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Article

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Visible-Light Initiated One-pot, Three-Component Synthesis of 2-Amino-4*H*-pyran-3,5-dicarbonitrile Derivatives

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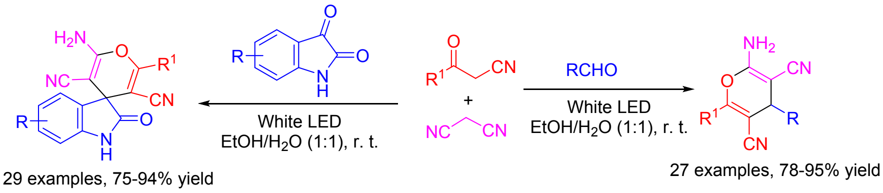
ABSTRACT: A novel approach for visible-light initiated synthesis of 2-amino-4*H*-pyran-3,5-dicarbonitrile derivatives via one-pot, three-component reaction of aldehydes or isatins, malononitrile and α-cyano ketones has been developed. The reaction was carried out at room temperature in ethanol/water to give the corresponding products with a wide range of functional groups in high yield. This process did not require any additives and chromatographic separation, and could be applied for the gram-scale synthesis.

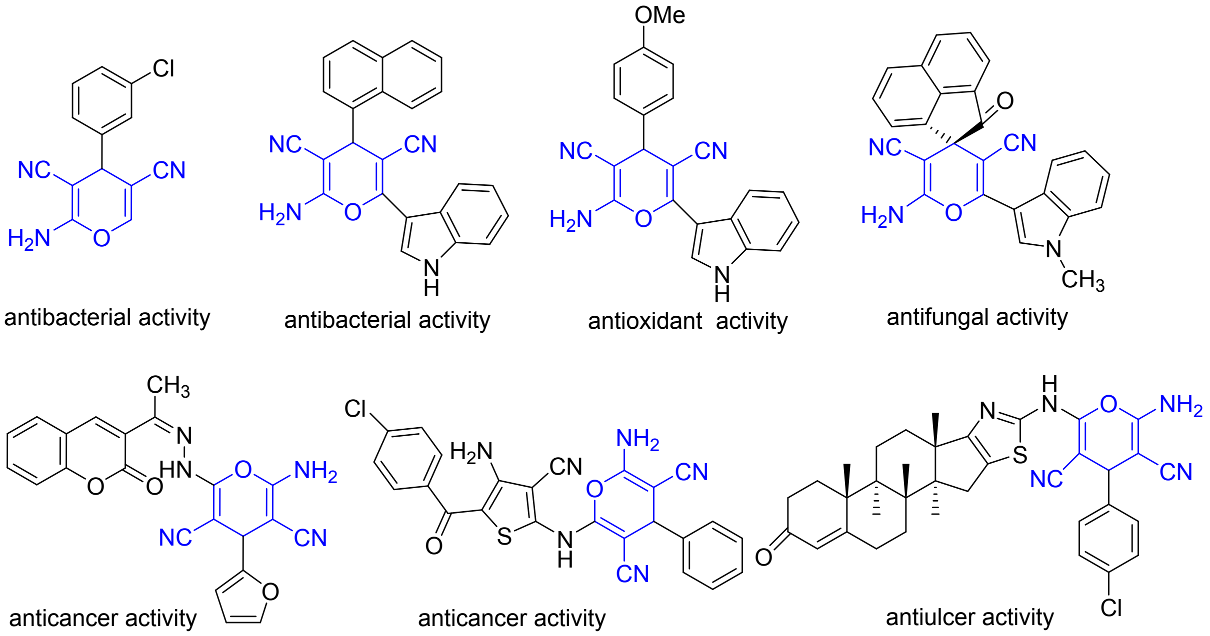
Keywords: Visible-light, Catalyst-free, 2-Amino-4*H*-pyran-3,5-dicarbonitrile Spirooxindoles, Multi-component reaction, Green synthesis



INTRODUCTION

With the increasing awareness of protecting our fragile environment and great progress in green and sustainable chemistry, the use of a renewable energy source for developing efficient and selective chemical transformations gained widespread attention.[1] In the past few years, visible light as clean, safe, non-polluting, inexpensive, abundant, and sustainable energy has been utilized for the design of a variety of organic reactions under mild reaction conditions and low-energy irradiation and remarkable achievements have already been demonstrated.[2-9] In a photo-promoted organic synthetic chemical reaction, light acts as a reagent for inducing conversion of a compound as it is usually carried out by a chemical reagent.[10] Moreover, multicomponent reactions (MCRs) have become a fascinating and powerful synthetic tool in organic synthesis, medicinal and combinatorial chemistry by the reaction of three or more different starting materials in a one-pot manner for the construction of complex molecular structures with shortened reaction time, increased yield, less side products and simple workup procedures compared to conventional reaction strategies.[11-22] At the same time, catalyst-free protocols have become an important strategy due to their simple workup, low cost, reduced contamination and avoiding the effects of catalysts on sensitive substrates.[23] These characteristics meet the requirements of green chemistry. Although some achievements have been made in this field, the study of visible light- initiated catalyst-free MCRs remains is still in its infancy and new MCRs remain to be further explored.[24-27]

