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ARTICLE

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Synthesis of 4*H*-chromene-isoxazole hybrids via *ortho*-hydroxy directing cyclization of isoxazole-styrenes and Michael addition of imino-chromenes in aqueous medium

Sakkani Nagaraju | **Kota Sathish** | **Dhurke Kashinath**

Department of Chemistry, National Institute of Technology, Warangal, India

Correspondence
Dhurke Kashinath, Department of Chemistry, National Institute of Technology, Warangal 506 004, India.
Email: kashinath@nitw.ac.in; kashinath.dhurke@gmail.com

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Abstract

A green, efficient, and one-pot method synthesis of functionalized 4*H*-chromene-isoxazole hybrids is reported via *o*-hydroxy group directing cyclization of isoxazole-styrenes and Michael addition of 3,5-dimethyl-4-nitroisoxazole on 2-imino-2*H*-chromene-3-carbonitrile (independent methods). The developed methodology was further extended for nitromethane, malononitrile, and alkylcyanoacetates as Michael donors.

1 | INTRODUCTION

The isoxazole is an important heterocyclic compound seen in many natural, and synthetic drugs such as AMPA, Ibotenic acid [1], cloxacillin (antibiotic), isoxicam (NSAID), leflunomide (immunosuppressive agent), muscimol (GABA agonist), and COX-2 inhibitors. The synthetic derivatives of isoxazoles are known to show insecticidal, antibacterial, antibiotic, antitumor, antifungal, anti-tubercular, ulcerogenic properties and used as inhibitors of heat shock protein 90 activity (Hsp 90), initiators of neurogenesis [1,2].

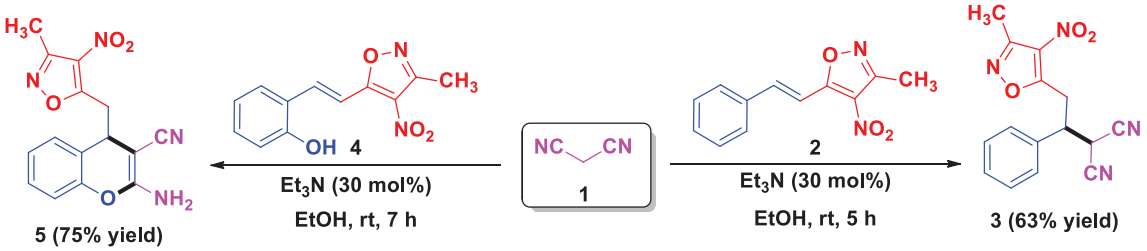
Chromene scaffold found in tocopherols, flavonoids, anthocyanins, medicinally important compounds and considered as privileged structures [3]. 2-Amino-3-nitrile-4*H*-chromenes known as anticancer agents (tubulin-binding), antagonists for anti-apoptotic Bcl-2 proteins, apoptosis-inducing agents, and antagonists for excitatory amino acid transporter subtype-1. In addition to these, 4*H*-chromenes are part of marketed drugs used for asthma, hypertension, ischemia, urinary incontinence, and used in pigments, cosmetic, and agrochemical industries [4]. Coumarins are isomeric structures of chromenes present in wide range of biologically active molecules. The substituted coumarins at position 4 are used as drugs for tuberculosis, HIV, pesticides, perfumes, and cosmetics. Especially, the coumarin-4-carboxymethyl compound and its derivatives are used as dye-sensitized solar cells, in fluorogenic assay for the detection of β-D-glucosidase, fluorescent probes, and organogelators [5]. The preparation of 2-amino-3-cyano-4*H*-chromenes using salicylaldehydes is known method through multicomponent reactions which are economic, time-saving with simple operation and separation techniques. Due to this, one-pot reactions got attention in academic and industrial research [6a], [6b]. 2-Amino-3-cyano-4*H*-chromenes can also be prepared from aromatic unsaturated compounds using multicomponent approach [6c–h].

