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DBUH-I_3: A next-generation organocatalyst for arylidene isoxazolone synthesis

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Abstract. A next-generation approach to arylidene isoxazolone synthesis is introduced using the versatile, sustainable 3,5,6,7,8,9-hexahydro-2H-imidazo[1,2-a]azepin-1-ium-iodine-iodide (DBUH-I_3) organocatalyst. This one-pot, three-component condensation of ethyl acetoacetate, substituted aryl aldehydes, and hydroxylamine hydrochloride under ethanol reflux yielded excellent results (up to 92%) across a diverse substrate range. DBUH-I_3 showed unparalleled catalytic efficiency and substrate versatility among screened amine–iodine–iodide complexes. The protocol offers operational simplicity, mild conditions, and rapid reaction rates, making it broadly applicable for the synthesis of isoxazolones. All products were structurally confirmed by FT-IR, ^{1}H NMR, and ^{13}C NMR spectroscopy. Importantly, DBUH-I_3 overcomes iodine's drawbacks, such as sublimation and moisture sensitivity, providing a stable, user-friendly alternative. Its compatibility with both electron-rich and electron-deficient substrates underscores its broad utility. This work establishes DBUH-I_3 as an eco-friendly, cost-effective catalyst that advances the synthesis of biologically relevant isoxazolone scaffolds and supports green chemistry applications..

***Keywords*:** DBUH-iodine-iodide complex; isoxazolones; multicomponent reaction.

1. Introduction

Isoxazolones are valuable five-membered heterocycles, common in natural and medicinal products [1]. They are key precursors for organic molecules and pharmaceuticals, showing anticancer [4], antitubercular [5], anti-inflammatory [6], antiviral [7], antiplatelet [8], anticonvulsant and anti-diabetic properties [9], tyrosine kinase inhibitor [10]. These properties make them important in human and veterinary medicine and useful in organic synthesis, attracting strong interest from synthetic organic chemists [11].

Traditionally, the synthesis of 3-methyl-4-arylmethylene-isoxazole-5-(*4H*)-one involves two steps [12, 13]. First, ethyl acetoacetate reacts with hydroxylamine hydrochloride to form an oxime. This then undergoes cyclization to yield 3-methyl-isoxazole-5-(4H)-one. In the second step, this intermediate undergoes a Knoevenagel condensation with an aryl aldehyde. The final compound is produced.

A recent one-pot, three-component synthesis of 3-methyl-4-arylmethylene-isoxazole-5-(4H)-one uses hydroxylamine hydrochloride (a salt form of hydroxylamine, commonly used as a nucleophile), ethyl acetoacetate (a beta-keto ester), and an aryl aldehyde (an aromatic compound with a formyl group) in a single vessel viz sodium silicate [12], boric acid [13], $FeCl_2$ [14], magnesium bromide [15], guanidine hydrochloride [16], pyridinium *p*-toluene sulfonate [17], sodium sulfide [18], tartaric acid [19], citric acid [20], imidazole [21], Dowex1-x8OH [22], sulfated polyborate [23], DES [24], sonochemical [25], ZnO@Fe_3O_4 core–shell nanocatalyst [26], Cu/TCH-pr@SBA-15 nano-composite [27], gluconic acid [28], tomato fruit extract [29], pyruvic acid [30], sodium benzoate [31], visible light in aqueous ethanol [32], amine-modified montmorillonite nanoclay [33], grinding [34], microwave irradiations [35], concentrated solar radiation [36], ZSM-5 [37]. In addition to this approach, another efficient method uses DBU (an organic base) to promote a 1,3-dipolar cycloaddition, which is a reaction type where a 1,3-dipole, like an aldoxime, reacts with an alkene or alkyne. This yields 2,5-disubstituted isoxazolones [38].

Figure 1 presents representative bioactive molecules containing the isoxazolone scaffold, highlighting its importance in medicinal chemistry.

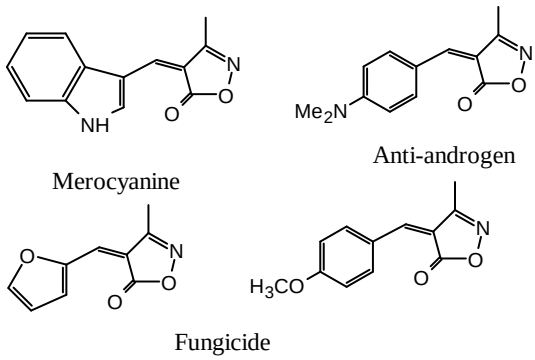

Figure 1. Representative structure of valuable isoxazolone-containing molecules.

Our current protocol is eco-friendly and sustainable, and it provides excellent substrate (reactive molecules) and functional group (specific groups of atoms in molecules) compatibility. Furthermore, the amine-

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iodine-iodide complex catalyst offers several advantages [39]. These include using an organocatalyst (an organic molecule as a catalyst) instead of a metal catalyst, simplified reaction steps, mild reaction conditions, lower costs, and easy, quick product isolation. Additionally, the catalyst overcomes molecular iodine's issues, such as sublimation and moisture sensitivity [40], by forming stable amineH-iodide complexes [41]. As a result, it provides the benefits of iodine catalysis with greater stability and easier handling.

In our previous studies, we prepared and confirmed several amineH-I_3 complexes [42] (morpholineH-I_3, DBUH-I_3, urotropineH-I_3, *N*-methyl piperazineH-I_3, and piperazineH-I_3) using a reported procedure with minor modifications, such as substituting potassium iodide for ammonium iodide [43, 44] (Figure 2). These iodine-bearing complexes serve as effective alternatives to molecular iodine, bypassing issues of sublimation and moisture sensitivity. Each complex contains quaternary nitrogen, molecular iodine, and iodide ion, key components for catalytic activity and iodination.

