiles, mild reaction conditions, short reaction times, high to quantitative yields, and straightforward work-up.

Graphical abstract



Keywords Phthalimide-*N*-oxyl salts · Organocatalysis · Multicomponent reactions (MCRs) · 3-Methyl-4-(arylmethylene)isoxazole-5(4*H*)-ones · In water synthesis · Green chemistry

Introduction

Multicomponent reactions (MCRs) have recently emerged as a powerful strategy for the synthesis of structurally diverse chemical libraries of drug like compounds since the products are formed in a single step as well as diversity can be achieved by simply varying each component [1–8]. However, sometimes MCRs may produce alternative products by altering one component and/or catalysts. In this context, competition between formation of (*Z*)-4-arylidene-3-methylisoxazole-5(4*H*)-one (**A**) and *N*-hydroxy derivative of Hantzsch 1,4-dihydropyridine (**B**) scaffolds is illustrative when hydroxylamine is used as nitrogen source (Fig. 1) [9].

Literature survey shows that Hantzsch pseudo-four-component reaction has been intensively investigated and reviewed for different nitrogen sources such as ammonia or amines [9–14]. However, less attention has been paid to the synthesis of alternative products containing 4-(arylmethylene)isoxazole-5(4*H*)-one scaffold in their structure. Furthermore, only aldehydes containing electron-donating substituents are involved in this alternative reaction path despite of pseudo-four-component Hantzsch reaction [15]. Isoxazole scaffold represents a class of heterocyclic compounds demonstrating pharmacological and biological activities such as anti-HIV [16], antifungal [17], analgesic [18], antitumor [19], COX-2 inhibitor [20], activator of the enzyme responsible for inflammation and pain, antiviral [21], antioxidant [22], antimicrobial [23], and androgen antagonists [24]. Furthermore, the isoxazole-5(4*H*)-one

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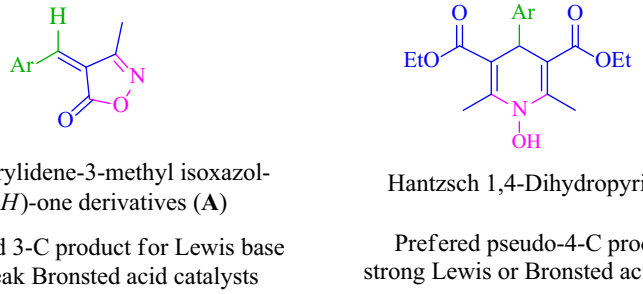


Fig. 1 Competition between formation of (*Z*)-4-arylidene-3-methylisoxazole-5(4*H*)-one (**A**) and *N*-hydroxy derivative of Hantzsch 1,4-dihydropyridine (**B**) scaffolds

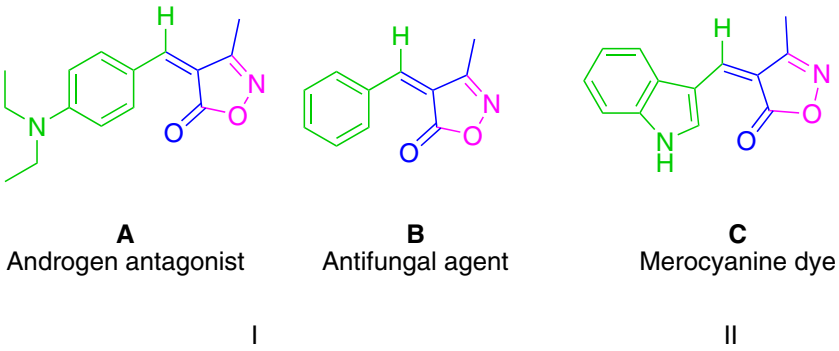


Fig. 2 Selected examples of isoxazole-5(4*H*)-one derivatives demonstrating pharmacological and biological activity (I) or as ingredient of merocyanine dyes (II)

scaffold can also be found as the central moiety of merocyanine dyes which are used in optical recording and nonlinear optical research [25] (Fig. 2).

