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A novel synthetic approach to pyran-2,4-dione scaffold production: microwave-assisted dimerization, cyclization, and expeditious regioselective conversion into β -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 β -diketone systems into β -enaminones were achieved using 18 primary amines and four amino acid esters. Microwave-assisted further cyclization of 3-(β -

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; β -enaminones; intramolecular cyclization

Introduction

Pyrone nucleus is extensively found in nature.¹⁻³ Molecules containing pyrone ring exhibit a wide range of pharmaceutical properties such as cytotoxic,⁴ antitumor,^{5,6} and antimicrobial activity.⁷ 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.⁸⁻¹¹ Furthermore, pyrone compounds have been reported to have pharmacological usefulness as selective COX-2 inhibitors^{12,13} and HIV protease inhibitors.¹⁴⁻¹⁶ 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.¹⁷ Many other compounds in nature have the structural feature of a pyrone scaffold; indeed, Schäberle¹⁸ 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 PdCl₂(PPh₃)₂ and CuI,^{19,20} cyclo-isomerization of 3-ethynyl-indole-2-carboxylic acid in the presence of gold(III) chloride,²¹ allenyl propiolates and terminal

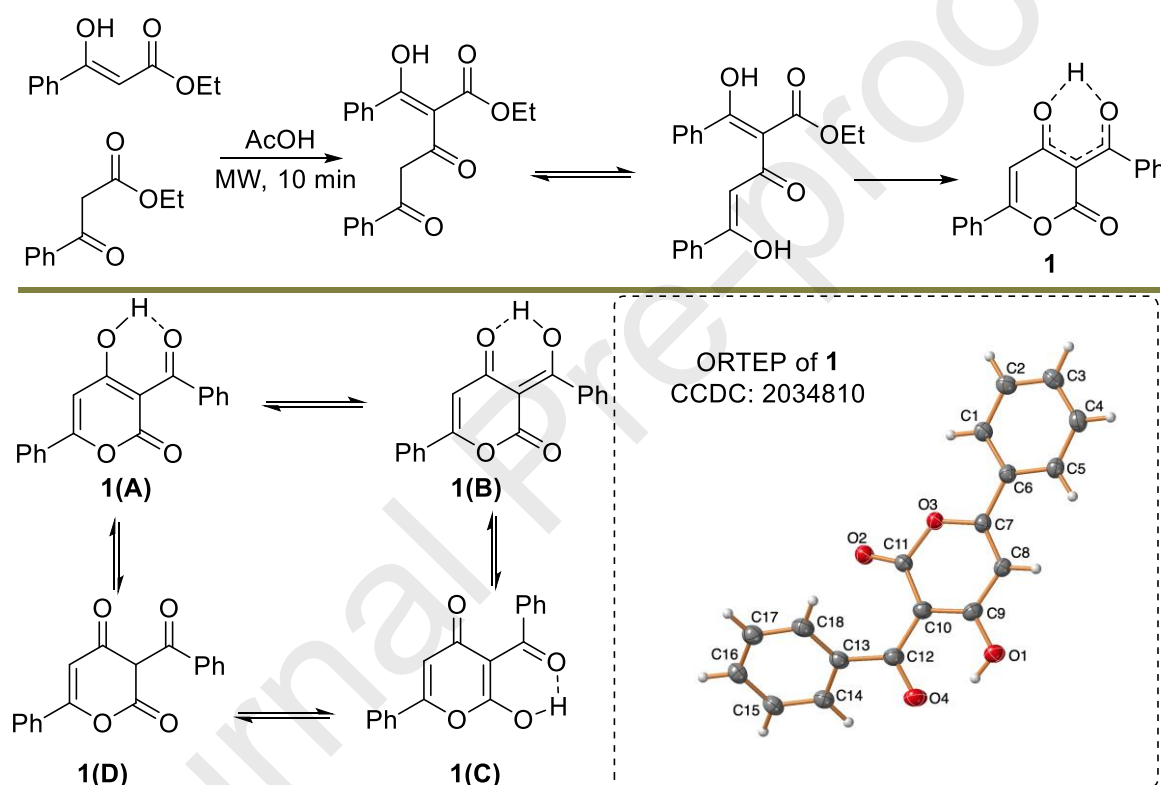
alkynes catalyzed using gold(I) catalyst,^{22,23} annulation of alkynes by acrylic acid promoted by ruthenium(II),²⁴ Baylis-Hillman adducts,²⁵ 1,2-allenyl ketones and electron-withdrawing group substituted acetates using a base catalyst,^{26,27} and aryl-4,4,4-trifluorobutane-1,3-diones, PCl_5 , and sodium diethyl malonate.²⁸

