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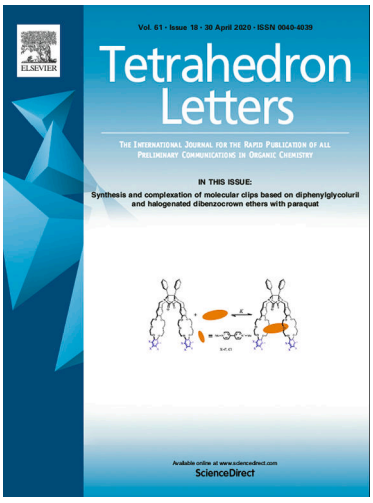

A novel synthetic approach to pyran-2,4-dione scaffold production: microwave-assisted dimerization, cyclization, and expeditious regioselective conversion into β-enamino-pyran-2,4-diones

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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*-

substitutedvinyl)-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, Schäberle[18] 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 $PdCl_2(PPh_3)_2$ 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

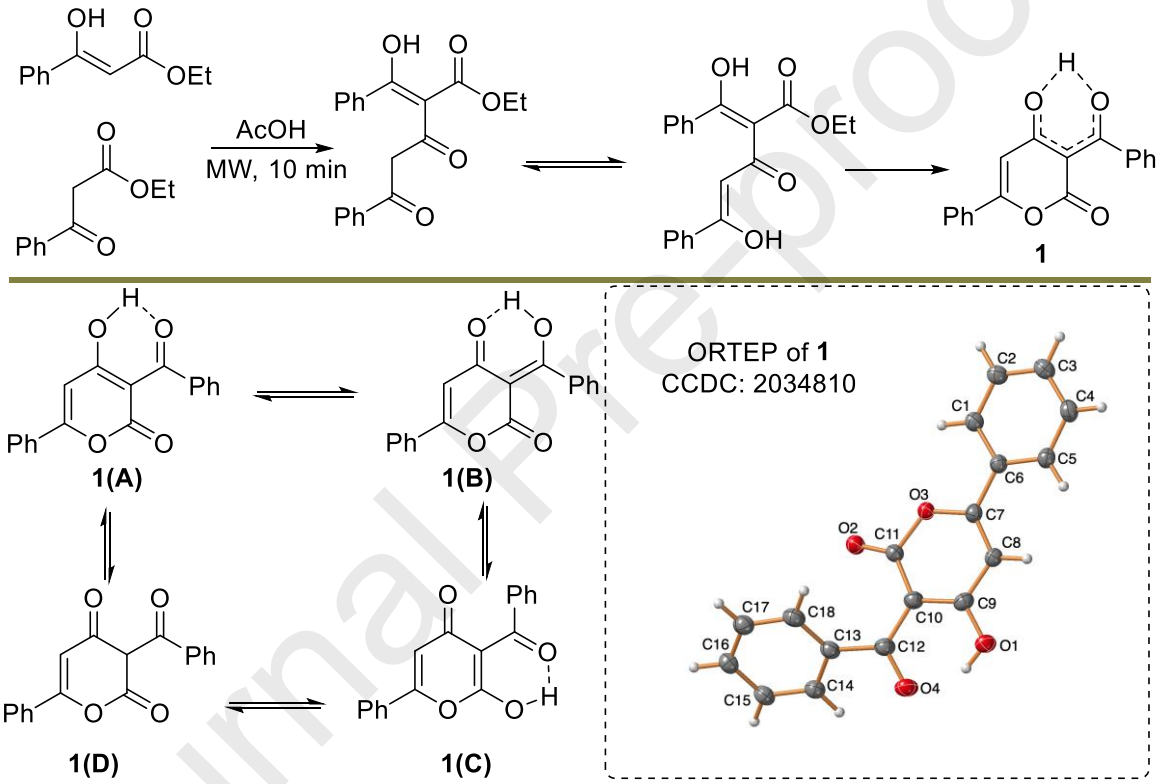
alkynes catalyzed using gold(I) catalyst,[22,23] annulation of alkynes by acrylic acid promoted by ruthenium(II),[24] Baylis-Hillman adducts,[25] 1,2-allenyl ketones and electron-withdrawing group substituted acetates using a base catalyst,[26,27] and aryl-4,4,4-trifluorobutane-1,3-diones, PCl_5, and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