3-Methyl-4-nitro-5-styrylisoxazole is known as a masked ester for the generation of carboxylic acid [7a]. Also, the methyl group present at position 3 has been used in Knoevenagel, Aldol, Michael, and cycloaddition reactions [7]. However, the formation of two new bonds with Michael addition followed by a neighboring group directed cycloaddition/Pinner type reaction is not yet explored in the literature. Also, there are no reports of C—C, C—O bond formation followed by annulation and isomerization (Pinner type reaction) in an intramolecular fashion. Owing to the biological importance of isoxazoles, 4*H*-chromenes [4], coumarins [5], and in continuation of our efforts in developing new synthetic methods under

green conditions ("on-water" concept) [8], [9], herein, we report the synthesis of functionalized isoxazole-chromene/coumarin hybrids using *o*-hydroxy directing cyclization and Michael addition reactions as a key step.

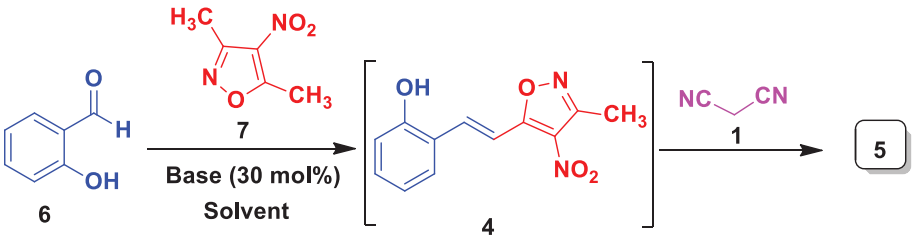
2 | RESULTS AND DISCUSSION

Towards the synthesis 4*H*-chromene-isoxazole hybrids, isoxazole-styrene (**2**) was reacted with malononitrile (**1**) in the presence of Et_3N (30 mol%) in ethanol to give 1,6-Michael adduct (**3**) with 63% yield (Scheme 1). Similarly, a reaction was attempted using 2-hydroxy-isoxazole-styrene (**4**) with malononitrile (**1**) in the presence of Et_3N (30 mol%) to give 4*H*-chromene-isoxazole hybrid (**5**) with 75% yield (Scheme 1). These observations prompted us to explore the role of —OH group at *ortho* position to unsaturated bond and isoxazole for the cyclization under similar conditions. Therefore, it was decided to adopt a one-pot approach for the synthesis of the 4*H*-



SCHEME 1 1,6-Michael addition reaction of malononitrile (**1**) and isoxazole styrenes (**2** and **4**)

TABLE 1 Optimization of the conditions for synthesis of product **5** in one pot method



S. No.	Solvent (2 mL)	Catalyst (30 mol%)	Reaction time (h)	Yield (%)[a]
1	CH_3CN	DABCO	24	Trace
2	DMF	DABCO	24	Trace
3	DMSO	DABCO	24	Trace
4	MeOH	DABCO	24	10
5	EtOH	DABCO	24	25
6	CH_3CN	DBU	24	Trace
7	MeOH	DBU	24	30
8	EtOH	DBU	24	67
9	Water	DBU	24	70
10	MeOH	TEA	24	25
11	EtOH	TEA	24	45
12	Water	TEA	24	50
13	CH_3CN	Piperidine	24	30
14	MeOH	Piperidine	06	70
15	**EtOH**	**Piperidine**	**02**	**93**
16	**Water**	**Piperidine**	**02**	**95**

Note: All of the reactions were performed with 1 mmol scale at 65°C.

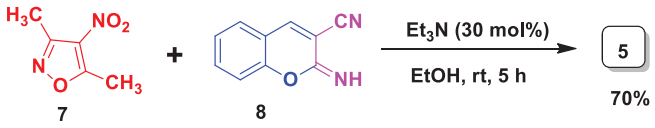
[a]Isolated yields. Bold values indicates the best results.

chromene-isoxazole hybrids. Thus, the styrene (**4**) was generated in situ by the reaction of salicylaldehyde (**6**) and 3,5-dimethyl-4-nitroisoxazole (**7**) and treated with malononitrile (**1**) to give the cyclized product (**5**) with 45% yield (Table 1; Entry-11).

