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# **A novel synthetic approach to pyran-2,4-dione scaffold production: microwave-assisted dimerization, cyclization, and expeditious regioselective conversion into $\beta$ -enamino-pyran-2,4-diones**

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## **Abstract**

Here, we report a novel, green, simple, low-cost, and rapid methodology for the high-yield production of pyran-2,4-dione scaffolds under microwave irradiation. Regio- and stereoselective conversions of  $\beta$ -diketone systems into  $\beta$ -enaminones were achieved using 18 primary amines and four amino acid esters. Microwave-assisted further cyclization of 3-( $\beta$ -

substituted vinyl)-6-phenyl-pyran-2,4-dione into 3-benzoyl-4,7-diphenyl-2*H*,5*H*-pyrano[4,3-*b*]pyran-2,5-dione *via* reaction with ethyl benzoyl acetate.

## Keywords

pyran-2,4-dione; microwave;  $\beta$ -enaminones; intramolecular cyclization

## Introduction

Pyrone nucleus is extensively found in nature.<sup>1-3</sup> Molecules containing pyrone ring exhibit a wide range of pharmaceutical properties such as cytotoxic,<sup>4</sup> antitumor,<sup>5,6</sup> and antimicrobial activity.<sup>7</sup> 4-Hydroxy-2*H*-pyran-2-one, is a core structure of triacetic lactone and is utilized as a building block in synthetic chemistry. Another representative example of pyrone class compounds, kavalactones, possess many biological activities such as antituberculosis, anti-inflammatory, analgesic, anticonvulsant, antimalarial, local anesthetic, sleep-inducing, and sedative activities.<sup>8-11</sup> Furthermore, pyrone compounds have been reported to have pharmacological usefulness as selective COX-2 inhibitors<sup>12,13</sup> and HIV protease inhibitors.<sup>14-16</sup> As another representative example, photopyrones occur naturally in *Photorhabdus luminescens*; they been investigated as signaling molecules in the cell-cell communication system of this bacterium.<sup>17</sup> Many other compounds in nature have the structural feature of a pyrone scaffold; indeed, Schäberle<sup>18</sup> reported a wide range of biologically active metabolites in a 2016 review.

Several methods have been reported for the synthesis of 2-pyrones which mostly include an expensive catalyst. For example 2-pyrones could be obtained from: 3-iodoacrylic acid and terminal acetylenes using PdCl<sub>2</sub>(PPh<sub>3</sub>)<sub>2</sub> and CuI,<sup>19,20</sup> cyclo-isomerization of 3-ethynyl-indole-2-carboxylic acid in the presence of gold(III) chloride,<sup>21</sup> allenyl propiolates and terminal