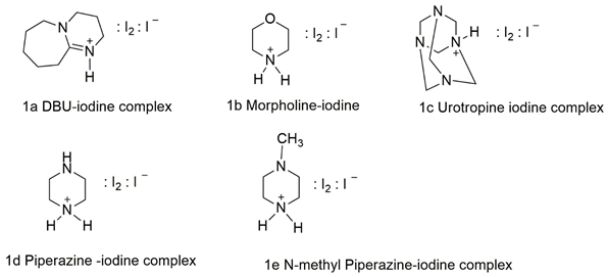
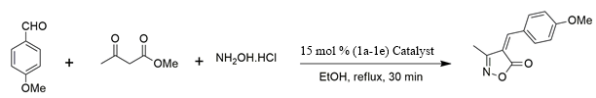


Figure 2. AmineH-I_3 Complex used as a catalyst for synthesis of arylidene isoxazolones

AmineH-I_3 complexes, formed from amines, ammonium iodide, and iodine (I_2), catalyze the synthesis of 3-methyl-4-arylmethylene-isoxazole-5-(*4H*)-one in ethanol (Scheme 1) through a one-pot, multi-step process. First, hydroxylamine reacts with ethyl acetoacetate to form an oxime intermediate. This oxime undergoes a Knoevenagel condensation with an aryl aldehyde, yielding the target isoxazolone. AmineH-I_3 catalyzes each stage efficiently, supporting green chemistry principles that reduce waste and use safer chemicals.



Scheme 1. Model reaction for screening of catalysts.

2. Experimental

2.1. Materials and reagents

Melting points were taken in open capillaries and are uncorrected. All reagents and solvents were purchased from commercial suppliers (substituted benzaldehydes from Sigma-Aldrich and Merck; ethyl acetoacetate, hydroxylamine hydrochloride, and solvents from Loba, SD FINE Chemicals) and used without further purification unless otherwise stated.

2.2. General procedure for synthesis of isoxazolone using the DBUH-I_3 catalyst

Hydroxylamine hydrochloride (1 mmol, 0.007 g), ethyl acetoacetate (1 mmol, 0.1300 g), and substituted benzaldehydes were used in equimolar amount (1 mmol each); the corresponding mass varied depending on the molecular weight of the particular aldehyde were dissolved in 10 mL of ethanol in a 25 mL round-bottom flask with a condenser. DBUH-I_3 catalyst (15 mol% 0.07798 g) was added. The mixture was refluxed for 30 minutes. Completion was monitored by the thin layer chromatography (TLC). The solvent was evaporated, and the reaction was stopped by adding excess 20% sodium thiosulfate (2 g in 8 mL water). The product was extracted with ethyl acetate, dried over sodium sulfate, and isolated as a solid. Most of the compounds were purified by recrystallization and compound 4l, 4m, 4s, 4t and 4q were purified by column chromatography. Yield was recorded.

Pure products were characterized by ^{1}H- and ^{13}C-NMR and physical constants, and the data were then compared with reported data for similar molecules. The NMR (^{1}H and ^{13}C) spectra were recorded on a Bruker 500 and 125 MHz spectrometer, using $CDCl_3$ or DMSO-d_6 as solvent,

3. Results and discussion

Firstly, we studied the catalytic effect in a multicomponent reaction involving 4-methoxy benzaldehyde, hydroxylamine hydrochloride, and ethyl acetoacetate, using this reaction as a model to optimize conditions.

We systematically compared various amineH-I_3 complex catalysts and found that DBUH-I_3 showed the highest catalytic efficiency for isoxazolone synthesis (*see* Table 1), with other catalysts yielding lower yields under identical conditions. We optimized the process across different temperatures and catalyst amounts. The superior activity of DBUH-I_3 likely results from its efficient proton release due to resonance stabilization of its conjugate base - a property not found in other amineH-I_3 complexes.

Table 1. Screening of catalyst in synthesis of 3-methyl-4-(4-methoxyaryl) methylene-isoxazole-5-(4H)-one

Entry	Catalyst	Time (min)	Yield* (%)
1	Without catalyst	30	Trace
2	Iodine	30	65
3	MorpholineH-I_3 complex	30	73
4	UrotropineH-I_3 complex	30	80
5	**DBUH-I_3 Complex**	**30**	**92**
6	PiperazineH-I_3 complex	30	71
7	*N*-Methyl piperazineH-I_3 complex	30	68

*Isolated yield after purification

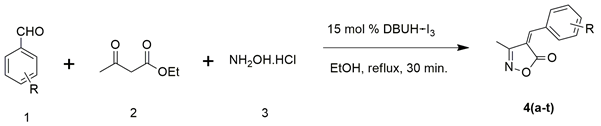
In this study, we explored the DBUH-I_3 catalyst in a three-component reaction to synthesize the 3-methyl-4-

arylmethylene-isoxazole-5-(*4H*)-one molecule (4a-t), as shown in Scheme 2. We used ethyl acetoacetate, hydroxylamine hydrochloride, and various substituted aryl aldehydes as substrates in the multicomponent reaction. DBUH-I_3 efficiently catalyzed the isoxazolone synthesis. DBUH-I_3-catalyzed reactions with aryl aldehydes bearing electron-donating groups, such as methoxy, hydroxy, and amino, were more efficient and produced higher yields (*see* Table 2, entries 4a, 4c, 4d, 4e, 4f, and 4i).