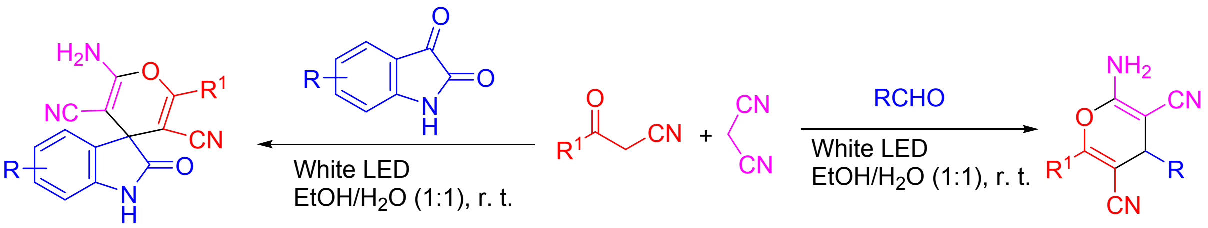
As one of the major classes of valuable oxygen-containing heterocyclic compounds, pyrans are a prevalent structural motif found in a number of natural products, synthetic pharmaceuticals and functional materials. Moreover, these compounds have been efficiently used as pigments and biodegradable agrochemicals.[28] Among them, 2-amino-4*H*-pyran-3,5-dicarbonitriles have received considerable attention due to their well-documented biological properties in the fields of natural products, pharmaceuticals and agrochemicals. They can be used as antibacterial,[29-30] antioxidant,[30] antifungal,[31] anticancer,[32-33] and antiulcer[34] agents, as exemplified in Figure 1. Owing to their intriguing biological activities, a plethora of methods have been developed for the preparation of these important compounds. In 2010, Lakshmi et al developed $InCl_3$-catalyzed tandem Knoevenagel–Michael reaction of 3-cyanoacetyl indole, aromatic aldehydes and malononitrile for synthesis of 3-pyranyl indole derivatives in ethanol under reflux conditions.[30] Also in 2010, they disclosed the reaction of isatin, malononitrile and 3-cyanoacetyl indole could be carried out in the presence of in Et_3N to prepare spirooxindoles including 2-amino-4*H*-pyran-3,5-dicarbonitrile skeleton.[31] In 2016, Wu' group have reported the first organocatalytic Michael/cyclization cascade reaction sequence between 3-oxo-3-phenylpropanenitrile and isatylidene malononitriles in CH_2Cl_2 for the construction of spiro[4*H*-pyran-oxindoles] derivatives.[35] Despite these advances, the established protocols are insufficient to meet green chemistry standards suffering from several limitations, such as the requirement of multistep synthesis of the precursors and expensive catalysts, high energy consumption under harsh reaction conditions. Therefore, the development of an environmentally friendly and practical method with high generality for synthesis of 2-amino-4*H*-pyran-3,5-dicarbonitriles under mild reaction conditions remains appealing and challenging.


antibacterial activity antibacterial activity antioxidant activity antifungal activity

anticancer activity anticancer activity antiulcer activity

Figure 1. Selected bioactive molecules with 2-amino-4*H*-pyran-3,5-dicarbonitrile substructure

Our laboratory has focused on the development of environmentally friendly approaches for organic transformations.[36-38] Herein, we report a novel, visible-initiated, catalyst free transformation to construct functionalized 2-amino-4*H*-pyran-3,5-dicarbonitrile derivatives via one-pot, three-component reaction of aldehydes or isatins, malononitrile and α-cyano ketones at room temperature (Scheme 1).

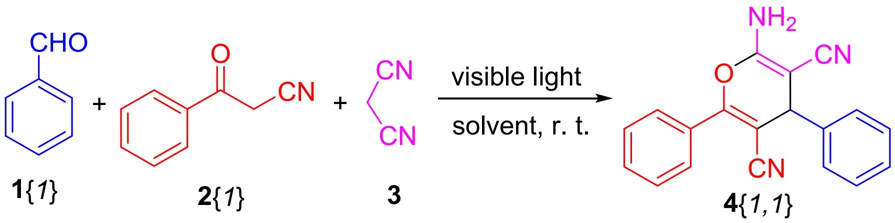


Scheme 1. Visible-light-initiated one-pot synthesis of 2-amino-4*H*-pyran-3,5-dicarbonitrile derivatives

RESULTS AND DISCUSSION

At first, the reaction conditions were optimized using model reaction of benzaldehyde **1**{*1*}, 3-oxo-3-phenylpropanenitrile **2**{*1*} and malononitrile under various reaction conditions (Table 1). Various solvents such as CH_2Cl_2, $CHCl_3$, CH_3CN, EtOAc, THF, ethyl lactate (EL), EtOH, DMF, glycerol, PEG 400 and choline chloride (ChCl)/glycerol (1:1) were screened in the absence of any catalyst under visible light illumination with an 18 W white light-emitting diode (LED) under an air atmosphere at room temperature. It was found the reaction indeed occurred to give desired product **4**{*1,1*} in 18-56% yields. The yield of **4**{*1,1*} was improved when the reaction was performed in a mixed solvent of PEG 400/H_2O, EL/H_2O, and EtOH/H_2O. Different ratios of EtOH and H_2O were tested and found that its ratio of 1:1 was suitable for this transformation, giving the expected product in 92% (entry 15). The effect of different sources of visible light was also examined. The investigation indicated that the light source has no significantly effect on product yield. With a green LED, the yield was only slightly improved (entry 20). From a practical standpoint, white light was chosen as light source. When the reaction was performed under darkness, only 13% yield of product was formed (entry 22). This observation indicated that visible light is a critical factor for this reported reaction procedure in the absence of catalyst conditions.