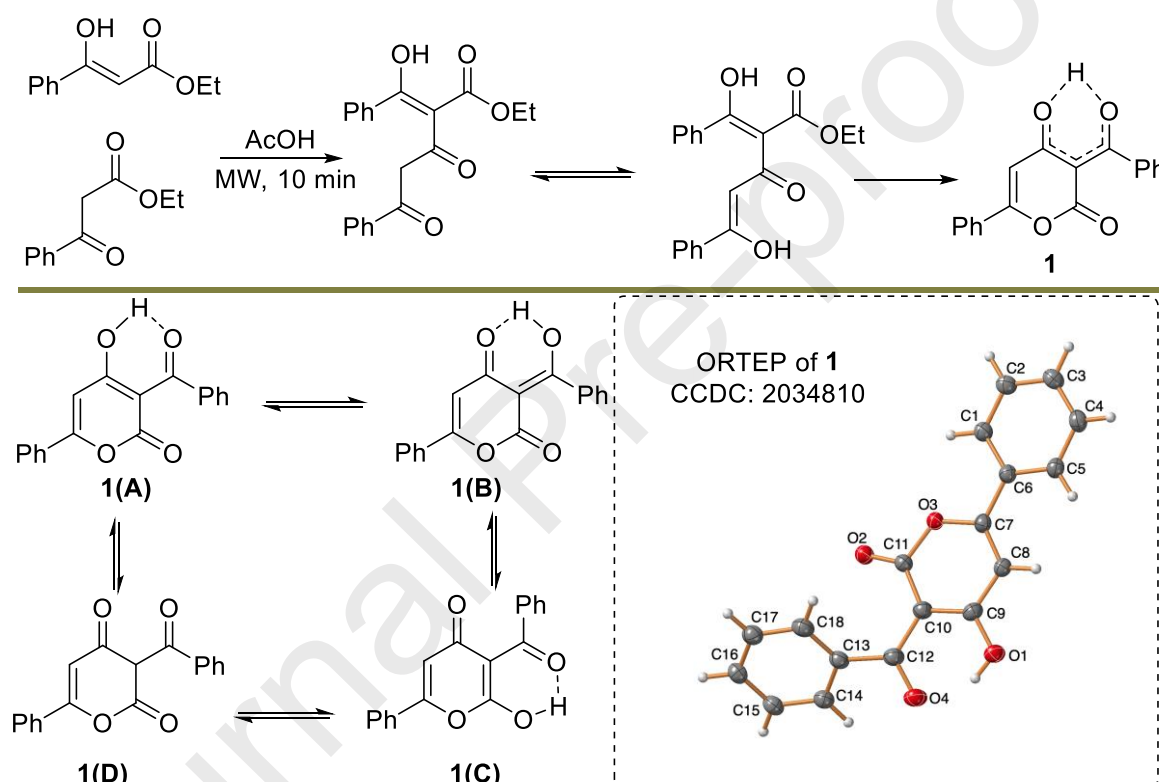
alkynes catalyzed using gold(I) catalyst,<sup>22,23</sup> annulation of alkynes by acrylic acid promoted by ruthenium(II),<sup>24</sup> Baylis-Hillman adducts,<sup>25</sup> 1,2-allenyl ketones and electron-withdrawing group substituted acetates using a base catalyst,<sup>26,27</sup> and aryl-4,4,4-trifluorobutane-1,3-diones, PCl<sub>5</sub>, and sodium diethyl malonate.<sup>28</sup>

Developing a direct method for the simple, efficient, and green construction of particular heterocyclic motifs that makes use of available materials remains an ongoing challenge for chemists from both a synthetic and mechanistic perspective. Among the many available construction strategies,<sup>29–37</sup> microwave-assisted synthesis of heterocycles is perhaps the most promising. Herein, we introduce a novel and simple method for the synthesis of substituted pyran-2,4-dione and its conversion into  $\beta$ -enamino-pyran-2,4-diones. Importantly, this method could be applied to any  $\beta$ -ketoester for the production of biologically and photochemically active motifs.