In contrast, aryl aldehydes bearing electron-withdrawing groups such as 3-methoxy, 3-hydroxy, and nitro also react, but they produce lower yields (*see* Table 2, entries 4b, 4g, 4o, and 4p). Aldehydes with methyl and halogen groups produce moderate yields (entries 4j, 4k, and 4l). Furthermore, o-substituted and heterocyclic aryl aldehydes perform poorly (entries 4h, 4m, 4q, 4s, and 4t).

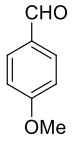
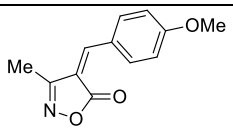
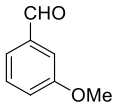
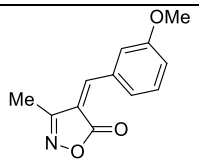
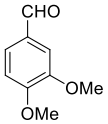
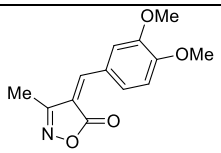
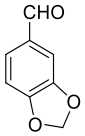
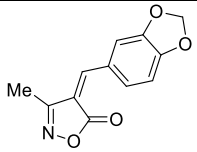
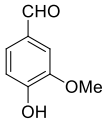
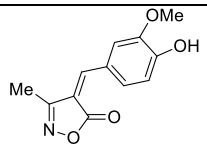
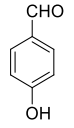
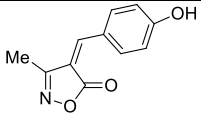
Aryl aldehydes with electron-donating mesomeric effects gave excellent yields. This is attributed to better stabilization of reactive intermediates under acidic conditions. Crude product 4d (Table 2, entry 4) was analyzed by NMR. All other products were purified by recrystallization or column chromatography. Most products were recrystallized in ethanol (4a, 4b, 4e, 4h, 4i, 4j, 4k, 4n, 4r). Some (4c, 4o, 4p) were recrystallized in ethyl acetate. A few (4f, 4q) used chloroform. Column chromatography with silica gel (60-120 mesh) and hexane:ethyl acetate purified certain compounds (4l, 4s, 4t). Chloroform was used as the mobile phase for others (4m, 4q).

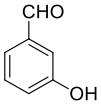
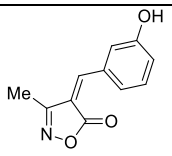
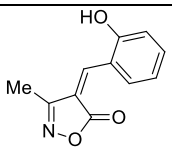
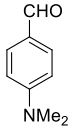
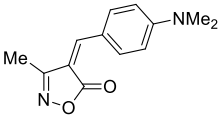
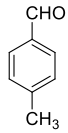
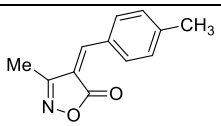
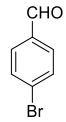
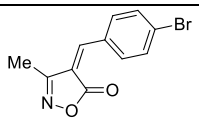
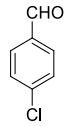
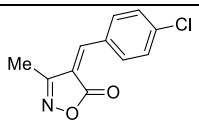
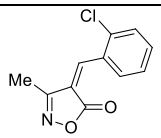
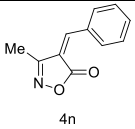
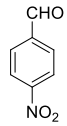
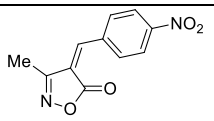
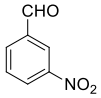
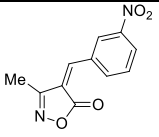
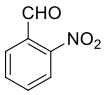
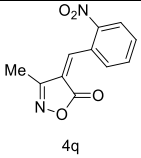
To further characterize the products, formation was confirmed by the ^{1}H NMR methyl signal (~2.25 δ), the olefinic hydrogen singlet, and the ^{13}C NMR signal. It should be noted that reported yields are post-purification, and physical constants were compared with known values.

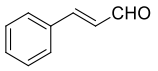
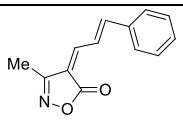
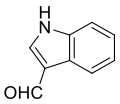
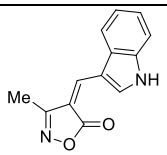
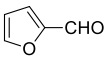
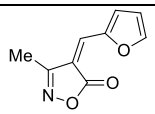


Scheme 2. Synthesis of 3-methyl-4-(4-methoxyaryl) methylene-isoxazole-5-(4H)-one

Table 2. Synthesis of 3-methyl-4-arylmethylene-isoxazole-5-(*4H*)-one

Entry	Arylaldehyde	Product (4)	Yield* (%)	Observed M.P.	Reported M.P.
1		 4a	92[b]	174-176 °C	176 °C [34]
2		 4b	80[b]	132-134 °C	134-136 °C [45]
3		 4c	90[c]	134-136 °C	135 °C [34]
4		 4d	90	203-205 °C	204 °C [34]
5		 4e	85[b]	214-216 °C	112 °C [34]
6		 4f	87[d]	202-204 °C	212-214 °C [32]

Entry	Arylaldehyde	Product (4)	Yield* (%)	Observed M.P.	Reported M.P.
7		 4g	83[d]	198-200 °C	201-203 °C [27]
8		 4h	79[b]	197-198 °C	198-200 °C [32]
9		 4i	91[b]	223-225 °C	218-220 °C [45]
10		 4j	71[b]	130-132 °C	131-132 °C [45]
11		 4k	75[b]	123-125 °C	123-125 °C [38]
12		 4l	73[e]	130-131 °C	135-136 °C [45]
13		 4m	62[f]	162-164 °C	163-165 °C [38]
14		 4n	82[b]	142-144 °C	140-144 °C [27]
15		 4o	65[c]	175-177 °C	177-179 °C [38]
16		 4p	72[c]	118-119 °C	117-119 °C [38]
17		 4q	40[f]	228-231 °C	226-227 °C [38]