Table 1. Investigation of the reaction conditions for the synthesis of product 4{*1,1*}[a]

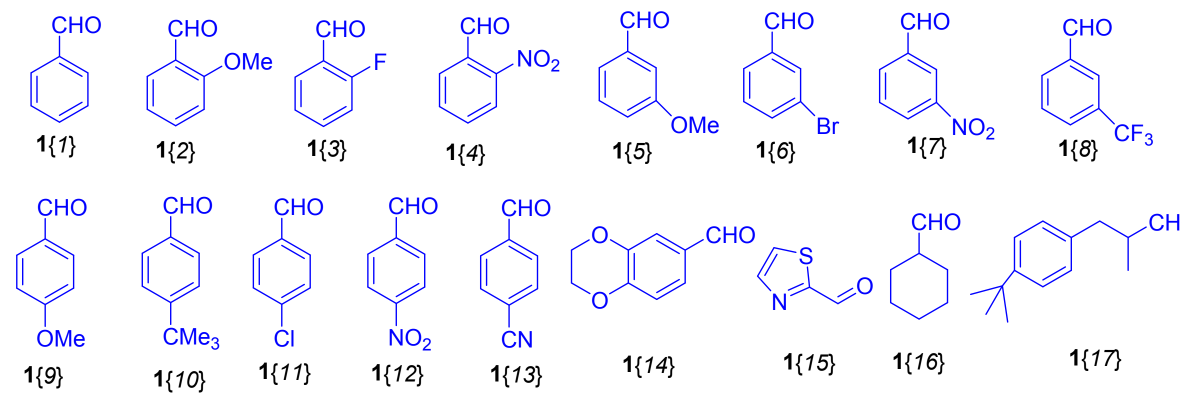


Entry	Light source	Solvent	Time (h)	Yield (%)[b]
1	White light	H_2O	5	36
2	White light	CH_2Cl_2	5	20
3	White light	$CHCl_3$	5	21
4	White light	CH_3CN	5	22
5	White light	EtOAc	5	24
6	White light	THF	5	26
7	White light	EL	5	28
8	White light	EtOH	5	30
9	White light	DMF	5	42
10	White light	Glycerol	5	18
11	White light	PEG 400	5	56
12	White light	ChCl/Glycerol (1:1)	5	20
13	White light	PEG 400/H_2O (1:1)	5	61
14	White light	EL/H_2O (1:1)	5	70
15	White light	EtOH/H_2O (1:1)	5	92
16	White light	EtOH/H_2O (2:1)	5	57
17	White light	EtOH/H_2O (3:2)	5	60
18	White light	EtOH/H_2O (9:1)	5	38
19	Blue light[c]	EtOH/H_2O (1:1)	5	90
20	Green light[d]	EtOH/H_2O (1:1)	5	94
21	Ultraviolet light[e]	EtOH/H_2O (1:1)	5	87
22	Dark	EtOH/H_2O (1:1)	12	13

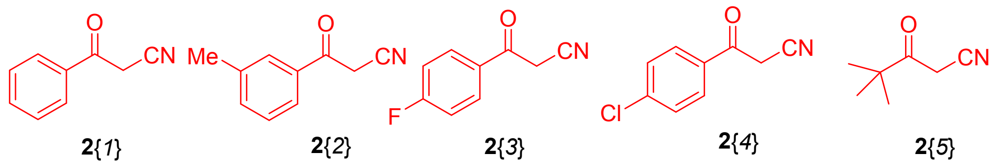
[a]Reaction conditions: benzaldehyde (1 mmol), 3-oxo-3-phenylpropanenitrile (1.0 mmol), malononitrile (1 mmol), solvent (2 ml), light irradiation (18 W, wavelength in the range 390–750 nm), room temperature unless otherwise specified in the Table. [b]Isolated yields. [c]Blue light (460–470 nm). [d]Green light (520–530 nm). [e]Ultraviolet light (390–400 nm).

Based on the establishment of the optimal reaction conditions, the scope and generality of this visible-light promoted three-component reaction were further evaluated. The structural diversity of the starting materials is shown in Figure 2. First, a variety of aldehydes were examined and the representative results are compiled in Scheme 2. Benzaldehydes bearing both electron-donating or -withdrawing substitutions at the phenyl ring reacted smoothly under the optimal reaction conditions, furnishing the corresponding 2-amino-4*H*-pyran-3,5-dicarbonitriles (**4**) with high to excellent yields. Furthermore, it was observed that the position of the substituent on the benzene ring did not significantly affect the reaction. An array of versatile functional groups, including base- and acid-sensitive moieties, such as alkyl, methoxy, phenoxy, hydroxyl, trifluoromethyl, nitro, cyano, boric acid, halogen groups were compatible under the standard reaction conditions. Besides the arene aldehydes, the heterocycle aldehyde such as thiazole-2-carbaldehyde **1**{*15*} has been proved to be compatible, and generated the expected products **4**{*15,1*} in high yields. We were pleased to find that alkyl aldehyde such as cyclohexanecarbaldehyde **1**{*16*} was still a suitable reactant under the standard conditions, leading to the desired product **4**{*16,1*} with 85% yield. Lilialdehyde was then subjected to the established reaction conditions, effectively exhibiting good performance to deliver the respective product **4**{*17,1*} in 78% yield.

