A New Approach to the Synthesis of Benzo[b]naphtho[2,3-b]furan-6,11-diones and 2-Benzyl-3-hydroxynaphthalene-1,4-diones

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Abstract Here we describe modified syntheses of o-acetylbenzoic acids and o-acetylphenylacetic acids by Heck palladium-catalysed arylation of n-butyl vinyl ether with o-iodobenzoic acids or with o-iodophenylacetic acids, respectively. General syntheses of benzo[b]naphtho[2,3-b]furan-6,11-diones from o-acetylbenzoic acids and 2-benzyl-3-hydroxynaphthalene-1,4-diones from o-acetylphenylacetic acids are also reported.

Key words fused-ring systems, Heck reaction, quinones, palladium, heterocycles, halides, furans

The synthesis of naphthoquinones is of great significance because of the widespread occurrence of the 1,4-naphthoquinone nucleus in numerous natural and synthetic compounds of biological and industrial interest.1–8 Specifically, considerable attention has been devoted to 2-hydroxy-1,4-naphthoquinones (I) and 2-hydroxy-3-phenyl-1,4-naphthoquinones (II) (Figure 1), on account of their biological properties, their industrial applications, and their potential as intermediates in the synthesis of oxygenated and nitrogenated heterocyclic quinones, including 5H-benzo[b]carbazole-6,11-diones (benzocarbazolequinones)9,10 benzo[b]naphtho[2,3-b]furan-6,11-diones (benzofuranonaphthoquinones)11,12 and 5H-dibenzo[c,g]chromene-5,7,12-triones (benzopyronaphtho-quinones).13,14 Benzo-carbazolequinones (III, Figure 1) became important synthetic targets once their antineoplastic activity was established.15–18 On the other hand, a representative example of benzofuronaphthoquinones is compound IV (Figure 1) and a representative example of benzopyronaphthoquinones V (Figure 1) is the quinonoid anticoccidial antibiotic WS-5995-A.19–21 The antineoplastic activity displayed by compounds III, IV and V has been related to the well-known antitumor properties of ellipticine (Figure 1).15–18 The antineoplastic activity of these compounds has been attributed to their ring systems, which contain an embedded 2-phenylnaphthalene-like structure in a planar conformation, which facilitates its intercalation between adjacent pairs of DNA bases, thereby interfering with DNA replication and transcription.22 In addition, the quinone moiety present in the ring skeleton explains the cytotoxic properties of these compounds and enhances the strength of intercalative binding to DNA through the formation of charge-transfer interactions with the electron-rich DNA bases.23–25

From a chemical point of view, particular interest has been devoted to 2-hydroxy-3-phenyl-1,4-naphthoquinones (VI, m = 0, Scheme 1), because they proved to be convenient
precursors for the synthesis of naphthoquinone derivatives VII, VIII and IX, and related compounds.13–18 Accordingly, a range of methods for the preparation of these powerful scaffolds have been developed, including our previously reported general syntheses from o-acetylphenylacetic acids XI (route a)26 and from o-acetylbenzoic acids XII (route b).27 Route a was found to be of limited scope because it only allowed benzocarbazolequinones III to be prepared. These tetracyclic naphthoquinones were alternatively obtained through route b, by a sequence involving the condensation of isochroman-1,4-diones XII with p-nitrobenzaldehydes, followed by rearrangement of the resulting 3-benzyldieneisochroman-1,4-diones XIII (X = NO₂) to the corresponding naphthoquinones (m = 0) and subsequent generation of the nitrogen ring.28,29 These two general approaches to benzocarbazolequinones allowed the limitations of previous syntheses of these targets to be overcome.10,11,10–12 As a continuation of this work, herein we report studies on the synthesis of benzofurannaphthoquinones VII and benzopyronaphthoquinones VIII from o-acetylbenzoic acids XI, via 3-hydroxy-2-phenylnaphthoquinones VI (Scheme 1). The synthesis of 2-benzyl-3-hydroxynaphthalene-1,4-diones (VI, m = 1) and o-acetylphenylacetic acids X is also described.