Entry	Arylaldehyde	Product (4)	Yield* (%)	Observed M.P.	Reported M.P.
18		 4r	74[b]	178-180 °C	180-182 °C [30]
19		 4s	61[e]	242-244 °C	240 C [34]
20		 4t	56[e]	241-243 °C	242-243 °C [38]

* Isolated yield after purification; [b] Recrystallisation in ethanol; [c] Recrystallisation in ethyl acetate; [d] Recrystallisation in chloroform; [e] Column purified hexane:ethyl acetate; [f] Column purified chloroform.

Spectral analysis of arylidene isoxazolones

1. 4-(4-methoxybenzylidene)-3-methylisoxazol-5(4H)-one (Table 2, Entry 1, 4a): Yellow solid; ^{1}H NMR (500 MHz, $CDCl_3$) δ:8.44 (s, 1H), 7.26 (d, *J* = 9.2 Hz, 2H), 7.01 (d, *J* = 9.2, 2H), 3.92 (s, 3H), 2.28 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 168.78, 164.61, 161.29, 150.22, 149.34, 136.96, 133.86, 125.83, 116.35, 114.66, 55.72, 11.65.
2. 4-(3-methoxybenzylidene)-3-methylisoxazol-5(4H)-one (Table 2, Entry 2, 4b): Yellow solid; ^{1}H NMR (500 MHz, DMSO-d_6) δ: 8.21 (s, 1H), 7.97-7.99 (d, *J* = 2.3 HZ, 1H), 7.96 (dd, *J* = 6.5, 2.3 Hz, 1H), 7.60 (d, *J* = 6.5 Hz, 1H), 7.28 (s, 1H), 3.81 (s, 3H) 2.26 (s, 3H); ^{13}C NMR (125 MHz, DMSO-d_6) δ: 169.09, 163.12, 159.87, 151.96, 134.27, 130.37, 126.02, 121.32, 120.57, 117.86, 56.00, 11.85.
3. 4-(3,4dimethoxybenzylidene)-3-methylisoxazol-5(4H)-one (Table 2, Entry 3, 4c): Yellow solid; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 8.76 (s, 1H), 7.60 (d, *J* = 2.0 Hz, 1H), 7.26 (dd, *J* = 6.4, 2.0 Hz, 1H), 6.96 (d, *J* = 6.4 Hz, 1H), 4.01 (s, 3H), 3.99 (s, 3H), 2.29 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 169.00, 161.33, 154.57, 150.35, 149.79, 131.21, 126.36, 116.25, 115.07, 110.70, 56.17, 11.64.
4. 4-(2H-1,3-benzodioxol-5-yl)methylidene)-3-methylisoxazol-5(4H)-one (Table 2, Entry 4, 4d): Yellow solid; ^{1}H NMR: (500 MHz, $CDCl_3$) δ: 8.43 (s, 1H), 7.68 (d, *J* = 2.6 Hz, 1H), 7.26 (dd, *J* = 7.5, 2.6 Hz, 1H), 6.93 (d, *J* = 7.5 Hz, 1H), 5.94 (s, 2H), 2.27 (s, 3H);^{13}C NMR (125 MHz, $CDCl_3$) δ: 168.55, 161.17, 153.16, 149.32, 148.53, 132.89, 127.49, 116.86, 112.38, 108.77, 102.42, 11.64.
5. 4-(4-hydroxy-3-methoxybenzylidene)-3-methylisoxazol-5(4H)-one (Table 2, Entry 5, 4e): Yellow solid; ^{1}H NMR (500 MHz, DMSO-d_6) δ: 10.77 (s, 1H), 8.52 (s, 1H), 7.92 (d, *J* = 2.8 Hz, 1H), 7.80 (dd, *J* = 6.8, 2.8 Hz, 1H), 6.97 (d, *J* = 6.8 Hz, 1H), 3.85 (s, 3H), 2.25 (s, 3H); ^{13}C NMR (125 MHz, DMSO-d_6) δ: 169.46, 162.71, 154.30, 152.30, 147.94, 132.04, 125.52, 117.19, 116.28, 114.19, 56.01, 11.74.
6. 4-(4-hydroxybenzylidene)-3-methylisoxazol-5(4H)-one (Table 2, Entry 6, 4f): Yellow solid; ^{1}H NMR (500 MHz, DMSO-d_6) δ: 11.03 (s, 1H), 8.46 (s, 1H), 7.80 (d, *J* = 8.4 Hz, 2H), 6.94 (d, *J* = 8.4 Hz, 2H), 2.25 (s, 3H); ^{13}C NMR (125 MHz, DMSO-d_6) δ: 169.31, 164.34, 162.76, 152.03, 138.00, 128.39, 125.04, 116.64, 115.99, 114.33, 11.76.
7. 4-(3-hydroxybenzylidene)-3-methylisoxazol-5(4H)-one (Table 2, Entry 7, 4g): Yellow solid; ^{1}H NMR (500 MHz, DMSO-d_6) δ: 9.90 (s, 1H), 7.90 (s, 1H), 7.80 (s, 1H), 7.78 (m, 1H), 7.39 (m, 1H), 7.06 (m, 1H), 2.50 (s, 3H); ^{13}C NMR (125 MHz, DMSO-d_6) δ: 171.92, 162.72, 157.84, 152.47, 134.07, 130.30, 125.77, 121.84, 119.88, 118.98, 11.74.
8. 4-(2-hydroxybenzylidene)-3-methylisoxazol-5(4H)-one (Table 2, Entry 8, 4h): Yellow solid; ^{1}H NMR (500 MHz, DMSO-d_6) δ: 10.99 (s, 1H), 8.73 (s, 1H), 8.09 (m, 1H), 7.47-7.51 (m, 1H), 7.01 (m, 1H), 6.95 (m, 1H), 2.28 (s, 3H); ^{13}C NMR: (125 MHz, DMSO-d_6) δ: 168.74, 162.62, 160.07, 145.51, 137.21, 132.76, 120.04, 119.94, 117.38, 116.88, 11.63.
9. 4-(4-(dimethylamino)benzylidene)-3-methylisoxazol -5(4H)-one (Table 2, Entry 9, 4i): Red solid; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 8.41 (s, 1H), 7.22 (d, *J* = 8.5 Hz, 2H), 6.72 (d, *J* = 8.5 Hz, 2H), 3.15 (s, 6H), 2.24 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 170.11, 161.56, 154.22, 150.71, 149.23, 137.61, 135.49, 121.52, 111.50, 111.24, 40.10, 11.71.
10. 4-(4-methylbenzylidene)-3-methylisoxazol-5(4H)-one (Table 2, Entry 10, 4j): Yellow solid; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 8.29 (s, 1H), 7.39 (d, *J* = 8.2 Hz, 2H), 7.33 (d, *J* = 8.2 Hz, 2H), 2.45 (s, 3H), 2.29 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 168.21, 161.21, 150.66, 149.95, 145.73, 134.15, 131.03, 129.89, 129.64, 118.43, 22.07, 11.64.
11. 4-(4-bromobenzylidene)-3-methylisoxazol-5(4H)-one (Table 2, Entry 11, 4k): Brown solid; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.64 (s, 1H), 7.64 (d, *J* = 7.2 Hz, 2H), 7.26 (d, *J* = 7.4 Hz, 2H), 2.26 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 167.00, 159.12, 138.93, 138.37, 133.84, 130.23, 129.74, 128.48, 118.28, 117.11, 11.00.
12. 4-(4-chlorobenzylidene)-3-methylisoxazol-5(4H)-one (Table 2, Entry 12,4l): Orange solid; ^{1}H NMR