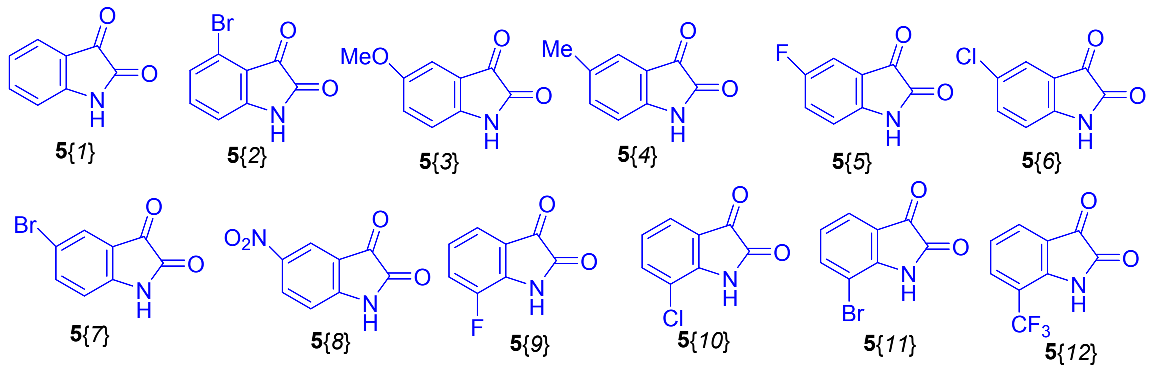
Subsequently, the reactions of different α-cyano ketones were also investigated under the optimized reaction conditions. The results demonstrated that electronic properties of the substituents on the benzene rings of α-cyano ketones had no obvious influence on the efficiency, and the corresponding products were obtained in high yields. In addition, this reaction could be applied to 4,4-dimethyl-3-oxopentanenitrile **2**{*5*} and achieved the desired products in 88-92% yield.



Chemset **1** Diversity reagents **1**{1-17}



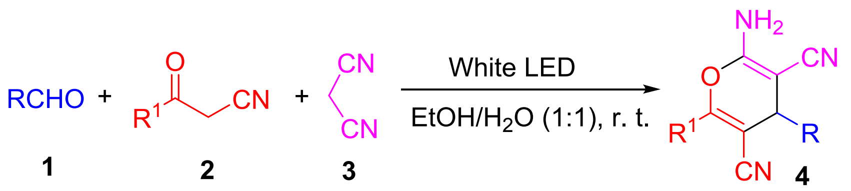
Chemset **2** Diversity reagents **2**{1-5}

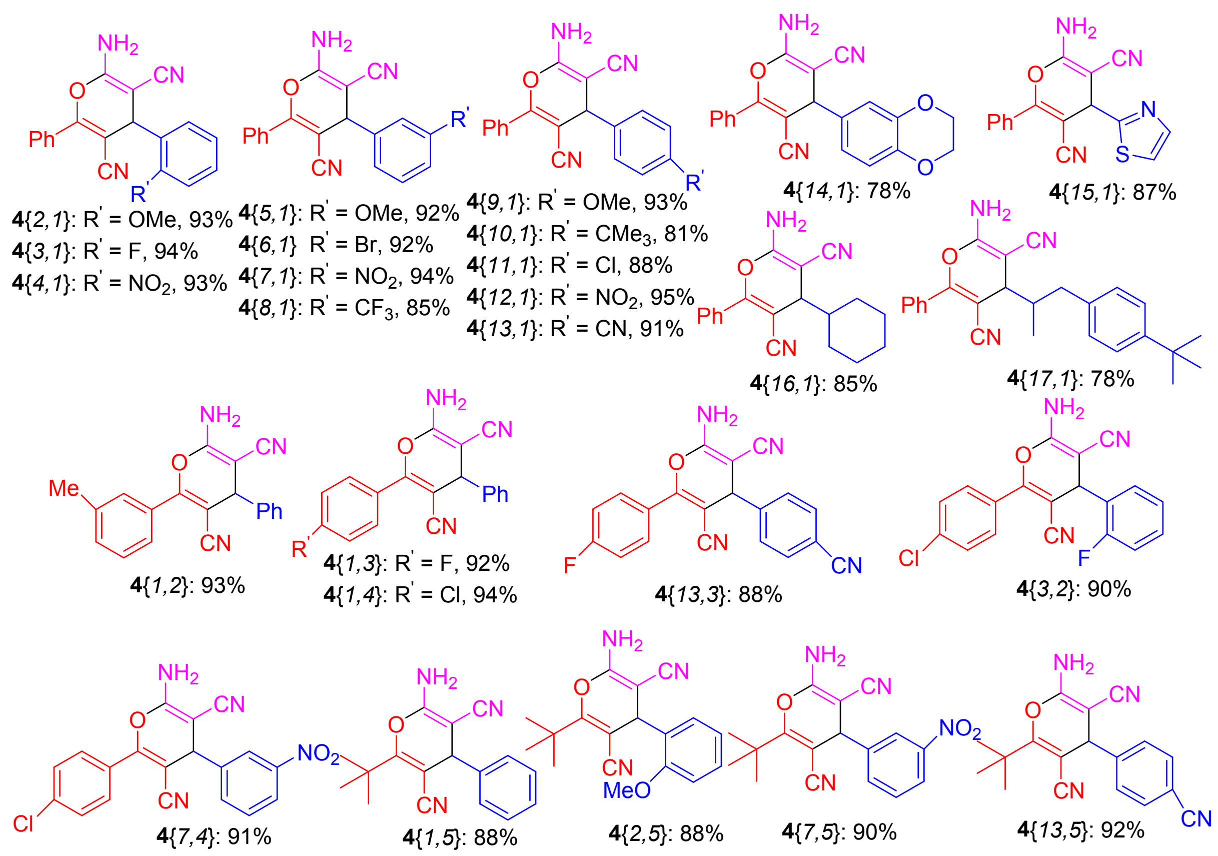


Chemset **5** Diversity reagents **5**{1-12}

Figure 2. Chemsets selected for the library of 2-amino-4*H*-pyran-3,5-dicarbonitriles: aldehydes (chemset 1), α-cyano ketones(chemset 2), and isatins (chemset 5).

