Tetrahedron Letters 75 (2021) 153215

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

Multicomponent synthesis of novel 3-benzoyl-4*h*-benzo[*g*]chromene-5,10-dione derivatives

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ARTICLE INFO

Article history:
Received 8 April 2021
Revised 19 May 2021
Accepted 25 May 2021
Available online 31 May 2021

Keywords:
-Benzoyl-4*H*-benzo[*g*]chromene-5
10-dione
Multicomponent domino reaction
2-Hydroxy-1
4-naphthoquinone

ABSTRACT

An efficient method was developed to prepare a series of novel 3-benzoyl-4*H*-benzo[*g*]chromene-5,10-dione derivatives from 2-hydroxy-1,4-naphthoquinone, aromatic aldehydes and arylenaminones in glacial acetic acid under microwave irradiation. This transformation presumably occurs *via* a Knoevenagel condensation – dehydration – Michael addition – *O*-cyclization – proton transfer - elimination - deprotonation – double bond isomerization sequence of reactions.

Introduction

Pyranonaphthoquinone is an important scaffold, which is found in various natural and unnatural products that possess pronounced biological activities, including antimicrobial, antiparasitic, antiviral and anticancer properties [1–2]. α-Lapachone and *β*-lapachone isolated from the bark of *Tabebuia* sp. [3], rhinacanthin O from the Asian medicinal plant *Rhinocanthus nasutus* [4], pyranokunthone B from a marine actinomycete [5], and frenolicin [6] (Fig. 1) are examples of this class of compounds. Due to their diversity of chemical structures and biological activities, the synthesis of 1,4-pyranonaphthoquinone derivatives has received extensive attention. Considerable efforts have been paid to the development of synthetic approaches towards 2-amino-3-cyano-4*H*-pyrano-[2,3-*b*]-naphthoquinone analogues (Fig. 1) with promising anticancer and antiparasitic activities [7–8]. Recently, we reported the synthesis of 1,3-disubstituted-3,4-dehydropyranonaphthoquinones (Fig. 1.) and their epoxy analogues, which were found to exhibit interesting cytotoxic inhibitory properties [9–11].

Literature methods for the synthesis of pyranonaphthoquinone analogues are mostly based on multi-component reactions (MCRs) in the presence of catalysts under conventional thermal heating conditions [11–15]. Microwave irradiation (MW) has been demonstrated as a useful and efficient method for the preparation of heterocyclic compounds [16–17], in particular, naphthoquinone derivatives [18–19]. With regard to the potential bioactivities of pyranonaphthoquinones and as a part of our ongoing project on the synthesis of naphthoquinone derivatives [2,18–22] herein we report an efficient synthetic route towards novel 3-benzoyl-4*H*-benzo[*g*]chromene-5,10-diones *via* the MW-assisted three-component reactions of 2-hydroxy-1,4-naphthoquinone, aromatic aldehydes and arylenaminones.

Results and discussion

Initially, the reaction of 2-hydroxy-1,4-naphthoquinone **1**, 4-methylbenzaldehyde **2a**, and enaminone **3a** (formed by the condensation of *N*,*N*-dimethyformamide dimethyl acetal with acetophenone in toluene at reflux for 1 h [23]) was chosen for developing the optimal reaction conditions. This reaction was carried out under MW irradiation in different solvents (CH_3CN, *t*-BuOH, EtOH, dioxane, toluene, AcOH) at a range of temperatures (80–120 °C) in the presence or absence of catalyst. As shown in Table 1, the reaction did not proceed without a catalyst (Entry 1). A number of procedures have been reported for the synthesis of 4*H*-benzo[*g*]chromene analogues, in which bases such as