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,²⁹⁻³⁷ 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 β -enamino-pyran-2,4-diones. Importantly, this method could be applied to any β -ketoester for the production of biologically and photochemically active motifs.

Results and Discussion

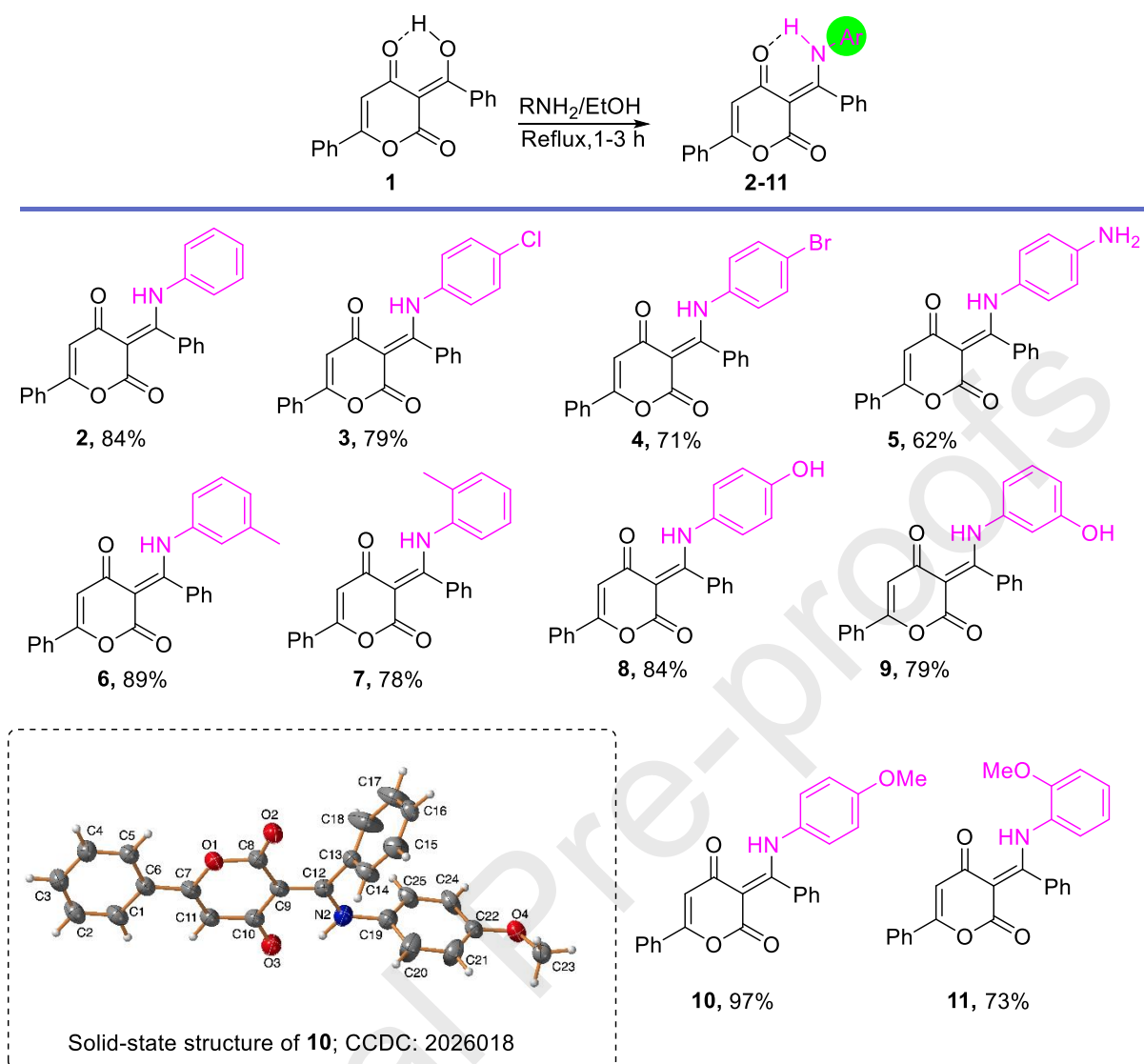
Microwave-assisted synthesis of a substituted pyran-2,4-dione **1** in one step from ethyl benzoyl acetate is shown in Scheme 1. When the reaction was conducted under microwave irradiation without a catalyst, the product was obtained with a chemical yield of <5%; when acetic acid was used as a promoter, 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_3 (nonpolar solvent) and $\text{DMSO}-d_6$ (polar solvent), which revealed that only two tautomeric transformations were present and the structure was highly dependent on solvent polarity. In CDCl_3 , the ^1H 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 ^{13}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 $\text{DMSO}-d_6$, the ^1H 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}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).