Scheme 2. Synthesis of 2-amino-4*H*-pyran-3,5-dicarbonitriles using aldehydes

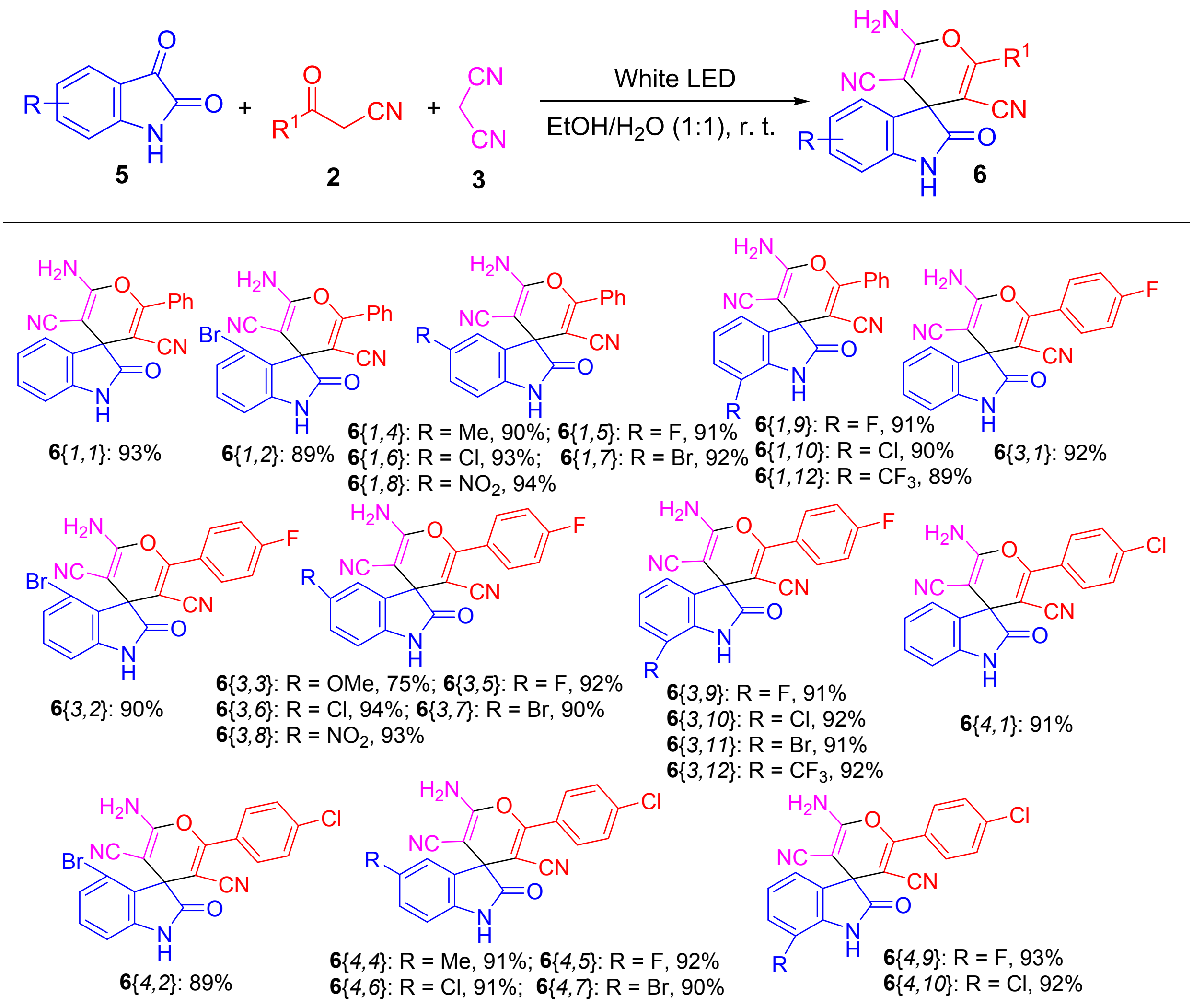




[a] Isolated yields.

Isatins and their derivatives have been shown to have a broad spectrum of biological activity. These interesting features prompted us to further explore the application of this reaction for synthesis of spirooxindole 2-amino-4*H*-pyran-3,5-dicarbonitriles using isatins. As shown in Scheme 3, isatins substituted with either electron-rich groups or electron-poor groups were all converted into their corresponding products **6** with high yields regardless of the electronic properties of the substituents on aromatic ring. The position of the substituents on the phenyl ring of isatins had little influence on the efficiency of the reaction. Halogen atoms such as fluoro, chloro, and bromo on the aromatic ring were not affected under the present reaction conditions, providing ample opportunity for further functionalization possible. The results from this section demonstrated that this approach was broadly applicable for the synthesis of 2-amino-4*H*-pyran-3,5-dicarbonitrile derivatives.