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https://doi.org/10.1016/j.tetlet.2021.153215
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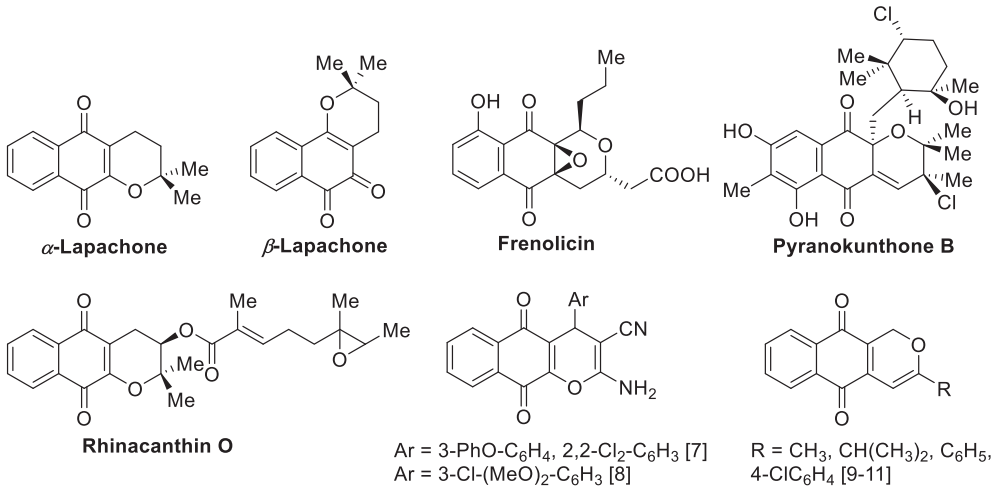
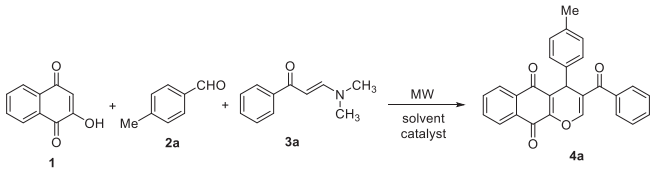


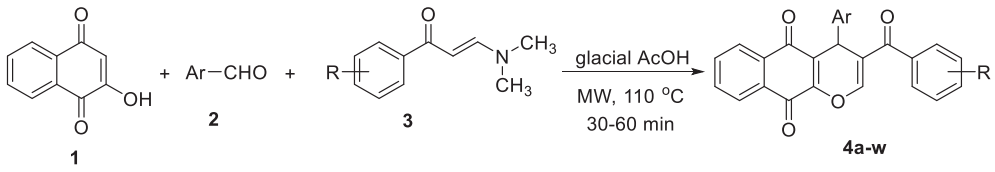
Fig. 1. Selected natural and synthetic bioactive pyranonaphthoquinones.

Table 1
Optimization of the reaction conditions.



Entry	Solvent	Catalyst	T (°C)	Yields **4a** (%)[a,b]
1	EtOH	–	Reflux	0
2	EtOH	DMAP (20 mol%)	Reflux	0
3	EtOH	Et_3N (20 mol%)	Reflux	0
4	EtOH	AcOH (20 mol%)	Reflux	trace
5	*t*-BuOH	AcOH (20 mol%)	Reflux	25
6	CH_3CN	AcOH (20 mol%)	Reflux	31
7	Dioxane	AcOH (20 mol%)	Reflux	38
8	Toluene	AcOH (20 mol%)	Reflux	41
9	AcOH	–	100	59
10	AcOH	–	110	84
11	AcOH	–	120	67
12	AcOH	–	110	38[c]