(500 MHz, $CDCl_3$) δ: 7.85 (s, 1H), 7.58 (d, *J* = 7.9 Hz, 2H), 7.38 (d, *J* = 7.9 Hz, 2H), 2.30 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 168.18, 160.92, 140.85, 140.21, 135.46, 131.00, 130.11, 129.54, 120.32, 118.91, 11.71.

13. 4-(2-chlorobenzylidene)-3-methylisoxazol-5(4H)-one (Table 2, Entry 13, 4m): Yellow solid; ^1H NMR: (500 MHz, $CDCl_3$) δ: 7.39 (s, 1H), 7.26 - 7.31 (m, 2H), 7.16 - 7.19 (m, 1H), 7.12 - 7.14 (m, 1H), 7.09 (m, 1H), 2.11 (s, 3H); ^{13}C NMR: (125 MHz, $CDCl_3$) δ: 171.57, 160.87, 134.35, 132.82, 130.78, 130.05, 128.68, 126.41, 127.34, 124.46, 12.14
14. 4-benzylidene-3-methylisoxazol-5(4H)-one (Table 2, Entry 14, 4n): brown solid; ^1H NMR (500 MHz, DMSO-d_6) δ: 8.35-8.37 (s, 1H) 7.58-7.61 (m, 2H), 7.43-7.57 (m, 2H), 7.26 (m, 1H), 2.25 (s, 3H); ^{13}C NMR (125 MHz, DMSO-d_6) δ: 167.86, 161.11, 149.92, 134.01, 133.80, 132.12, 130.45, 129.04, 128.79, 119.69, 11.64.
15. 4-(4-nitrobenzylidene)-3-methylisoxazol-5(4H)-one (Table 2, Entry 15, 4o): Yellow solid; ^1H NMR (500 MHz, $CDCl_3$) δ: 7.97 (s, 1H), 7.45 (d, *J* = 8.8 Hz, 2H), 7.12 (d, *J* = 8.8 Hz, 2H), 2.95 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 172.42, 163.54, 152.17, 143.00, 138.93, 133.67, 126.21, 123.85, 13.32.
16. 4-(3-nitrobenzylidene)-3-methylisoxazol-5(4H)-one (Table 2, Entry 16, 4p): Yellow solid; ^1H NMR (500 MHz, $CDCl_3$) δ: 8.43 - 8.45 (s, 1H), 8.23 - 8.25 (m, 1H), 7.90 - 8.00 (m, 1H) 7.58 - 7.61 (m, 1H), 7.31 (m, 1H), 2.20 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 170.96, 164.57,148.00, 133.14, 132.42, 130.23, 129.78, 126.39, 124.74, 121.89, 13.01.
17. 4-(2-nitrobenzylidene)-3-methylisoxazol-5(4H)-one (Table 2, Entry 17, 4q): Yellow solid; ^1H NMR: (500 MHz, $CDCl_3$) δ: 8.28-8.34 (s, 1H) 7.66 (m, 1H), 7.44 (m, 1H), 7.43 (m, 1H), 7.29 (m, 1H), 2.25 (s, 3H); ^{13}C NMR: (125 MHz, $CDCl_3$) δ: 171.16, 163.76, 149.40, 133.42, 132.66, 132.04, 131.78, 130.90, 128.64, 124.27, 12.51.
18. 3-methyl-4-(3-phenylallylidene)isoxazole-5(4H)-one (Table 2, Entry 17, 4r): Yellow solid; ^1H NMR: (500 MHz, $CDCl_3$) δ: 8.34 (s, 1H) 7.66 (m, 1H), 7.65 (m, 1H), 7.44 (m, 1H), 7.43 (m, 1H), 7.29 (m, 1H), 2.25 (s, 3H); ^{13}C NMR: (125 MHz, $CDCl_3$) δ:170.84, 168.97, 159.88, 151.57, 147.63, 134.95, 131.69, 129.31, 128.94, 122.39, 118.07, 117.86, 11.18.
19. 4-(1H-indol-3-yl)methylidene)-3-methylisoxazol-5(4H)-one (Table 2, Entry 19, 4s): Brown solid; ^1H NMR: (500 MHz, $CDCl_3$) δ: 12.79 (s, 1H), 9.51 (s, 1H), 8.20 (m, 1H), 8.16 (m, 1H) 7.60 (s, 1H), 7.32-7.34 (m, 2H), 2.34 (s, 3H); ^{13}C NMR: (125 MHz, $CDCl_3$) δ:170.87, 162.20, 140.94, 138.97, 136.83, 128.42, 124.44, 123.07, 119.30, 113.59, 113.13, 109.29, 11.66.
20. 4-(2-furylmethylene)-3-methylisoxazol-5(4H)-one (Table 2, Entry 20, 4t): Yellow solid ; ^1H NMR: (500 MHz, $CDCl_3$) δ: 8.61-8.68 (m, 1H), 8.12-8.15 (m, 1H), 7.83 (m, 1H), 7.31 (s, 1H), 2.33(s, 3H); ^{13}C NMR: (125 MHz, $CDCl_3$) δ: 169.86, 163.76, 160.34, 151.45, 138.86, 126.12, 116.58, 114.91, 11.62.