Scheme 3. Synthesis of spirooxindole 2-amino-4*H*-pyran-3,5-dicarbonitriles using isatins

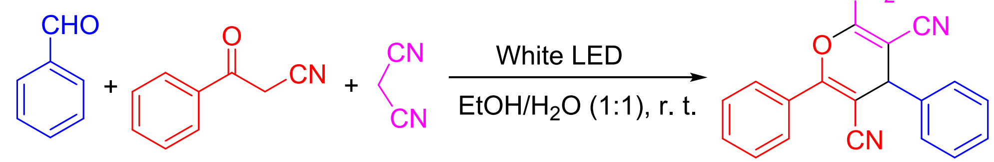


6{1,1}: 93%
6{1,2}: 89%
6{1,4}: R = Me, 90%; 6{1,5}: R = F, 91%
6{1,6}: R = Cl, 93%; 6{1,7}: R = Br, 92%
6{1,8}: R = NO_2, 94%
6{1,9}: R = F, 91%
6{1,10}: R = Cl, 90%
6{1,12}: R = CF_3, 89%
6{3,1}: 92%
6{3,2}: 90%
6{3,3}: R = OMe, 75%; 6{3,5}: R = F, 92%
6{3,6}: R = Cl, 94%; 6{3,7}: R = Br, 90%
6{3,8}: R = NO_2, 93%
6{3,9}: R = F, 91%
6{3,10}: R = Cl, 92%
6{3,11}: R = Br, 91%
6{3,12}: R = CF_3, 92%
6{4,1}: 91%
6{4,2}: 89%
6{4,4}: R = Me, 91%; 6{4,5}: R = F, 92%
6{4,6}: R = Cl, 91%; 6{4,7}: R = Br, 90%
6{4,9}: R = F, 93%
6{4,10}: R = Cl, 92%

[a] Isolated yields.

Furthermore, to demonstrate the scalability of our method of this visible light-initiated MCR process, we carried out the model reaction on a 10 mmol scale to provide the expected product **4**{*1,1*}in 94% yield (Scheme 4). This shows that our methodology be potentially scaled up to gram-scale synthesis.

Scheme 4. Gram-scale synthesis of 4{*1,1*}

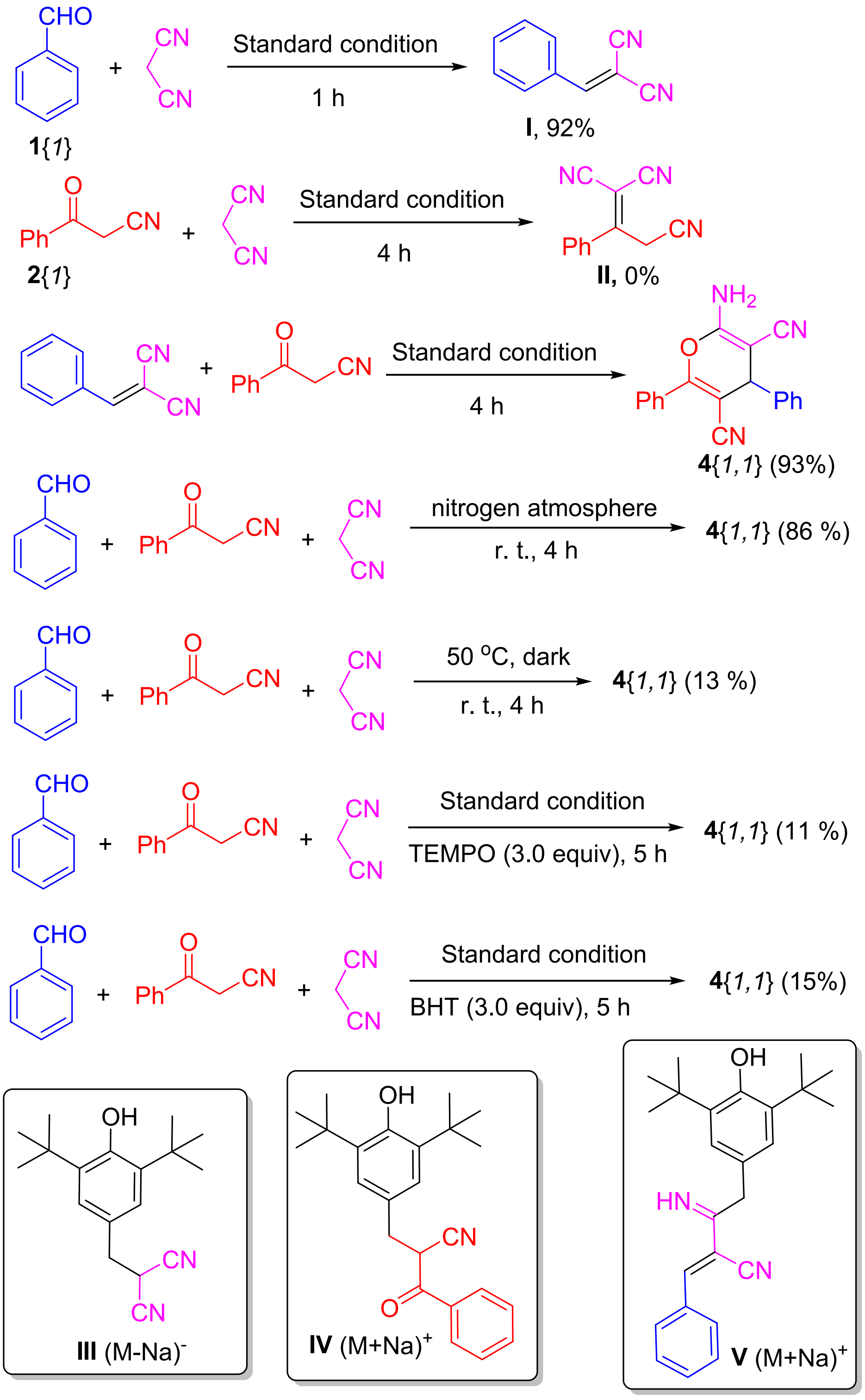


4{*1,1*} (2.80 g, 94%)