With the aim of improving yields, experiments were performed in the presence of different bases [1,4-diazabicyclo[2.2.2]octane (DABCO), 1,8-diazabicyclo [5.4.0]undec-7-ene (DBU), TEA, and piperidine] and solvents (aprotic polar, and protic) as indicated in (Table 1**)**. From these studies, it is observed that the bases DABCO, DBU, and TEA are not much effective for the generation of the intermediate (**4**). However, piperidine (30 mol%) gave desired product with 93%–95% yield in protic solvents (EtOH and water) for 2 h at 65°C temperature.

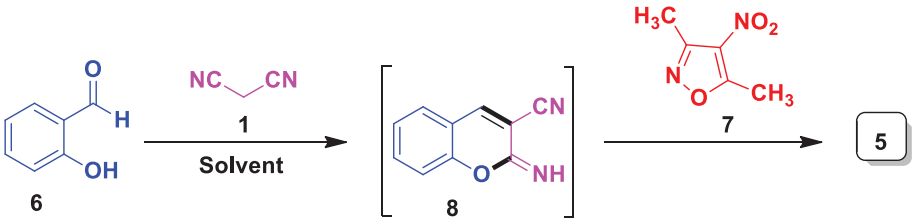
A simultaneous strategy for the synthesis of compound **5** was envisaged based on Michael addition reaction of 2-imino-2*H*-chromene-3-carbonitrile (as Michael acceptor) and 3,5-dimethyl-4-nitroisoxazole (as Michael donor). To achieve this, 2-imino-2*H*-chromene-3-carbonitrile (**8**) [prepared from salicylaldehyde and malononitrile] [10a] was reacted with 3,5-dimethyl-4-nitroisoxazole (**7**) in the presence of Et_3N (30 mol%) in EtOH to give the desired compound (**5**) in 70% yield (Scheme 2). Based on these observations, an attempt for a catalyst-free reaction of salicylaldehyde (**6**), malononitrile (**1**) in water at 60–80°C gave an imine in quantitative yield (99%, TLC conversion) for 30 min. To this (same reaction pot), 3,5-dimethyl-4-nitro-isoxazole (**7**) was added and heating continued for another 3 h to give the desired 4*H*-chromene-isoxazole hybrid (**5**) in 94% yield. To compare the efficiency of these results, the same reaction was performed for different concentrations of water and other solvents (polar aprotic and protic), brine, and D_2O. These experiments indicate that the water at 0.5 M concentration is ideal condition for obtaining best yield (94%; Table 2, Entry-4) and support "on-water" concept for the success of the reaction.

Having the reaction conditions in hand, toward the generalization and to check the subsrate scope in both the methods, different salicylaldehydes (**6b**-**6h**) were treated with 3,5-dimethyl-4-nitro-isoxazole (**7**) to generate isoxazole-styrenes (**4**; in situ). The compound was then reacted with malononitrile/methyl cyanoacetate/ethyl cyanoacetate to give 4*H*-chromene-isoxazole hybrids (**5a**-**5r**) in 85%–95% yields (Method A in Figure 1). Similarly, the iminochromenes (**8**) [generated