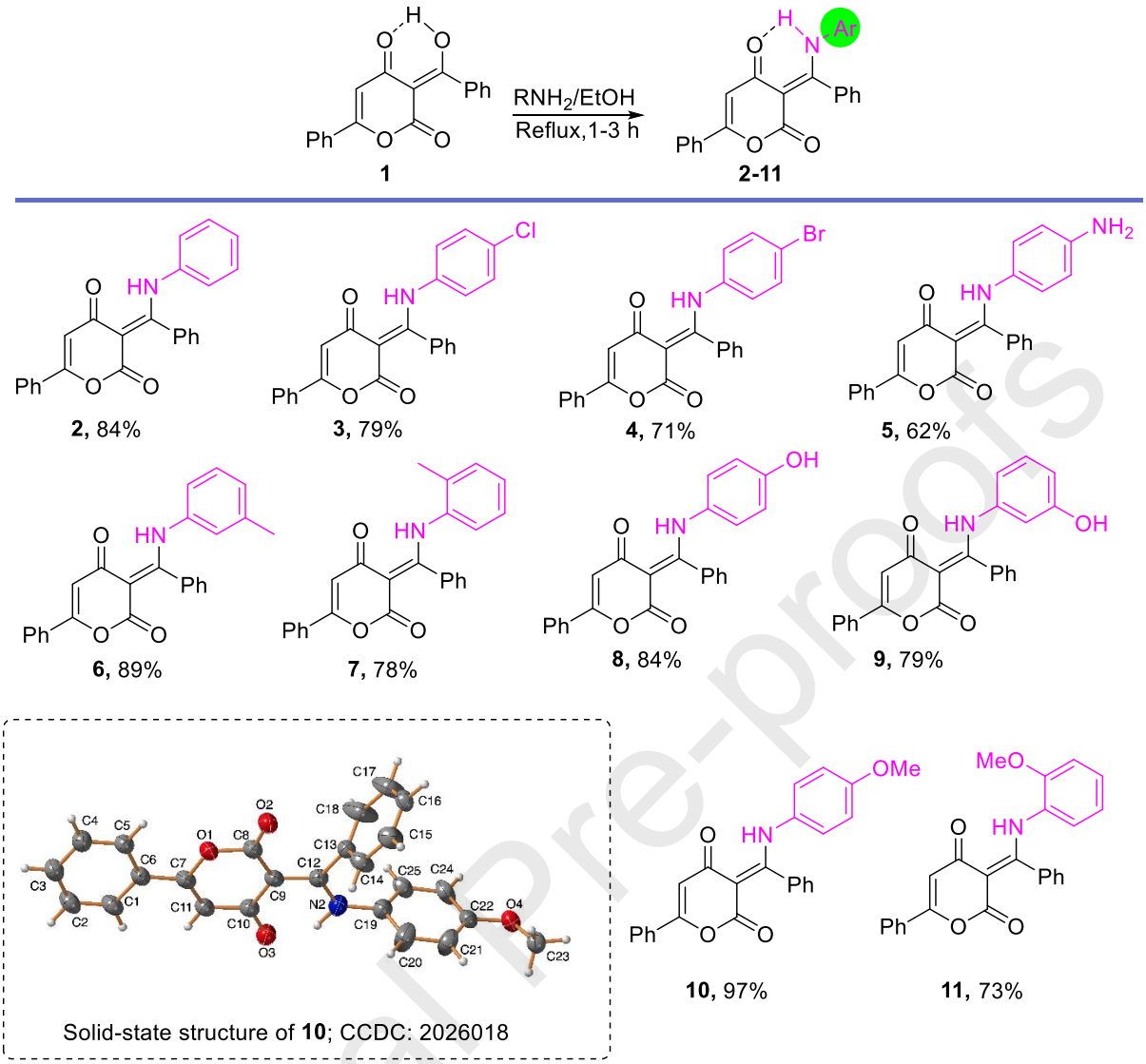
Microwave-assisted synthesis of a substituted pyran-2,4-dione **1** in one step from ethyl benzoyl acetate is shown in Scheme 1. When the reaction was conducted under microwave irradiation without a catalyst, the product was obtained with a chemical yield of <5%; when acetic acid was used as a promoter, 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 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 ^{1}H NMR of **1** showed the hydroxy1 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 DMSO-d_6, the ^{1}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}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).