4. Conclusions

We developed an efficient, environmentally friendly method for the synthesis of 3-methyl-4-arylmethylene-isoxazole-5-(*4H*)-one derivatives via a one-pot, three-component reaction using the DBUH–I_3 organocatalyst. This catalyst operates under mild conditions and delivers the desired products in moderate to excellent yields, demonstrating strong tolerance to various functional groups. Our studies found that aryl aldehydes bearing electron-donating groups gave higher yields, likely because they stabilise key reaction intermediates. In contrast, electron-withdrawing groups reduce reactivity.

The DBUH–I_3 catalyst is a stable and effective alternative to molecular iodine. It lowers volatility and moisture sensitivity while keeping high catalytic activity. Using ethanol as a green solvent, along with the method's simplicity and easy product isolation, makes the process even more sustainable.

This method offers a practical, scalable approach to producing isoxazolone derivatives. It also highlights the potential of amine–iodine–iodide complexes in green organocatalysis and multicomponent reactions.

Conflict of interest

Authors declare no conflict of interest.

References

[1]. J. Zhu, J. Mo, H.Z. Lin, Y. Chen, H. Sun, The recent progress of isoxazole in medicinal chemistry, Bioorganic and Medicinal Chemistry 26 (2018) 3065-3075. https://doi.org/10.1016/j.bmc.2018.05.013

[2]. C. Lamberth, Oxazole and isoxazole chemistry in crop protection, Journal of Heterocyclic Chemistry 55 (2018) 2035-2045. https://doi.org/10.1002/jhet.3252

[3]. G. Abbiati, E.M. Beccalli, G. Broggini, C.A. Zoni, Valuable heterocyclic ring transformation: from isoxazolin-5(*2H*)-ones to quinolines, Tetrahedron 59 (2023) 9887-9883. https://doi.org/10.1016/j.tet.2003.10.053

[4]. J.P. Yong, C.Z. Lu, X. Wu, Potential anticancer agents. I. Synthesis of isoxazole moiety containing quinazoline derivatives and preliminarily in vitro anticancer activity, Anti-Cancer Agents in Medicinal Chemistry 15 (2015) 131-136. https://doi.org/10.2174/1871520614666140812105445

[5]. K. Hajlaoui, A. Guesmi, N.B. Hamadi, M. Msaddek, Synthesis of carbohydrate-substituted isoxazoles and evaluation of their antitubercular activity, Heterocyclic Communications 23 (2017) 225-229. https://doi.org/10.1515/hc-2016-0185

[6]. T. Karabasahagouda, A.V. Adhikari, M. Girisha, Synthesis of some new pyrazolines and isoxazoles carrying 4-methylthiophenyl moiety as potential analgesic and anti-inflammatory agents, Indian Journal of Chemistry 48B (2009) 430-437.