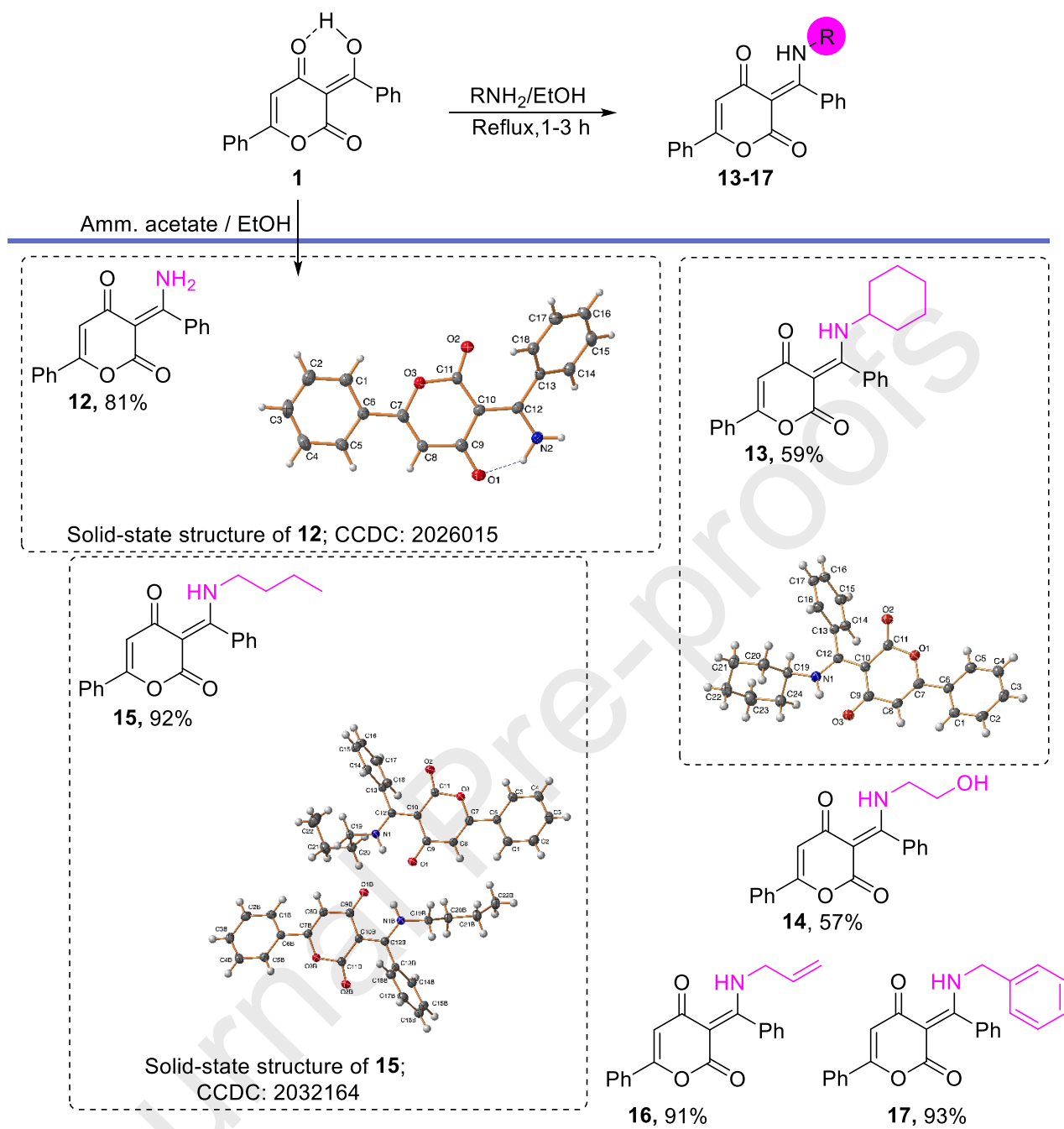
Scheme 1: Synthesis and possible tautomeric isomers of substituted pyran-2,4-dione **1**.