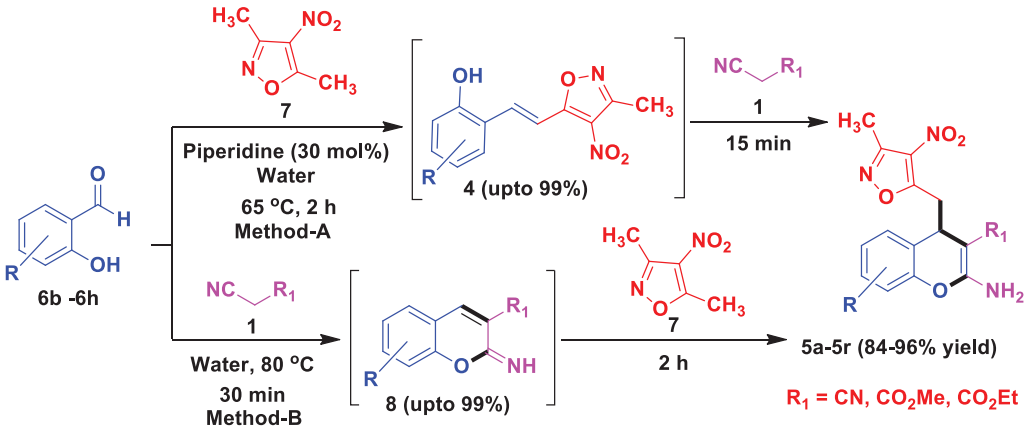
SCHEME 2 Synthesis of isoxazole-4*H*-chromene hybrids (**5a**) via Michael addition reaction of nitroisoxazole (**7**) and 2-imino-2*H*-chromene-3-carbonitrile (**8**)

TABLE 2 Optimization of the conditions for synthesis of **5** (one-pot method and catalyst-free condition)



S. No.	Solvent (2 mL)	Temp (°C)	Time (h)	Yield (%)[a]
1	MeOH	60	24	55
2	EtOH	60	24	65
3	Water	80	6	72
4	**Water (0.5 M)**	**80**	**03**	**94**
5	Water (4 mL) (0.25 M)	80	06	84
6	Water (3 mL) (0.33 M)	80	06	85
7	Water (1 mL) (1 M)	80	06	80
8	Brine	80	24	50
9	D_2O	80	24	20

Note: All of the reactions were performed with 1 mmol scale.
[a]Isolated yields. Bold values indicates the best results.