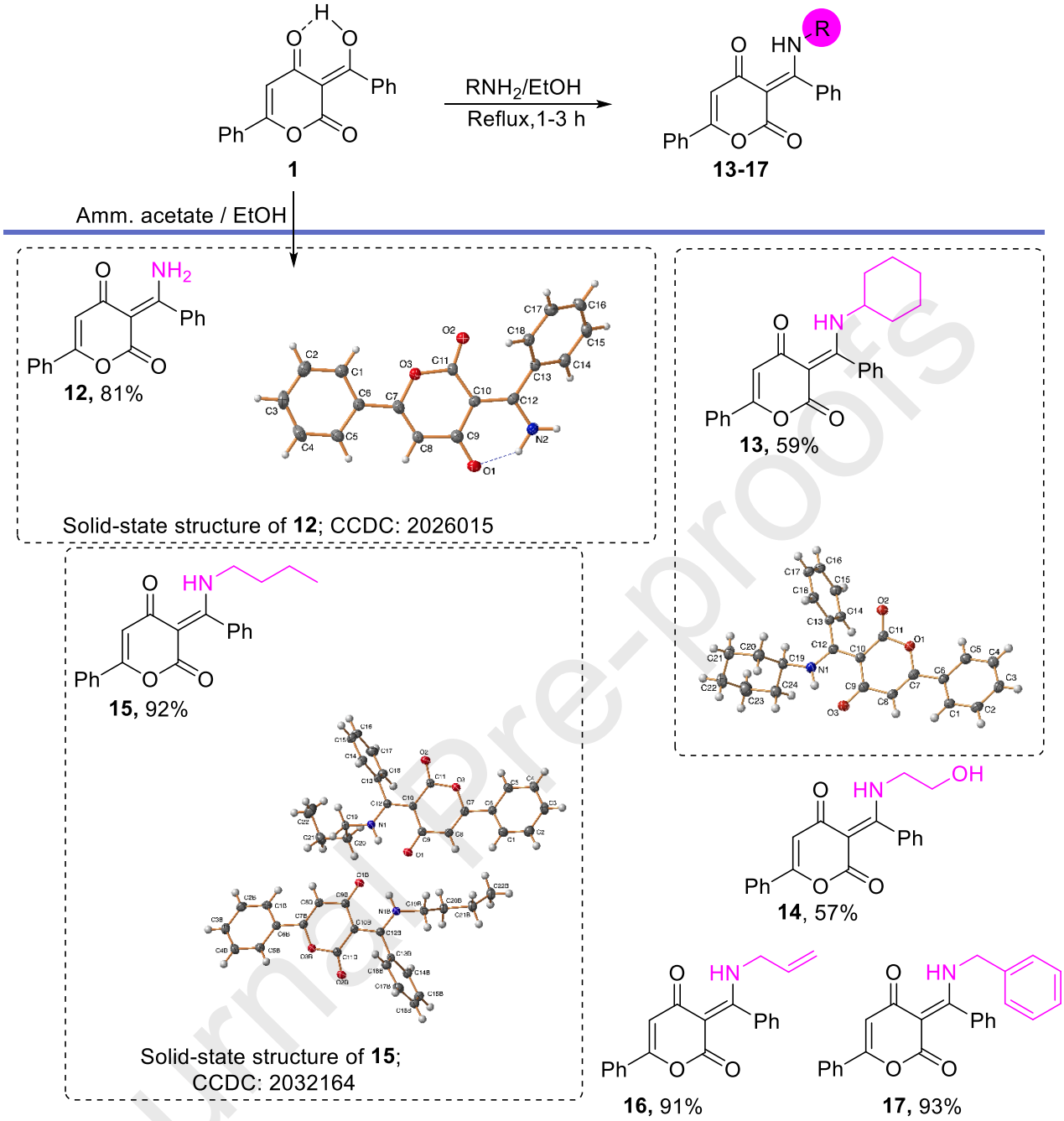
Scheme 1: Synthesis and possible tautomeric isomers of substituted pyran-2,4-dione **1**.