β -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 β -enamino-pyran-2,4-diones **2–11** (Scheme 2).



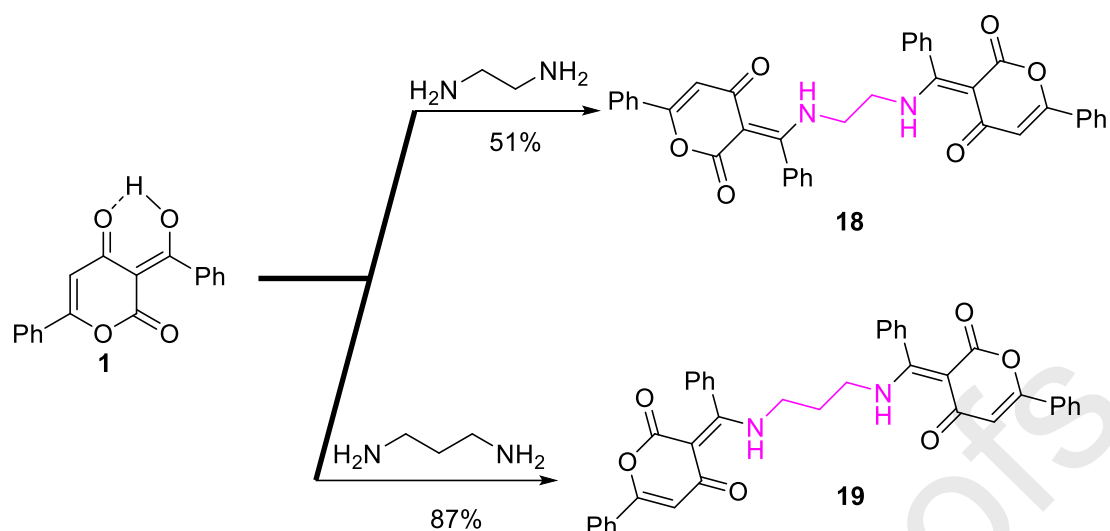
Scheme 2: Reaction of compound **1** with aromatic amines to give the β -enamino-pyran-2,4-diones **2–11**.

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 β -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** (C4-O ... NH).