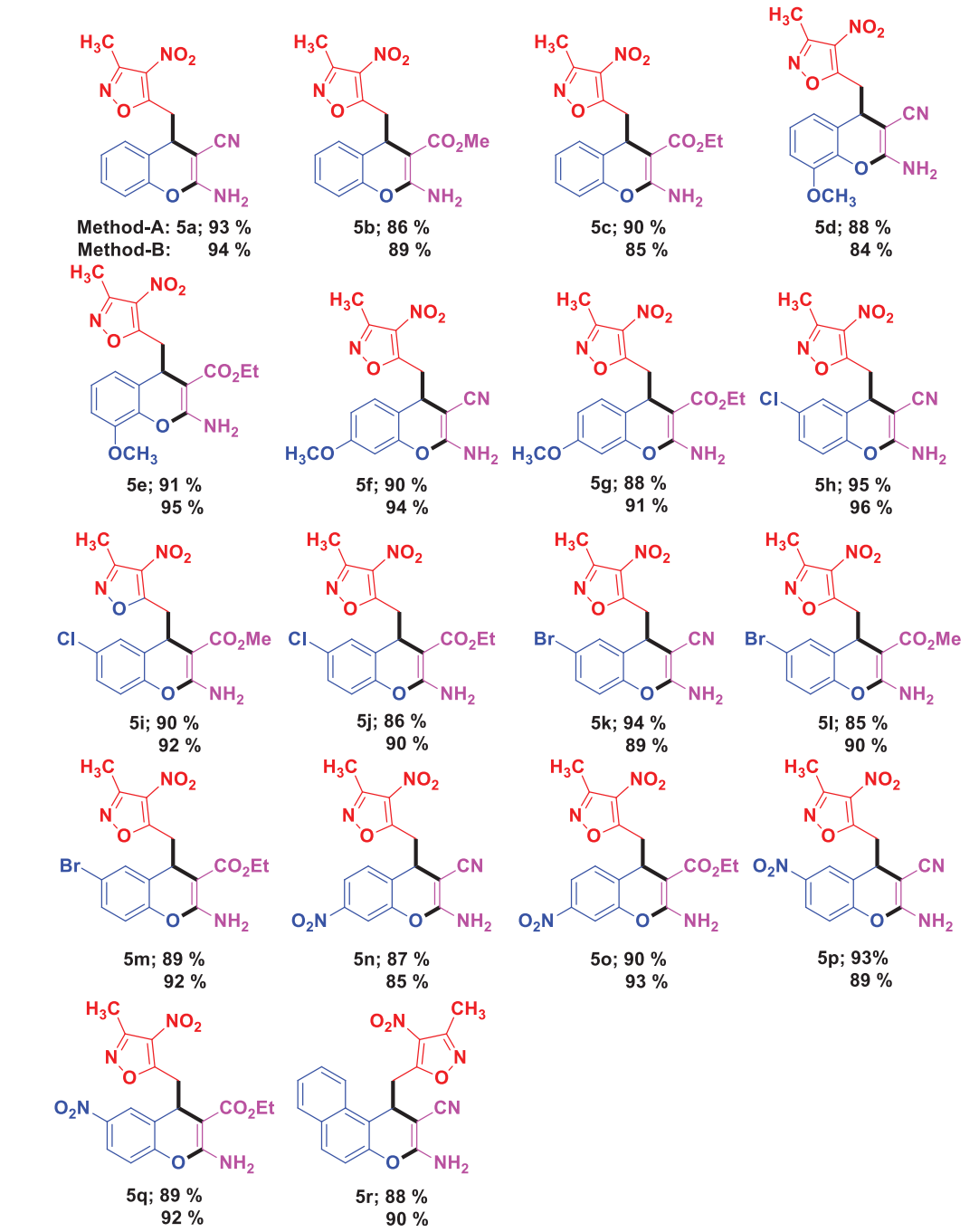


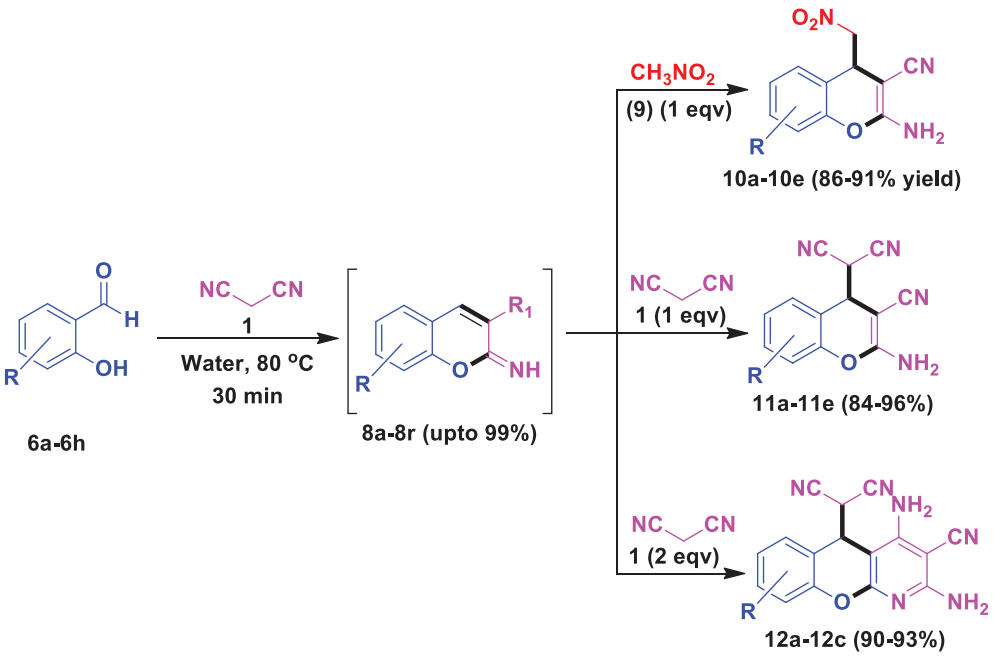
FIGURE 1 Substrate scope for the 4*H*-chromene-isoxazole hybrids (**5a**-**5r**) using method-A, and method-B

by the reaction of salicylaldehydes and malononitrile/methyl cyanoacetate/ethyl cyanoacetate at 80°C in water (catalyst-free)] on treatment with 3,5-dimethyl-4-nitroisoxazole (**7**) gave 4*H*-chromene-isoxazole hybrids (**5a**-**5r**) in 84%–96% yields (Method B in Figure 1).