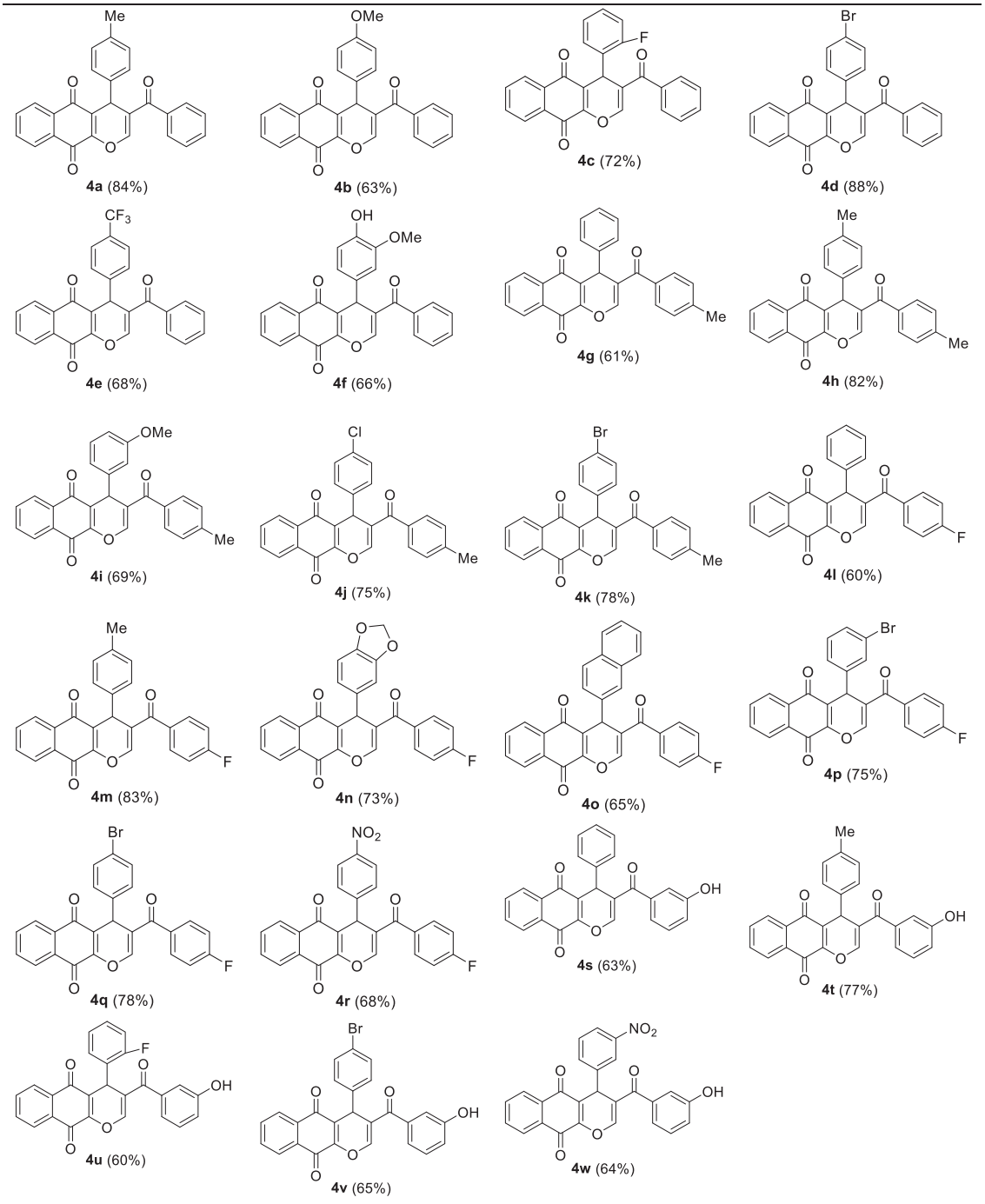
[a] Reagents and conditions: **1** (0.5 mmol), **2a** (0.5 mmol), **3** (0.5 mmol), solvent (10 mL), MW, 40 min.
[b] Isolated yields.
[c] Oil bath, 1 h.



Scheme 1. Synthesis of 3-benzoyl-4*H*-benzo[*g*]chromene-5,10-diones **4a-w**.