[7]. Y.S. Lee, S.M. Park, B.H. Kim, Synthesis of 5-isoxazol-5-yl-2′-deoxyuridines exhibiting antiviral

activity against HSV and several RNA viruses, Bioorganic Medicinal Chemistry Letter 19 (2009) 1126-1128. https://doi.org/10.1016/j.bmcl.2008.12.103

[8]. M. Gutiérrez, J. Amigo, E. Fuentes, I. Palomo, L. Astudillo, Synthetic isoxazole as antiplatelet agent, Platelets 25 (2014) 234-238. https://doi.org/10.3109/09537104.2013.807335

[9]. A. Sysak, B. Obmińska-Mrukowicz, Isoxazole ring as a useful scaffold in a search for new therapeutic agents, European Journal Medicinal Chemistry 137 (2017) 292-309. https://doi.org/10.1016/j.ejmech.2017.06.002

[10]. D. Villemin, B. Garrigues, Potassium fluoride on alumina: Dry condensation of 3-phenylisoxazol-5-one with aldehydes under microwave irradiation, Synthetic Communications 23 (1993) 2251-2257. https://doi.org/10.1080/00397919308013781

[11]. M. Cocivera, A. Effio, H.E. Chen, S. Vaish, Reaction of hydroxylamine with ethyl acetoacetate. Details of the addition and cyclization steps studied by flow nuclear magnetic resonance, Journal of the American Chemical Society 98 (1976) 7362-7366. https://doi.org/10.1021/ja00439a042

[12]. Q. Liu, R.T. Wu, Facile synthesis of 3-methyl-4-arylmethylene-isoxazol-5(4H)-ones catalysed by sodium silicate in an aqueous medium, Journal of Chemical Research 35 (2011) 598-599. https://doi.org/10.3184/174751911X13176501108975

[13]. H. Kiyani, F. Ghorbani, Boric acid-catalyzed multi-component reaction for efficient synthesis of 4*H*-isoxazol-5-ones in aqueous medium, Research on Chemical Intermediates 41 (2015) 2653-2664. https://doi.org/10.1007/s11164-013-1411-x

[14]. A. Abdukader, R. Wang, M. Mamat, C. Liu, $FeCl_2$-catalyzed intramolecular aerobic reaction for construction of isoxazoles heterocycle, Chinese Journal of Organic Chemistry 40 (2020) 1697-1703. https://doi.org/10.6023/cjoc201912041

[15]. Y.S. Walunj, P.C. Mhaske, P.S. Kulkarni, Magnesium bromide an efficient catalysis for synthesis of 3,4-disubstituted isoxazole-5(*4H*)-ones, Heterocyclic Letters 10 (2020) 259-266.

[16]. A.B. Barkule, Y.U. Gadkari, V.N. Telvekar, One-pot multicomponent synthesis of 3-methyl-4-(hetero)arylmethylene isoxazole-5(*4H*)-ones using guanidine hydrochloride as the catalyst under aqueous conditions, Polycyclic Aromatic Compounds 42 (2022) 5870-5881. https://doi.org/10.1080/10406638.2021.1959353

[17]. R. Laroum, A. Debache, New eco-friendly procedure for the synthesis of 4-arylmethylene-isoxazol-5(4*H*)-ones catalyzed by pyridinium *p*-toluenesulfonate in aqueous medium, Synthetic Communications 48 (2018) 1876-1882. https://doi.org/10.1080/00397911.2018.1473440

[18]. Q. Liu, X. Hou, One-pot three-component synthesis of 3-methyl-4-arylmethylene-isoxazol-5(*4H*)-ones catalyzed by sodium sulfide, Phosphorus, Sulfur, and Silicon and Related Elements 187 (2012) 448-453. https://doi.org/10.1080/10426507.2011.621003

[19]. A.U. Khandebharad, S. Swapnil, C.H. Gill, A. Brijmohan, Synthesis of 3-methyl-4-arylmethylene-isoxazol-5(*4H*)-ones catalyzed by tartaric acid in aqueous media, Research Journal of Chemical Science 5 (2015) 27-32.

[20]. A.B. Rikani, D. Setamdideh, One-pot and three-component synthesis of isoxazol-5(*4H*)-one derivatives in the presence of citric acid, Oriental Journal of Chemistry 32 (2016) 1433-1437. https://dx.doi.org/10.13005/ojc/320317

[21]. J. Safari, M. Ahmadzadeh, Z. Zarnegar, Ultrasound-assisted method for the synthesis of 3-methyl-4-arylmethylene isoxazole-5(*4H*)-ones catalyzed by imidazole in aqueous media, Organic Chemistry Research 2 (2016) 134-139.

[22]. S. Davood, One-pot green synthesis of isoxazol-5(*4H*)-one derivatives by Dowex1-x8OH in water, Journal of the Serbian Chemical Society 81 (2016) 971-978. https://doi.org/10.2298/JSC160202050S

[23]. M.S. Patil, C. Mudaliar, G.U. Chaturbhuj, Sulfated polyborate catalyzed expeditious and efficient three-component synthesis of 3-methyl-4-(hetero)arylmethylene isoxazole-5(*4H*)-ones, Tetrahedron Letters 58 (2017) 3256-3261. https://doi.org/10.1016/j.tetlet.2017.07.019

[24]. A. Ahad, M. Farooqui, Choline chloride and urea based deep eutectic solvent promoted synthesis of arylmethylidene-isoxazol-5(*4H*)-ones, International Journal of ChemTech Research 10 (2017) 269-273.

[25]. M. Ahmadzadeh, Z. Zarnegar, J. Safari, Sonochemical synthesis of methyl-4-(hetero)arylmethylene isoxazole-5(4*H*)-ones using Sn^{II}-montmorillonite, Green Chemistry Letters and Reviews 11 (2018) 78-85.