After synthesizing the 4*H*-chromene-isoxazole hybrids (**5a**-**5r**), we have decided to apply this method for the nitromethane as a nucleophile. Thus, the imines [generated from salicylaldehydes (**6**) and malononitrile (**1**)] were treated with nitromethane (**9**) under optimized conditions (catalyst-free) using water as reaction medium to give the desired 2-amino-4-(nitromethyl)-4*H*-chromene-3-carbonitriles (**10a-10e**) with good yields (86%–91%) for 30 min at 80°C (Scheme 3). Further to increase the complexity, the iminochromenes were also reacted with malononitrile (1 equiv and 2 equiv) under optimized conditions. It is noteworthy to mention that the stoichiometry of the malononitrile play an important role to give the expected Michael adducts (**11a**-**11e**) and chromene-pyridine hybrids (**12a-12c**) with good yields (Scheme 3). These results can be comparable with catalyst mediated reactions [10].

As mentioned in the introduction, coumarin acetic acids are important molecules in medicinal chemistry and can be used as fluorescent molecules [5]. The nitroisoxazole moiety is known as carboxylic acid equivalent [7a]. Also, it is known that the 2-aminochromenes can be converted into coumarins [11]. Considering this, the 4*H*-chromene-isoxazole (**5**) was reacted with known reagents [11] as indicated in Table 3. All the reagents could give the desired product. But, iodine was found to be better in a combination of ^{t}BuOH + H_2O as a reaction medium giving the desired isoxazole-coumarin (**13a-13e**) up to 96% yield (Scheme 4). The plausible mechanism for this transformation is given in the Supporting Information (Figure S3). Further, the isoxazole-coumarin (**13d**) was treated for iosaxazole ring opening to give 2-(6-chloro-3-cyano-2-oxo-2*H*-chromen-4-yl)acetic acid **14**. Similarly, the chromene-isoxazole amine **15** was obtained (in 93%) by nitro reduction of **5m** by treating in the presence of Zn powder in acetic acid for 1 h (Scheme 5).

Based on the experimental observations and reported mechanism for on-water mediated reactions [12], a