## Results and Discussion

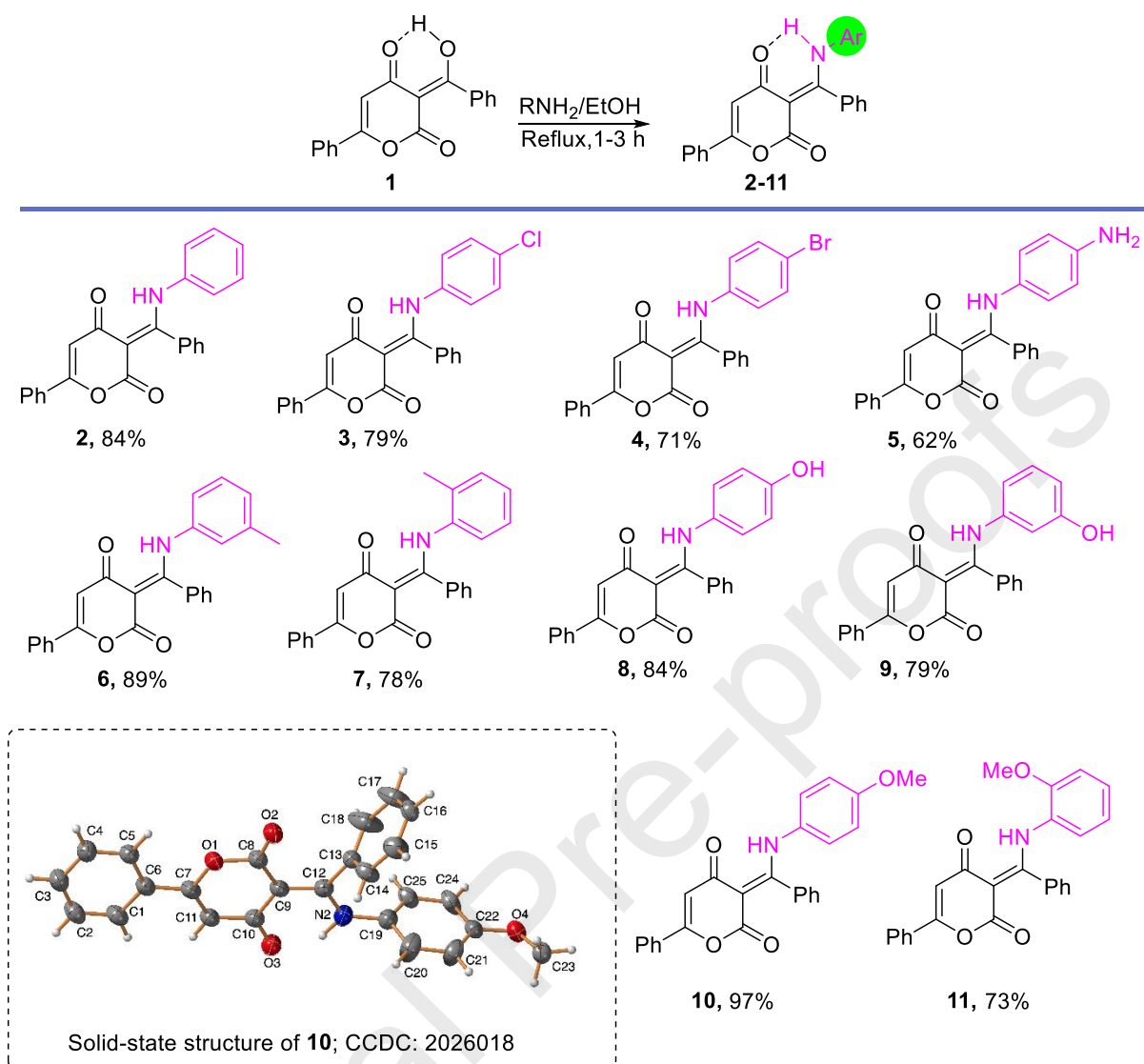
Microwave-assisted synthesis of a substituted pyran-2,4-dione **1** in one step from ethyl benzoyl acetate is shown in Scheme 1. When the reaction was conducted under microwave irradiation without a catalyst, the product was obtained with a chemical yield of <5%; when acetic acid was used as a promoter, the yield improved to 62%. Compound **1** can exist in four possible prototropic tautomeric forms: **1**(A-D) as shown in Scheme 1. The NMR of **1** was recorded in two deuterated solvents, CDCl<sub>3</sub> (nonpolar solvent) and DMSO-*d*<sub>6</sub> (polar solvent), which revealed that only two tautomeric transformations were present and the structure was highly dependent on solvent polarity. In CDCl<sub>3</sub>, the <sup>1</sup>H NMR of **1** showed the hydroxyl group proton at 15.97 ppm and the *ortho*- protons of the two phenyl groups at 7.93 and 7.72 ppm, respectively. In the same solvent, the <sup>13</sup>C NMR showed, in addition to the phenyl carbons, six carbons at 200.31, 180.92, 166.04, 160.20, 99.54, and 98.12 ppm. In DMSO-*d*<sub>6</sub>, the <sup>1</sup>H NMR