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).



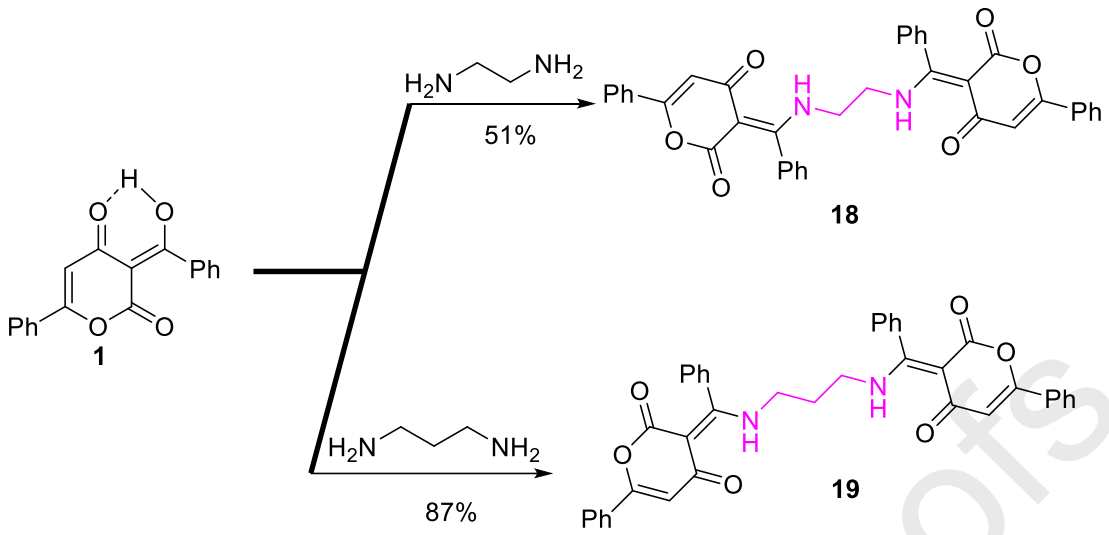
Scheme 2: Reaction of compound **1** with aromatic amines to give the *β*-enamino-pyran-2,4-diones **2–11**.

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).