Recent methodologies for the synthesis of isoxazole scaffold comprise the use of H_3BO_3 [15], sodium benzoate [26], $Na_2B_4O_7$ [27], Na_2S [28], sodium citrate [29], Na_2SiO_3 [30], sodium saccharin [31], and potassium phthalimide [32]. Furthermore, techniques such as visible light in the presence of NaOAc in aqueous EtOH [33], solid-state heating or solid-state grinding [34], ultrasonic irradiation in the presence of pyridine at ambient temperature [35], and microwave irradiation [36] have also been reported. However, most of reported methods for the synthesis of these compounds suffer from disadvantages including the use of toxic or odorous catalysts, tedious work-up procedures, troublesome waste discarding, long reaction times, and low yields. Thus, obviation of these limitations is necessary to develop more efficient and green synthesis of 3-methyl-4-(arylmethylene)isoxazole-5(4*H*)-one derivatives. To address these concerns, the use of water-soluble organocatalysts is very promising [37–40]. Recently, we have demonstrated the catalytic activity of phthalimide-*N*-oxyl (PINO) salts (**1**), as effective, easy to handle, and readily available Lewis bases, for the synthesis of 2-amino-4*H*-chromene derivatives in water [41] and cross-linked poly(urethane–isocyanurate) networks [42], cyanosilylation of carbonyl compounds [37, 43], cyclotrimerization of isocyanates [44, 45], and protection of alcohols and phenols with trimethylsilyl group [46]. In continuation of our interest to develop the catalytic scope of PINO salts, we decided to study a metal-free method for the synthesis of 3-methyl-4-

Scheme 1

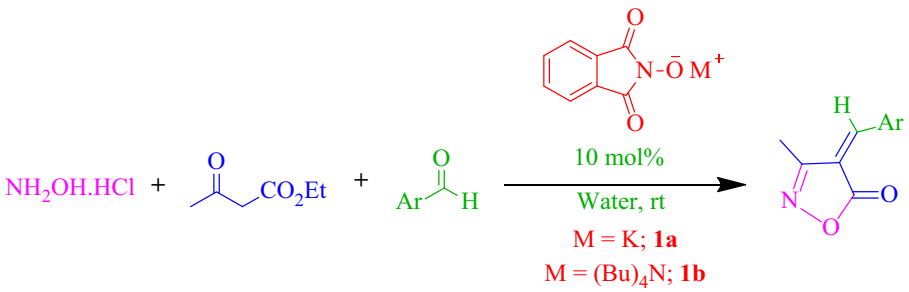
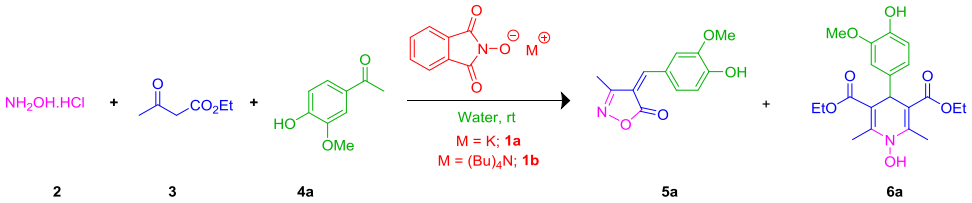


Table 1 Optimization of the three-component reaction of hydroxylamine hydrochloride (**2**), ethyl acetoacetate (**3**) and vanillin (**4a**) in the presence of phthalimide-*N*-oxyl salts **1a**, **1b** at ambient temperature