[26]. M. Shanshak, S. Budagumpi, J.G. Małecki, Green synthesis of 3,4-disubstituted isoxazol-5(4*H*)-ones using $ZnO@Fe_3O_4$ core–shell nanocatalyst in water, Applied Organometallic Chemistry 34 (2020) e5544. https://doi.org/10.1002/aoc.5544

[27]. M. Kalhor, S.M. Sajjadi, A. Dadras, Cu/TCH-pr@SBA-15 nano-composite: a new organometallic catalyst for facile three-component synthesis of 4-arylidene-isoxazolidinones, RSC Advances 10 (2020) 27439-27446. https://doi.org/10.1039/D0RA01314E

[28]. R.S. Ghogare, G.V. Shitre, A.R. Patel, Green synthesis of 3,4-disubstituted isoxazol-5(*4H*)-one using gluconic acid aqueous solution as an efficient recyclable medium, Organic Communications 16 (2023) 87-96. https://doi.org/10.25135/acg.oc.151.2304.2762

[29]. B.B. Popatkar, A.A. Mane, G.A. Meshram, Tomato fruit extract: an environmentally benign catalytic medium for the synthesis of isoxazoles derivatives, Indian Journal of Chemistry 60B (2021) 1362-1367.

[30]. S.R. Deshmukh, A.S. Nalkar, S.R. Thopate, Pyruvic acid-catalyzed one-pot three-component green synthesis of isoxazoles in aqueous medium: a comparable study of conventional heating versus

ultra-sonication, Journal of Chemical Sciences 134 (2022) 15. https://doi.org/10.1007/s12039-021-02016-y

[31]. Q. Liu, Y.N. Zhang, One-pot synthesis of 3-methyl-4-arylmethylene-isoxazol-5 (*4H*)-ones catalyzed by sodium benzoate in aqueous media: a green chemistry strategy, Bulletin of the Korean Chemical Society 32 (2011) 3559-3560. https://doi.org/10.5012/bkcs.2011.32.10.3559

[32]. F. Saikh, J. Das, S. Ghosh, Synthesis of 3-methyl-4-arylmethylene isoxazole-5(4*H*)-ones by visible light in aqueous ethanol, Tetrahedron Letters 54 (2013) 4679-4682. https://doi.org/10.1016/j.tetlet.2013.06.086

[33]. J. Safari, M. Ahmadzadeh, Z. Zarnegar, Sonochemical synthesis of 3-methyl-4-arylmethylene isoxazole-5(*4H*)-ones by amine-modified montmorillonite nanoclay, Catalysis Communications 86 (2016) 91-95. https://doi.org/10.1016/j.tetlet.2013.06.086

[34]. X.M. Hu, H. Dong, Y.D. Li, P. Huang, Z. Tian, P.A. Wang, Tandem grinding reactions involving aldol condensation and Michael addition in sequence for synthesis of 3,4,5-trisubstituted isoxazoles, RSC Advances 9 (2019) 27883 -27887. https://doi.org/10.1039/C9RA04864B

[35]. P. Kulkarni, An efficient solvent-free synthesis of 3,4-disubstituted isoxazole-*5(4H)*-ones using microwave irradiation, Journal of Indian Chemical Society 98 (2021) 100013. https://doi.org/10.1016/j.jics.2021.100013

[36]. Y.U. Gadkari, N.L. Jadhav, N.T. Hatvate, V.N. Telvekar, Concentrated solar radiation aided green approach for preparative scale and solvent-free synthesis of 3-methyl-4-(hetero)arylmethylene isoxazole-5(*4H*)-ones, ChemistrySelect 5 (2020) 12320-12323. https://doi.org/10.1002/slct.202003348

[37]. N.T. Hatvate, S.M. Ghodse, One-pot three-component synthesis of isoxazole using ZSM-5 as a heterogeneous catalyst, Synthetic Communications 50 (2020) 3676-3683. https://doi.org/10.1080/00397911.2020.1815786

[38]. S. Mohammed, R.A. Vishwakarma, S.B. Bharate, Metal-free DBU promoted regioselective synthesis of isoxazoles and isoxazolines, RSC Advances 5 (2015) 3470-3473. https://doi.org/10.1039/C4RA14694H

[39]. J.J. Koenig, M. Breugst, Halogen bonding in solution: Catalysis by molecular iodine, p. 232. Stefan Huber Ed., 1st ed., Wiley Online Library (2021).

[40]. R. Gawade, P.S. Kulkarni, DBUH+I3 complex an efficient catalyst for the synthesis of 2-phenyl benzimidazole and benzothiazole derivatives, Journal of the Serbian Chemical Society 88 (2023) 959-974. https://doi.org/10.2298/JSC220526007G

[41]. R. Gawade, P. Jadhav, S. Shinde, P. Kulkarni, DBUH-I_3 complex catalysed synthesis of arylidene derivatives of pyrazole, Heterocyclic Letters 12 (2022) 767-778.

[42]. R. Gawade, R. Varala, P. Kulkarni, DBUHI3-catalyzed efficient synthesis 2,4,5-triaryl substituted imidazoles, Current Chemistry Letters 14 (2025) 843-850. https://doi.org/10.5267/j.ccl.2025.7.004

[43]. L.C.R. M. da Frota, R.C.P. Canavez, S.L. da Silva Gomes, P.R.R. Costa, A.J.M. da Silva, Iodination of phenols in water using easy to handle amine-iodine complexes, Journal of the Brazilian Chemical Society 20 (2009) 1916-1920. https://doi.org/10.1590/S0103-50532009001000021

[44]. M.S. Refat, H. Didamony, K.M.A. El-Nour, L. El-Zayat, Synthesis and spectroscopic characterization on the tri-iodide charge transfer complex resulted from the interaction between morpholine as donor and iodine σ-acceptor, Journal of Saudi Chemical Society 14 (2010) 323-330. https://doi.org/10.1016/j.jscs.2010.04.004

[45]. Z. Faramarzi, H. Kiyani, Organocatalyzed three-component synthesis of isoxazol-5(4H)-ones under aqueous conditions, Heterocycles 102 (2021) 1779-1790. https://doi.org/10.3987/COM-21-14488

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