To obtain insights into the reaction mechanism of this visible light-initiated three-component reaction, a series of control experiments were performed. As shown in Scheme 5, the Knoevenagel condensation of malononitrile with benzaldehyde took place in standard condition with the elimination of water to give the corresponding 2-benzylidenemalononitrile (**I**) in 92% yield. However, when the reaction of 3-oxo-3-phenylpropanenitrile with malononitrile was conducted under same condition, no 2-phenyl-1-propene-1,1,3-tricarbonitrile (**II**) were detected. Carrying out the reaction of 2-benzylidenemalononitrile (**I**) and 3-oxo-3-phenylpropanenitrile under the standard conditions generated the desired product **4**{*1,1*} in 93% yield. Additionally, the fact that a slight decrease in yield of product (86%) was observed under a nitrogen atmosphere ruled out the role of oxygen in this reaction. When the reaction was carried out in the dark at 50 °C, the corresponding product **4**{*1,1*} was obtained in 13% yield.

In addition, 2,2,6,6-tetramethyl-1-piperidinyloxy (TEMPO), a radical scavenger, was added to the model reaction, only 11% yield of the desired product **4**{*1,1*} was obtained. Moreover, when the above reaction was treated with 2,6-di-*tert*-butyl-4-methyl-phenol (BHT), another free radical trapping reagent, the reaction was severely inhibited and only 15% of the **4**{*1,1*} was obtained. Meanwhile, radical adducts **III**, **IV** and **V** were detected in the reaction solution by HPLC-MS analysis, indicating that radicals were produced and trapped by BHT. These results indicated that radical intermediates were involved in this transformation.

Scheme 5. Control experiments



Although the exact mechanism for this reaction pathway remains unclear at this stage, on the basis of the aforementioned control experiments and recent literatures,[24] a plausible mechanism is proposed in Scheme 6. Firstly, the intermediate **A** was formed via tautomerization of malononitrile under light irradiation. Subsequently, intermediate **A** and benzaldehyde underwent Knoevenagel condensation to generate intermediate **I** with the elimination of a water molecule. UV/Vis absorption spectra showed that benzaldehyde **1**{*1*}, 3-oxo-3-phenylpropanenitrile **2**{*1*} and malononitrile (3) have no absorption at the wavelength of visible light (Figure 3). The intermediate **I** has a weak absorption in the visible region and it may absorb light under the irradiation conditions. Consequently, visible light irradiation of intermediate **I** results in its conversion into the excited state of **I** (intermediate **B**).

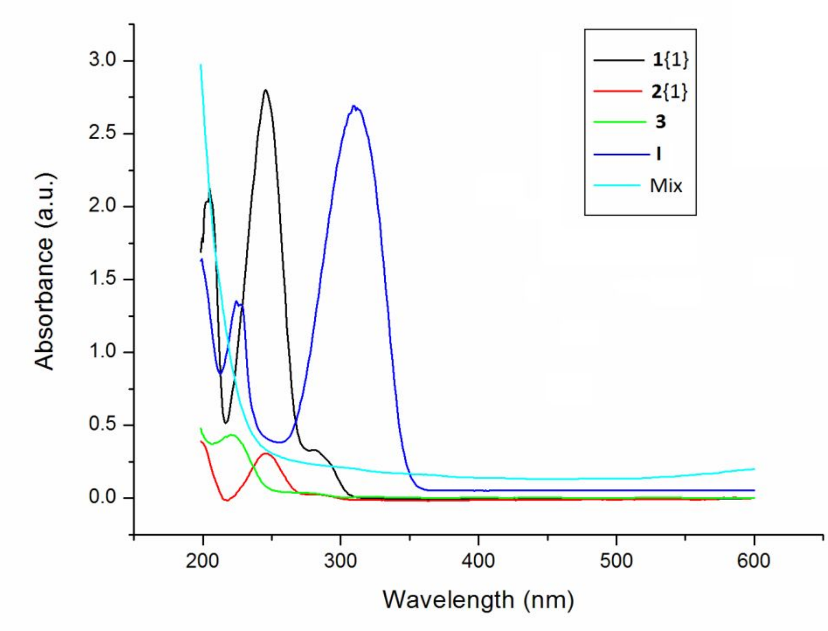
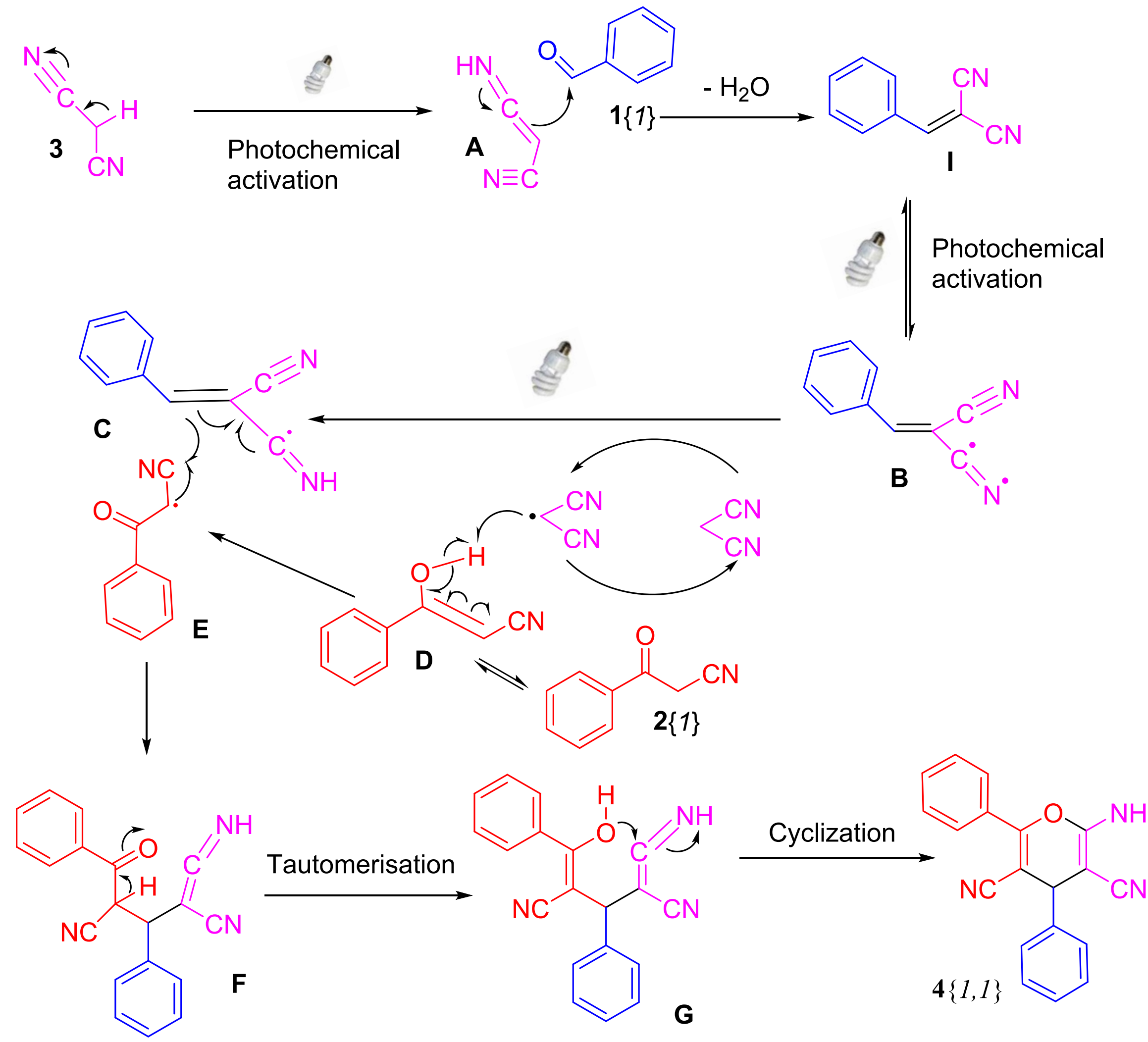