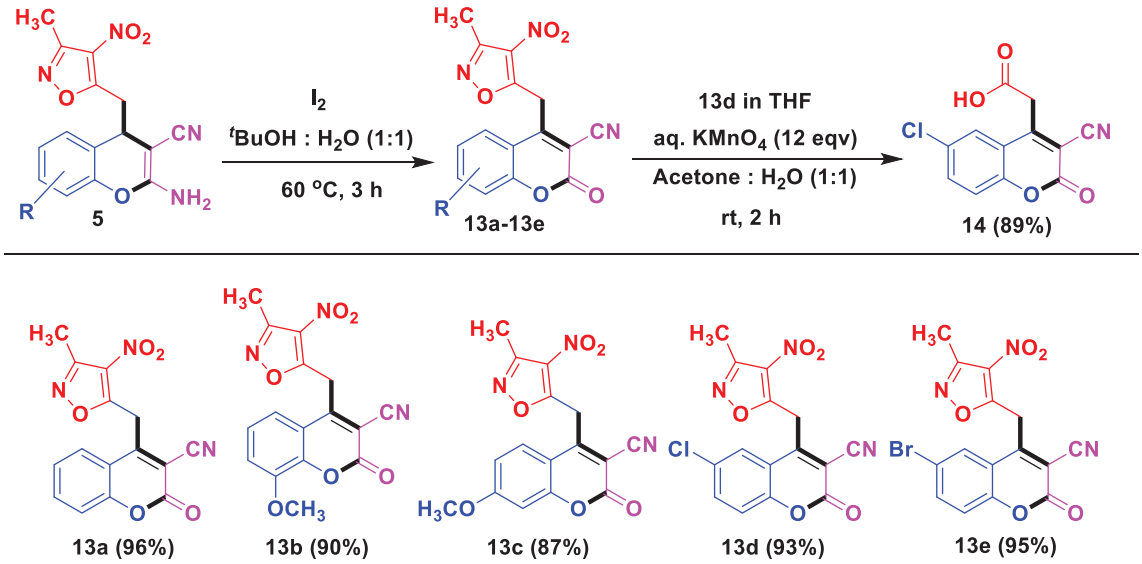


SCHEME 3 One-pot approach for the Michael adducts (**10a**-**10e** and **11a**-**11e**) and chromene-pyridine hybrids (**12a**-**12c**) under catalyst-free conditions

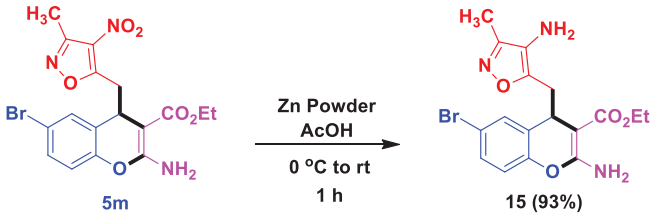
TABLE 3 Optimization of the conditions for the synthesis of compound (**13**)

S. No.	Solvent (2 mL)	Oxidizing agent	Time (h)	Yield (%)[a]
1	DMF	$SOCl_2$ (1.5 Eqv)	10	70 [11a]
2	$CH_3CO_2H + H_2O$	I_2O_5 (0.5 Eqv)	10	60 [11b]
3	THF	HCl (1 M)	10	55 [11c]
4	^{t}BuOH + H_2O	I_2 (1.1 Eqv)	2	96 [11d]

Note: All of the reactions were performed with 1 mmol scale.
[a]Isolated yields.



SCHEME 4 Synthesis of isoxazole-coumarin hybrids and 2-(3-cyano-2-oxo-2*H*-chromen-4-yl)acetic acid



SCHEME 5 Reduction of the nitro group of isoxazole into amine (**15**)

plausible transition states are proposed as shown in Supporting Information for both strategies (Figure S2). In the method-A, salicylaldehyde reacts with an activated 3,5-dimethyl-4-nitroisoxazole to give Knoevenagel condensation product (**I**) and (**II**). The generated isoxazole styrene further proceeds via 1,6-Michael addition with malononitrile followed by Pinner type reaction (**III**) then, the resulted compound fruther undergo proton migration to give (**IV**). In the overall process, water is helping to enhance the reaction kinetics in a synergistic way in the presence of piperidine (Figure S1).

Whereas the method-B (catalyst-free reaction), an intermediate (imine) is generated by Knoevenagel condensation followed by cyclization to give 2-iminochromene. This reacts with the activated 3,5-dimethyl-4-nitroisoxazole in Michael fashion to give the Michael adduct (**III**). The Michael adduct further undergo proton migration to deliver the final product (**IV**). In this case, poor solubility of the starting materials in water helps aggregation. Also, the hydrophobic effects of water (as reaction medium) support the "on-water" concept for the success of the reaction (Figure S2).

3 | CONCLUSION

In conclusion, we have demonstrated an efficient and green method for one-pot synthesis of functionalized isoxazole-4*H*-chromene hybrids. Two independent methods, *o*-hydroxy group directing cyclization of isoxazole-styrenes and Michael addition of 3,5-dimethyl-4-nitroisoxazole on 2-imino-2*H*-chromene-3-carbonitrile are adopted using the "on-water" concept. The developed methods were extended for nitromethane, malononitrile, and alkylcyanoacetates as Michael donors to give chromene-pyridine hybrids. The resulting isoxazole-4*H*-chromene hybrids were converted in to coumarins **13a**-**13e** acetic acids.

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DATA AVAILABILITY STATEMENT

Supporting data is available

ORCID

Dhurke Kashinath https://orcid.org/0000-0002-2509-0386

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of this article.

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