Entry	Catalyst	Catalyst loading/mol%	Solvent	Time/h	Yield[a]/%		TON[b]	TOF[c]/h^{-1}
					5a	**6a**		
1	–	–	H_2O	3.5	22	0	–	–
2	POPINO (**1a**)	15	H_2O	1	90	0	6	6
3	POPINO (**1a**)	10	H_2O	1	94	0	9.4	9.4
4	POPINO (**1a**)	7	H_2O	2	89	0	12.7	6.4
5	POPINO (**1a**)	10	EtOH	2	70	0	7	3.5
6	POPINO (**1a**)	10	EtOH/H_2O	2.5	72	0	7.2	2.9
7	POPINO (**1a**)	10	DMSO	2.5	80	0	8	3.2
8	POPINO (**1a**)	10	Cyclohexane	4	Trace	0	–	–
9	TBAPINO (**1b**)	15	H_2O	0.75	93	0	6.2	8.3
10	TBAPINO (**1b**)	10	H_2O	0.75	97	0	9.7	12.9
11	TBAPINO (**1b**)	7	H_2O	1.25	90	0	12.9	10.3
12	TBAPINO (**1b**)	10	EtOH	1.5	75	0	7.5	5
13	TBAPINO (**1b**)	10	EtOH/H_2O	2	82	0	8.2	4.1
14	TBAPINO (**1b**)	10	DMSO	2	90	0	9	4.5
15	TBAPINO (**1b**)	10	Cyclohexane	2.5	Trace	0	–	–

Reaction conditions: hydroxylamine hydrochloride (**2**, 1 mmol), ethyl acetoacetate (**3**, 1 mmol), vanillin (**4a**, 1 mmol), 2 cm^3 water and required amount of the catalysts

[a] The yields refer to the isolated product

[b] Turn over number

[c] Turn over frequency

(arylmethylene)isoxazole-5(4*H*)-ones in the presence of potassium phthalimide-*N*-oxyl (POPINO, **1a**) or tetrabutylammonium phthalimide-*N*-oxyl (TBAPINO, **1b**) in water at ambient temperature (Scheme 1).

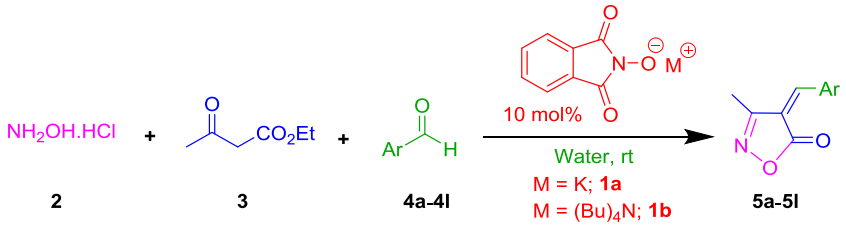
Results and discussion

To optimize reaction conditions, the effect of different loadings of POPINO (**1a**) or TBAPINO (**1b**) was studied for the reaction of hydroxylamine hydrochloride (**2**), ethyl acetoacetate (**3**), and vanillin (**4a**, Ar = 4-hydroxy-3-methoxyphenyl) (molar ratio: 1:1:1), as the model reaction, in water at ambient temperature. The results are summarized in Table 1.

It is noteworthy that a poor yield of the desired product of (*Z*)-4-(4-hydroxy-3-methoxybenzylidene)-3-methylisoxazole-5(4*H*)-one (**5a**) was obtained in water in the absence of any catalyst (entry 1). Interestingly, the yield of the adduct **5a** was significantly improved when catalytic amount of POPINO (**1a**) or TBAPINO (**1b**) was added to the reaction mixture (entries 2-4 and 9-11). TBAPINO (**1b**) required shorter reaction times to afford slightly higher yields of the desired product **5a** than POPINO (**1a**). This can be attributed to lower interaction of the bulky tetrabutylammonium cation in **1b** (entries 9–11) with the phthalimide-*N*-oxyl (PINO) anion which makes it more efficient for its catalytic activity compared to potassium cation in **1a** (entries 2–4). These findings are entirely consistent with our earlier research [37, 43–45]. The effect of other solvents or their mixture on the progress of the model reaction was further studied in the presence of 10 mol% loading of **1a** or **1b** (entries 5–8 and 12–15). According to the obtained results, water was found to be the solvent of choice in terms of the yield of product and required time for completion of the model reaction in comparison with other solvents.