did not show the hydroxyl group signal, while the *ortho*- protons of the two phenyl groups were found together at 7.92–7.87 ppm. The  $^{13}\text{C}$  NMR in the same solvent also displayed, in addition to the phenyl carbons, six carbons at 193.40, 170.91, 161.83, 161.22, 102.59, and 98.47 ppm. This NMR data suggests that **1** is present solely in the exocyclic ketone (benzoyl) tautomer **A** in a nonpolar solvent, whereas the unique exocyclic enol tautomer **B** is favored in a polar solvent. In a solid state, the crystal structure shows that compound **1** exists exclusively in the tautomer **A** as well as the non-polar solvent (Scheme 1) (CCDC No. 2034810).



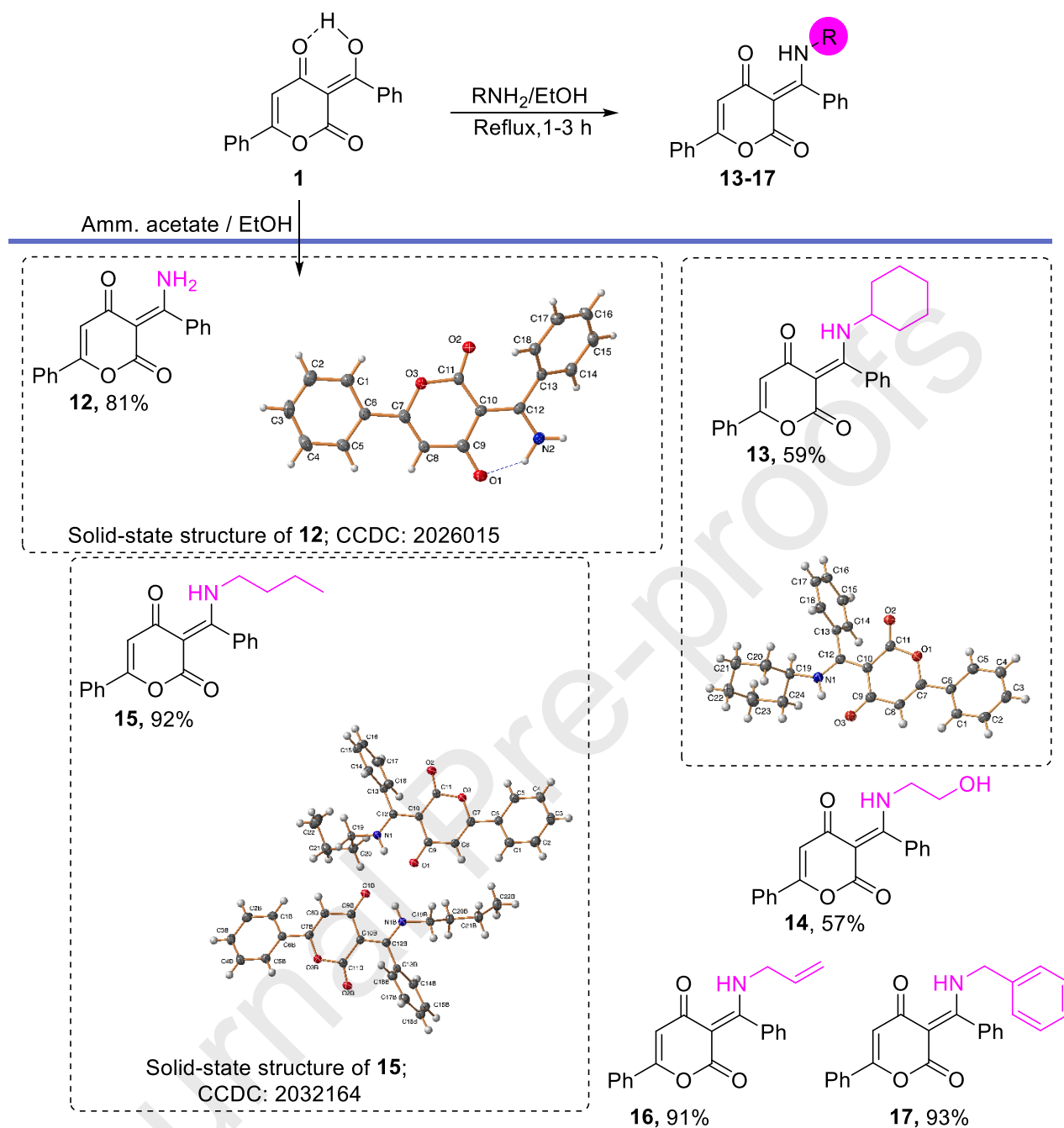
**Scheme 1:** Synthesis and possible tautomeric isomers of substituted pyran-2,4-dione **1**.