Our previous, general and straightforward synthesis o-acetylbenzoic acids involved a Heck coupling reaction between electron-rich n-butyl vinyl ether (BVE) and 2-bromo-iodobenzoates 1a–b, using the conditions described by Cabri et al.33 (Scheme 2).27 Firstly, a Heck reaction between BVE and methyl o-bromobenzoate (1a) provided the expected α-arylation product 2a only. This regiochemical outcome was attributed to the presence of TiOAc and a chelating phosphine in the reaction medium. The aryl vinyl ether 2a was immediately reacted with 10% aqueous HCl for 1 hour at room temperature, to afford ketoester 3a in 90% yield. On the other hand, the coupling reaction between the electron-rich methyl 2-bromo-4,5-dimethoxybenzoate dimethoxy derivative 1b and BVE, under the same conditions, gave ketoester 3b in lower yield, via aryl vinyl ether 2b.

Surprisingly, the same regioselectivity was observed when the coupling reaction of 1a and 1b with BVE was performed under classical Heck conditions, which required longer reaction times, but avoided the use of toxic thallium salts and expensive phosphines. The uncommonly high α-regioselectivity achieved under these classical conditions may be the result of an interaction between the o-carbomethoxy group of aryl halides 1 and the palladium complex involved in the Heck coupling.

Scheme 1 Retrosynthetic plan towards benzofurannaphthoquinones VII, benzopyronaphthoquinones VIII and 2-hydroxy-3-benzyl-1,4-naphthoquinones VI (m = 1)

Scheme 2 Heck coupling of methyl o-iodobenzoates 1c,d and methyl o-iodophenylacetates 1g,h and with BVE: synthesis of methyl o-acetylbenzoates 3a,b and methyl o-acetylphenylacetates 3c,d
Table 1  Formation of 3a,b and 3c,d

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate</th>
<th>Catalyst a</th>
<th>Solvent</th>
<th>Time</th>
<th>Product</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1c</td>
<td>Pd(OAc)2/Ph3P (7.5 mol%)</td>
<td>CH3CN</td>
<td>4 h</td>
<td>3a</td>
<td>90</td>
</tr>
<tr>
<td>2</td>
<td>1d</td>
<td>Pd(OAc)2/Ph3P (10 mol%)</td>
<td>CH3CN</td>
<td>16 h</td>
<td>3b</td>
<td>84</td>
</tr>
<tr>
<td>3</td>
<td>1g</td>
<td>Pd(OAc)2/Ph3P (2.5 mol%)</td>
<td>CH3CN</td>
<td>16 h</td>
<td>3c</td>
<td>68</td>
</tr>
<tr>
<td>4</td>
<td>1h</td>
<td>Pd(OAc)2/Ph3P (2.5 mol%)</td>
<td>CH3CN</td>
<td>1 week</td>
<td>3d</td>
<td>60</td>
</tr>
</tbody>
</table>

a All the experiments were carried out at 100 °C.
b See ref.23
c See ref.22

On the other hand, similar regioselectivities and yields were previously achieved for the coupling of o-bromophenylacetates 1e and 1f with BVE, both under the Cabri and classical conditions. o-Acetylphenylacetates 3c and 3d were obtained respectively, via the corresponding enol ethers 2c and 2d.

The similar reaction of BVE with methyl iodobenzoates 1c–d, and with methyl iodosphenylacetates 1g–h was then studied under these classical conditions, in order to assess the influence of the halogen on this Heck coupling reaction. A selective α-arylation was again observed, similar reaction times were required, and similar yields were achieved (Table 1, entries 1, 2 and 3, 4).