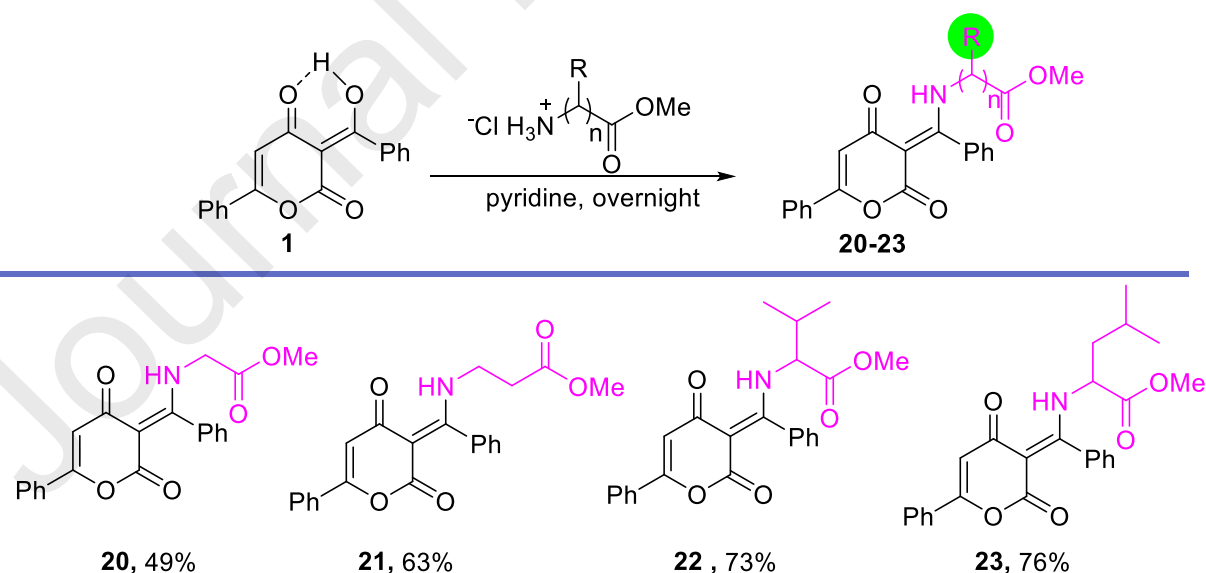
Scheme 3. Reaction of compound **1** with ammonium acetate and aliphatic amines to give β -enaminopyran-2,4-diones **12–17**.

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



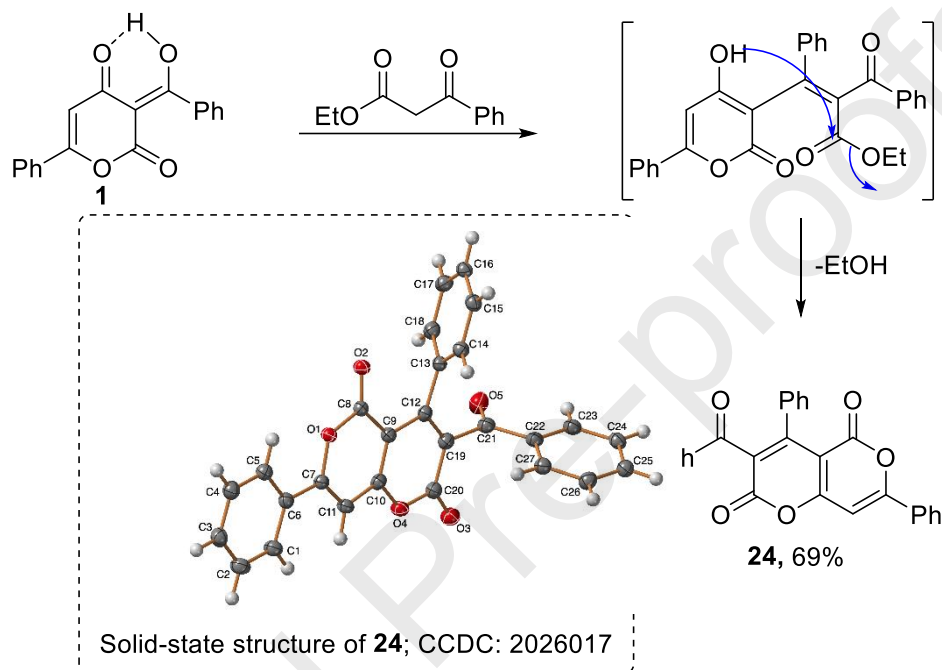
Scheme 4. Reaction of compound **1** with diamines to produce the bis(β -enamino-pyran-2,4-diones) **18** and **19**.

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, β -alanine, valine, and leucine in pyridine and stirring overnight to produce a good yields of the β -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 β -substituted vinyl-pyran-2,4-dione from ethyl benzoylacetate. A direct regioselective β -amination of the exocyclic enol-pyran-2,4-dione produced excellent yields of β -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 β -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 ^1H and ^{13}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 β -diketone systems into β -enamino-pyran-2,4-diones.
- Cyclization of 3-(β -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.