After optimizing the reaction conditions, different derivatives of 3-methyl-4-(arylmethylene)isoxazole-5(4*H*)-

Table 2 Synthesis of (*Z*)-3-methyl-4-(arylmethylene)isoxazole-5(4*H*)-ones **5a–5l** catalyzed by POPINO (**1a**) or TBAPINO (**1b**) in water at ambient temperature



Entry	Aryl (**4**)	Product[a] (**5**)	Time/h		Yield[b]/%		TOF/h^{-1}	
			1a	**1b**	**1a**	**1b**	**1a**	**1b**
1	4-Hydroxy-3-methoxyphenyl (**4a**)	**5a**	1	0.75	94	97	9.4	12.9
2	2,4-Dimethoxyphenyl (**4b**)	**5b**	1.5	1.1	89	90	5.9	8.2
3	4-Methylphenyl (**4c**)	**5c**	1.5	1.5	94	97	6.3	6.5
4	4-Methoxyphenyl (**4d**)	**5d**	1.1	1	90	93	8.2	9.3
5	4-Hydroxyphenyl (**4e**)	**5e**	1.25	1.25	93	95	7.4	7.6
6	3-Hydroxyphenyl (**4f**)	**5f**	1.1	1	90	93	8.2	9.3
7	2-Hydroxyphenyl (**4g**)	**5g**	2	2	88	91	4.4	4.6
8	4-Dimethylaminophenyl (**4h**)	**5h**	1	0.75	93	96	9.3	12.8
9	Phenyl (**4i**)	**5i**	1.1	1	92	95	8.4	9.5
10	2-Thienyl (**4j**)	**5j**	1.25	1	89	94	7.1	9.4
11	2-Furanyl (**4k**)	**5k**	1.25	1	90	93	7.2	9.3
12	(*E*)-2-Phenylethenyl (**4l**)	**5l**	1.3	1.1	85	90	6.5	8.2
13	4-Chlorophenyl (**4m**)	**5m**	3	3	Trace	Trace	–	–
14	4-Nitrophenyl (**4n**)	**5n**	3	3	NR	NR	–	–
15	3-Nitrophenyl (**4o**)	**5o**	3	3	NR	NR	–	–
16	4-Cyanophenyl (**4p**)	**5p**	3	3	NR	NR	–	–

Reaction conditions: hydroxylamine hydrochloride (**2**, 1 mmol), ethyl acetoacetate (**3**, 1 mmol), aldehydes (**4**, 1 mmol), 2 cm^3 water, r.t., and POPINO (**1a**, 10 mol %) or TBAPINO (**1b**, 10 mol %)

NR no reaction

[a] All compounds are known and their structures were established from their spectral data and melting points as compared with literature values [12, 15, 26, 28]

[b] The yields refer to isolated products

ones (**5a–5l**) were prepared from the one-pot reaction of hydroxylamine hydrochloride (**2**), ethyl acetoacetate (**3**), and aryl or heterocyclic aldehydes (**4**) in the presence of 10 mol % catalyst (**1**) in water at ambient temperature. The results are shown in Table 2. It was found that aldehydes containing electron donating groups afford high to quantitative yields of desired products (entries 1–12), while aromatic aldehydes having the electron withdrawing groups fail to afford the desired products under the same reaction conditions (entries 13–16). Indeed, aldehydes containing electron withdrawing groups (**4m–4p**) react exclusively with hydroxylamine hydrochloride (**2**) rather than ethyl acetoacetate (**3**) for oxime formation. Therefore, only the corresponding oximes of the used aldehydes were isolated from the reaction mixture in the later cases. Furthermore, *ortho*-substituted aromatic aldehydes afforded the corresponding isoxazole-5(4*H*)-one derivatives in relatively longer times and lower yields probably due to the steric hindrance effect (entries 2, 7). On the other hand, π-excessive heterocyclic aldehydes such as 2-thiophenecarboxaldehyde (**4j**) and furfural (**4k**) or cinnamaldehyde (**4l**), which are susceptible for polymerization under acidic conditions, in treatment with hydroxylamine hydrochloride (**2**) and ethyl acetoacetate (**3**) afforded excellent yields of the corresponding products **5j–5l**, respectively (entries 10–12).