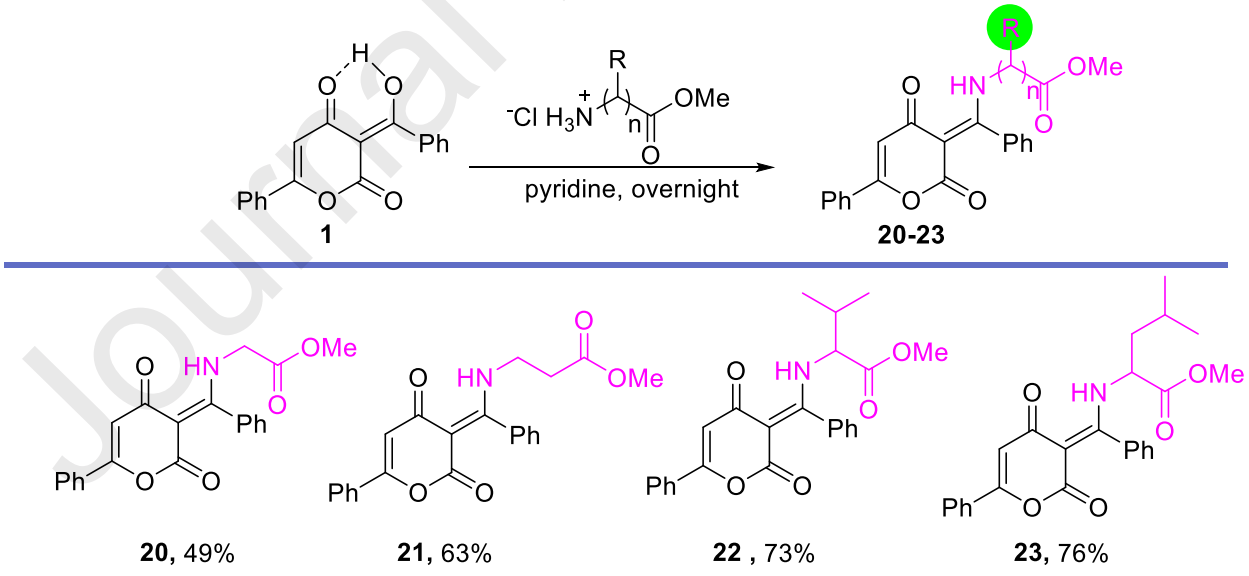
Scheme 3. Reaction of compound **1** with ammonium acetate and aliphatic amines to give *β*-enaminopyran-2,4-diones **12**–**17**.

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).



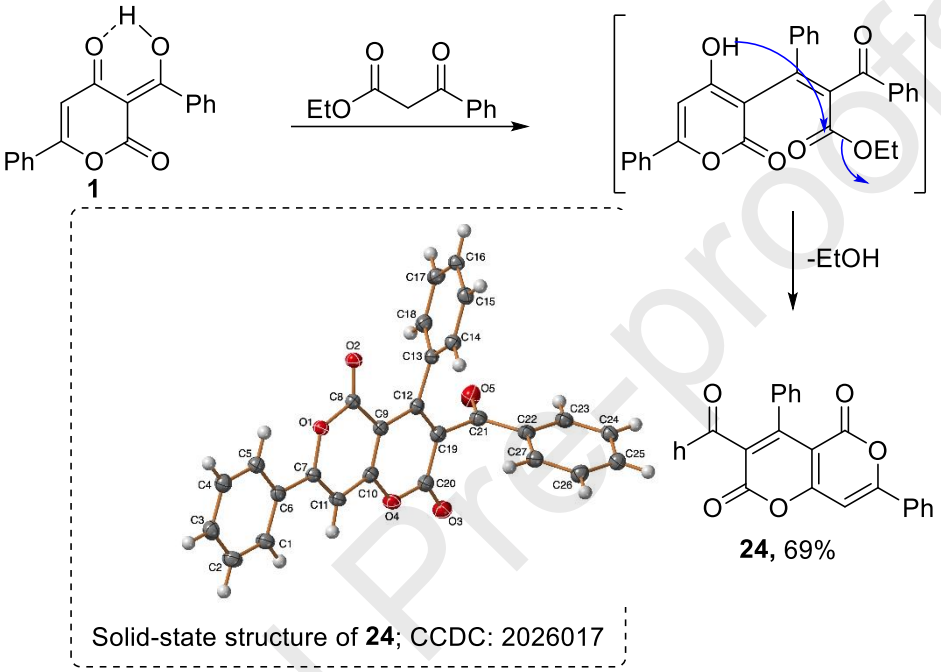
Scheme 4. Reaction of compound **1** with diamines to produce the bis(*β*-enamino-pyran-2,4-diones) **18** and **19**.

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*-substitutedvinyl-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 ^{1}H 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*-substitutedvinyl)-6-phenyl-pyran-2,4-dione into 3-benzoyl-4,7-diphenyl-2*H*,5*H*-pyrano[4,3-*b*]pyran-2,5-dione.