$\beta$ -amination of (*E*)-3-(hydroxy(phenyl)methylene)-6-phenyl-2*H*-pyran-2,4(3*H*)-dione (**1**) was achieved directly by a reaction with a set of aromatic amines, including aniline, 4-chloroaniline, 4-bromoaniline, *p*-phenylenediamine, *m*-toluidine, *o*-toluidine, 4-aminophenol, 3-aminophenol, *p*-anisidine, and *o*-anisidine, in ethanol to give excellent yields of the corresponding  $\beta$ -enamino-pyran-2,4-diones **2–11** (Scheme 2).



**Scheme 2:** Reaction of compound **1** with aromatic amines to give the  $\beta$ -enamino-pyran-2,4-diones **2-11**.

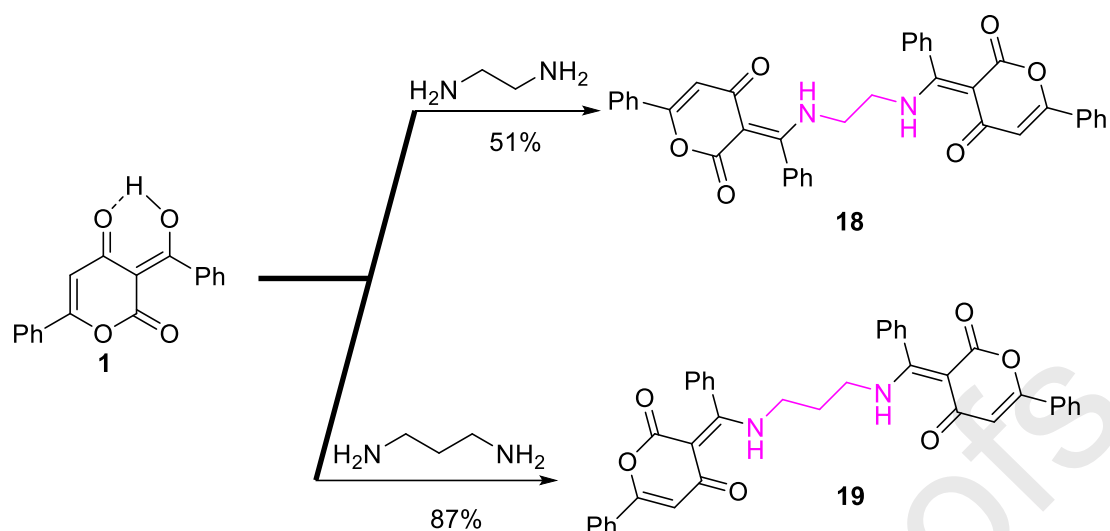
In addition, compound **1** was reacted with ammonium acetate and a set of aliphatic amines including cyclohexylamine, ethanolamine, *n*-butylamine, allylamine, and benzylamine; in this reaction, the amination produced the respective  $\beta$ -enamino-pyran-2,4-diones **12-17** (Scheme 3) exclusively, which were present in the *E*-form that was stabilized by the H-bond with the pyrandione carbonyl oxygen and amine NH ( $\text{C4-O} \cdots \text{NH}$ ).