Figure 3. UV/Vis absorption spectra

The excited state of **I** is a good hydrogen abstractor and a much better electron acceptor. An electron transfer from the enol **D** (Which is in equilibrium with its own ketone) to the electronically excited state of **I** would give a radical ion pair that can neutralize by proton transfer from the enol radical cation to the malodinitrile alkene radical anion. By that, the **C**/**E**-radical pair is formed, which can combine to give the intermediate **F**. Finally, intermediate **F** underwent a tautomerisation followed by cyclization, leading to the formation of the desired product **4**{*1*,*1*}.

Scheme 6. Plausible reaction mechanism



CONCLUSION

In summary, we have successfully developed a novel, simple, straightforward, and efficient strategy for the synthesis of functionalized 2-amino-4*H*-pyran-3,5-dicarbonitrile derivatives via visible light-initiated one-pot, three-component reaction of aldehydes or isatins, malononitrile and α-cyano ketones. Without the use of any catalyst and thermal energy, the reactions proceeded at ambient temperature to give the desired products in high yields. The present protocol provides a step-economic and convenient method for the synthesis of 2-amino-4*H*-pyran-3,5-dicarbonitrile derivatives and represents fringe benefits in terms of sustainability, operational feasibility, broad substrate scope and easy scalability. The developed protocol significantly broadens the scope of visible light-initiated multi-component reaction. We expect that this method can be readily adopted by pharmaceutical chemists to prepare potentially biologically active compounds that were previously difficult to access. Further investigations of the reaction mechanism and its application are ongoing in our laboratory.

EXPERIMENTAL

Unless otherwise noted, all reagents were obtained commercially and were used as received without further purification. Melting points were determined on an X-5 digital melting point apparatus and are not corrected. The FT-IR spectra were obtained on a Bruker Tensor 27 Fourier transform infrared spectroscope. The ^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker AV III-500 or Zhongke Niujin AS 400 spectrometer using TMS as internal standard. The mass spectra were performed on a 3200 Qtrap instrument with an ESI source. Irradiation experiments were performed using a WP-VLH-1020 photoreactor from Xi'an WATTECS experimental equipment co. LTD.

General procedure for synthesis of 2-amino-4*H*-pyran-3,5-dicarbonitriles

In a tube equipped with a magnetic stirrer bar, aldehydes or isatins (1 mmol), malononitrile (1 mmol) and α-cyano ketones (1 mmol) were added in EtOH/H_2O (1:1, 2 ml). Then resulting mixture was stirred at room temperature with the irradiation of an 18 W white LEDs. For each reaction, light source was placed app. 2.0 cm away from the reaction vessels. The reaction progress was monitored by TLC. Upon completion, water was added and the solid precipitate was filtered and purified by recrystallized from ethanol to obtain the desired pure products.

■ ASSOCIATED CONTENT

Supporting Information

Spectra data and copies of ^{1}H NMR and ^{13}C NMR spectra of all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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Mo Zhang and Meng-Nan Chen contributed equally.

Notes

The authors declare no competing financial interest.

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Visible-Light Initiated One-pot, Three-Component Synthesis of 2-Amino-4*H*-pyran-3,5-dicarbonitrile Derivatives

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