A comparison of the catalytic efficiency of POPINO (**1a**) and TBAPINO (**1b**) with the selected previously known catalysts for preparation of the product **5a** is shown in Table 3. Data in Table 3 clearly demonstrate that the present protocol is indeed superior to most of the others in terms of calculated TON and TOF values.

Table 3 Comparative synthesis of compound **5a** using the reported methods versus the present method

Entry	Catalyst	Mol%	Solvent	Temp.	Time/h	Yield/ %	TON	TOF/h^{-1}	References
1	Boric acid	10	H_2O	rt	1.42	95	9.5	6.7	[15]
2	Sodium benzoate	10	H_2O	rt	1.5	86	8.6	5.7	[26]
3	Sodium sulfide	5	EtOH	rt	1.5	89	8.9	5.9	[28]
4	Sodium tetraborate	10	H_2O	rt	1	95	9.5	9.5	[27]
5	Potassium phthalimide	10	H_2O	rt	1.17	95	9.5	8.1	[32]
6	Sodium saccharin	10	H_2O	rt	1	94	9.4	9.4	[31]
7	Sodium citrate	10	H_2O	rt	1.5	92	9.2	6.1	[29]
8	POPINO	10	H_2O	rt	1	94	9.4	9.4	This work
9	TBAPINO	10	H_2O	rt	0.75	97	9.7	12.9	This work

Conclusion

In summary, we have developed highly efficient, green, and one-pot three-component methods for the synthesis of (*Z*)-3-methyl-4-(arylmethylene)isoxazole-5(4*H*)-ones which are often encountered in biologically and pharmacologically actives compounds. The present procedures have been accomplished by the use of phthalimide-*N*-oxyl salts as metal-free, cost-effective, and mild organocatalysts. Further important advantages of these methods include in water synthesis, affording high to excellent yields, clean reaction profile, and simple work-up, and avoidance of using organic solvents in most cases.

Experimental

All commercially available chemicals were purchased from Merck and Aldrich, and used without further purifications, except for benzaldehyde, which was used as a fresh distilled sample. Analytical thin-layer chromatography (TLC) for monitoring reactions was performed using Merck 0.2 mm silica gel 60 F-254 Al-plates. Melting points were determined using an Electrothermal 9100 apparatus. Infrared (IR) spectra were acquired on a Shimadzu FT IR - 8400S spectrometer. ^{1}H NMR (500 MHz) spectra were obtained using a Bruker DRX-500 AVANCE spectrometer in DMSO-d_6 at ambient temperature. All yields refer to the isolated products.

General procedure for synthesis of isoxazole-5(4H)-ones ***5***

A mixture of hydroxylamine hydrochloride (**2**, 1 mmol), ethyl acetoacetate (**3**, 1 mmol), aromatic aldehyde (**4**, 1 mmol), and POPINO (**1a**) or TBAPINO (**1b**, 10 mol %) in 2 cm^3 of distilled water was stirred at room temperature for the time mentioned in Table 2. The reaction progress was monitored by TLC along with precipitating out of the products from the reaction mixture. After completion of the reaction (monitored by TLC), pure products were simply isolated by filtration of the reaction mixture and washing the solid with cold distilled water. The solid products were recrystallized from EtOH if necessary.

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