Scheme 3. Reaction of compound **1** with ammonium acetate and aliphatic amines to give  $\beta$ -enaminopyran-2,4-diones **12–17**.

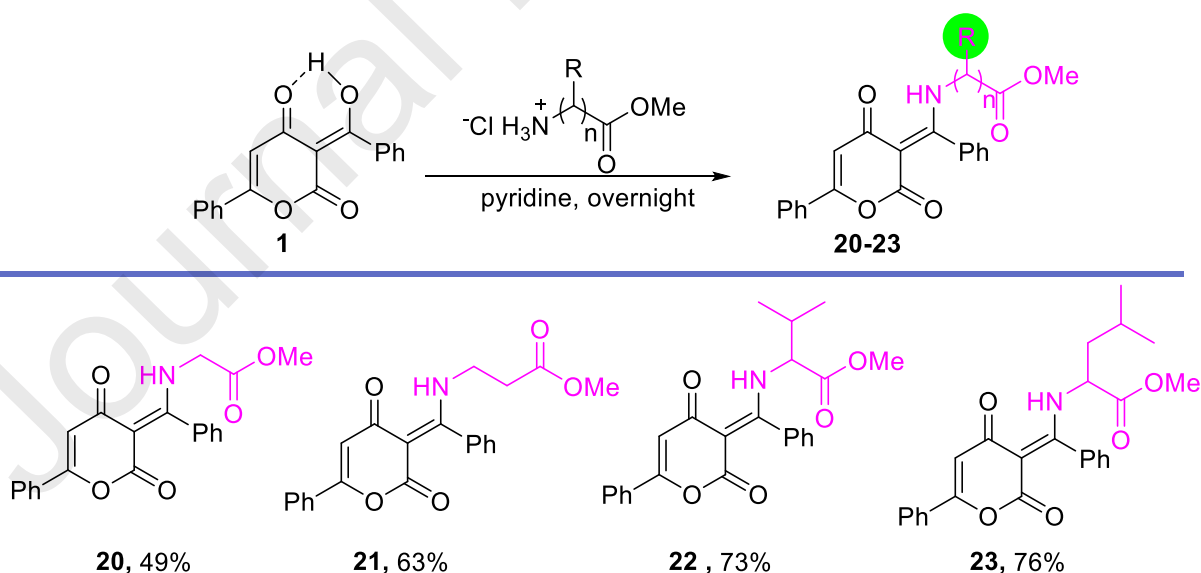
In addition, the reaction of the pyran-2,4-dione **1** with 1,2-diaminoethane and 1,3-diaminopropane produced the bis( $\beta$ -enamino-pyran-2,4-diones) **18** and **19** (Scheme 4).





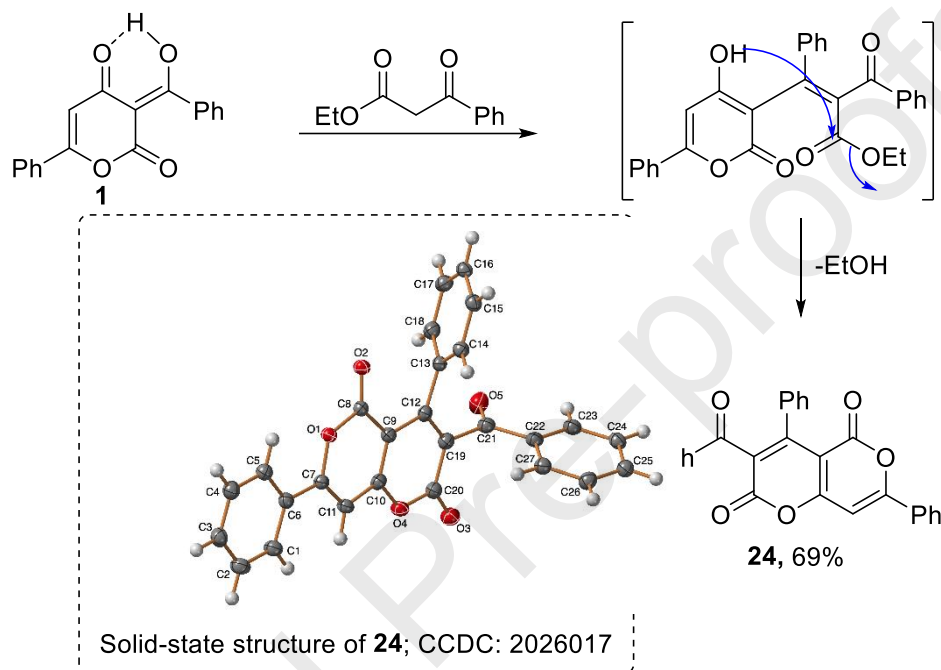
**Scheme 4.** Reaction of compound **1** with diamines to produce the bis( $\beta$ -enamino-pyran-2,4-diones) **18** and **19**.