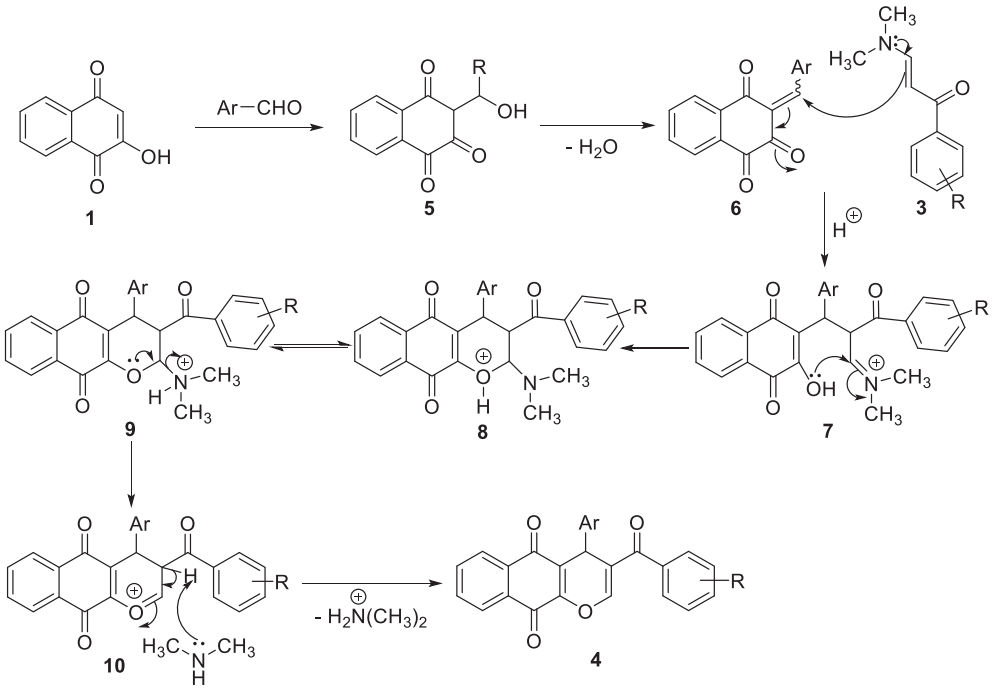
triethylbenzylammonium chloride [24], triethylamine [7], triethanolamine [13], potassium fluoride [25], urea [26], NH_4OAc [27], DBU [12], or ionic liquids [28] were employed as catalysts. However, the reaction between 2-hydroxy-1,4-naphthoquinone **1**, 4-methylbenzaldehyde **2a** and enaminone **3a** in ethanol at reflux using 20 mol% DMAP or Et_3N as a base led to the formation of compound 3,3′-(4-methylphenyl)*bis*(2-hydroxynaphthalene-1,4-dione) [29] instead of the desired compound **4a** (Entries 2–3). Replacing DMAP with glacial acetic acid gave the desired 3-benzoyl-4-(*p*-tolyl)-4*H*-benzo[*g*]chromene-5,10-dione **4a** in 25–41% isolated yield (Entries 5–8). Interestingly, the use of glacial acetic acid as a solvent gave higher yields than other organic solvents. The reaction yield increased significantly when the temperature was 100 °C (Entry 9), and the yield was highest (84%) at 110 °C (Entry 10). Further increasing of the reaction temperature led to a decreased yield of compound **4a** due to the formation of a complex product mixture (Entry 11). We also examined the reaction under conventional thermal heating conditions and compound **4a** was obtained in 38% yield (Entry 12). Thus, the optimal reaction conditions were confirmed as heating at 110 °C in glacial acetic acid under microwave irradiation for 40 min (Entry 10).

Table 2
Substrate scope and yields of products **4a-w**.



Using the optimized reaction conditions, a series of 3-benzoyl-4*H*-benzo[*g*]chromene-5,10-dione derivatives **4a-w** with different substitutions on the aryl groups were synthesized (Scheme 1, Table 2). This methodology can be applied to aromatic aldehydes and arylenaminones with either electron-withdrawing groups (such as halogen, nitro, trifluoromethyl) or electron-donating groups (including methyl, methoxy) with moderate to high yields. These results indicated that the electronic nature of the substituents has no significant effect on the reaction outcome. The structures of all synthesized compounds **4a–w** were elucidated using HRMS, ^{1}H, ^{13}C, and 2D NMR spectroscopic techniques (see ESI).

A plausible reaction mechanism was proposed for the formation of 3-benzoyl-4*H*-benzo[*g*]chromene-5,10-diones **4** (Scheme 2). In the initial step, 3-[1-aryl-methylidene]-1,2,3,4-tetrahydro-1,2,4-naphthalenetriones **6** were obtained *via* the Knoevenagel condensation of 2-hydroxy-1,4-naphthoquinone **1** with aldehydes **2** followed by dehydration. Michael addition of 1,2,4-naphthalenetriones **6** with arylenaminones **3** gave intermediates **7**, which were subjected to intramolecular cyclization to furnish intermediates



Scheme 2. Proposed reaction mechanism for the preparation of 3-benzoyl-4*H*-benzo[*g*]chromene-5,10-diones **4**.

8. The latter underwent proton transfer and elimination of the amine to give oxoniums **10**. Finally, deprotonation and double bond isomerization of oxoniums **10** afforded the final compounds **4**.

Conclusion

In summary, the efficient and straightforward approach for the synthesis of novel 3-benzoyl-4*H*-benzo[*g*]chromene-5,10-diones was developed *via* the three-component domino reaction of 2-hydroxy-1,4-naphthoquinone, aromatic aldehydes, and arylenaminones in glacial acetic acid under microwave irradiation. This reaction shows extensive functional group tolerance and high regioselectivity. Further studies for these 3-benzoyl-4*H*-benzo[*g*]chromene-5,10-dione derivatives focusing on medicinal chemistry are in progress and shall be reported in due course.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgements

The authors are indebted to Vietnamese National Foundation for Science and Technology Development (NAFOSTED) Grant number: 104.01-2020.09 for financial support.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.tetlet.2021.153215.

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