In another reaction, (*E*)-3-(hydroxy(phenyl)methylene)-6-phenyl-2*H*-pyran-2,4(3*H*)-dione (**1**) was reacted with the amino-acid methyl ester hydrochlorides of glycine,  $\beta$ -alanine, valine, and leucine in pyridine and stirring overnight to produce a good yields of the  $\beta$ -enamino-pyran-2,4-diones **20–23** (Scheme 5) of the relative amino-acid methyl esters.



**Scheme 5.** Reaction of the enol **1** with amino-acid methyl ester hydrochlorides.

Finally, microwave irradiation methodology was extended to convert (*E*)-3-(hydroxy(phenyl)methylene)-6-phenyl-2*H*-pyran-2,4(3*H*)-dione **1** to 3-benzoyl-4,7-diphenyl-2*H*,5*H*-pyrano[4,3-*b*]pyran-2,5-dione **24** via a reaction with ethyl benzoylacetate in acetic acid for 15 min. The final product was believed to proceed by condensation followed by a subsequent intramolecular cyclization (Scheme 6).



**Scheme 6.** Microwave-assisted condensation and intramolecular cyclization of 3-benzoyl-4,7-diphenyl-2*H*,5*H*-pyrano[4,3-*b*]pyran-2,5-dione (**24**).

## Conclusion

In conclusion, the method reported here is a simple and green microwave-assisted strategy for the synthesis of  $\beta$ -substituted vinyl-pyran-2,4-dione from ethyl benzoylacetate. A direct regioselective  $\beta$ -amination of the exocyclic enol-pyran-2,4-dione produced excellent yields of  $\beta$ -enamino-pyran-2,4-diones. Further cyclization of pyran-2,4-dione **1** with another molecule of ethyl benzoylacetate in microwave produced fused pyrano[4,3-*b*]pyran-2,5-dione system **24**. Importantly, these transformations can produce highly functionalized, substituted,

exocyclic pyran-2,4-diones and  $\beta$ -enamino-pyran-2,4-diones from low-cost commercial substrates.

## Supporting Information

The experimental procedure for the synthesis of the target compounds along with copies of  $^1\text{H}$  and  $^{13}\text{C}$  NMR spectra and x-ray data are supplied as Supporting Information.

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### Conflicts of Interest

“The authors declare no conflict of interest.”

### Highlights

- A novel synthetic approach to pyran-2,4-dione scaffold.
- Microwave-assisted dimerization, and cyclization to afford pyran-2,4-dione.
- Expeditious regioselective conversion  $\beta$ -diketone systems into  $\beta$ -enamino-pyran-2,4-diones.
- Cyclization of 3-( $\beta$ -substituted vinyl)-6-phenyl-pyran-2,4-dione into 3-benzoyl-4,7-diphenyl-2*H*,5*H*-pyrano[4,3-*b*]pyran-2,5-dione.