A tentative explanation for the role played by the carboxymethoxy group of both types of substrates (1a–d or 1e–h) in the Heck reaction is depicted in Scheme 3. The insertion of Pd(0) into the carbon–halogen bond of the starting aryl halide would lead to complex B, via complex A. Dissociation of the halogen atom should give a cationic complex C, with internal association of the methoxycarbonyl group. Removal of a ligand L provided a free position that can be used to link a BVE unit. Next, the o-carboxymethoxy group could assist the insertion of Pd(0) through chelation (complex D). It has been proposed that chelation between the carboxyl group and the palladium atom could play an important role in promoting high regioselectivities. This may be supported by the fact that the regioselectivity in Heck reactions is dependent on the ionic versus neutral mechanisms proposed for this reaction, and that branched alkylides are mainly obtained from electron-rich alkylides, such as BVE, under ionic mechanism conditions. The predominance of electronic over steric effects is responsible for the regioselectivity observed in this reaction.

According to our synthetic plan, methyl o-acetylenbenzoate 3a was hydrolysed, by refluxing a solution of this ketoster and 20% aqueous H2SO4 under reflux for 2 h. This afforded the corresponding benzoic acid lactol 4a in 95% yield (Scheme 4), which readily provided bromomethyl lactol 5a in 96% yield, upon treatment with bromine in acetic acid/toluene. Finally, treatment of 5a with NaOAc in ethanol gave isochroman-1,4-dione 6a in 98% yield. Ketoester 3b was similarly and efficiently converted into isochroman-1,4-dione 6b via compounds 4b and 5b.

Reaction of isochroman-1,4-dione 6a with o-bromobenzaldehyde (7a) in ammonium acetate/acetic acid provided the new benzylideneisochroman-1,4-dione 8a in 81% yield. Treatment of 8a with sodium methoxide in methanol gave the known 3-bromophenyl-2-hydroxy-1,4-naphthoquinone 10a in 65% yield, through rearrangement of intermediate 9a. A similar condensation of isochroman-1,4-dione 6b with 2-bromo-4,5-dimethoxybenzaldehyde (7b), resulted in the formation of benzylideneisochroman-1,4-dione 8b, which rearranged readily to the expected 3-bromophenyl-2-hydroxy-1,4-naphthoquinone 10b. As quinones 10a and 10b were previously converted into benzofuranaphthoquinones 11a and 11b, respectively, the present approach constitutes a novel, general synthesis of these tetracyclic quinones, that overcomes limitations of our previous routes.

In an attempt to apply this synthetic strategy to the preparation of 5H-dibenzo[c,g]chromene-5,7,12-triones, when isochroman-1,4-dione 6a was reacted with o-methoxycarbonylbenzaldehyde, under the same conditions as for 8a, the expected benzylideneisochroman-1,4-dione 11 was obtained in 75% yield (Scheme 5). However, when this compound was reacted with sodium methoxide in methanol, the resulting compound was not the desired 3-methoxycarbonyl-2-hydroxy-5naphthoquinone 15 that should result from intermediate 12. Compound 14 was obtained in 70% yield. Probably, the favoured process is now the lactonisation of enol 13 of intermediate 12.
On the other hand, it is interesting to note that 3-alkyl-2-hydroxy-1,4-naphthoquinones have received considerably less attention than the corresponding 3-phenyl-2-hydroxy-1,4-naphthoquinones. Its most significant component is lapachol, a natural occurring phenolic compound isolated from the bark of the lapacho tree, which possess antitumor and antiparasitic properties.\textsuperscript{41–44} A family of compounds structurally related to lapachol are 3-benzyl-2-hydroxy-1,4-naphthoquinones, which were previously prepared by alkylation of 2-hydroxy-1,4-naphthoquinones with alkyl halides or by condensation with aldehydes. Thus, alkylation of lawsone with benzyl chlorides, under basic conditions, provided the 3-benzyl-2-hydroxy-1,4-naphthoquinones with a range of 38–43% yield.\textsuperscript{42,45} Thus 3-benzyl-2-hydroxy-1,4-naphthoquinones were alternatively obtained by condensation of lawsone with benzaldehydes, in a range of 75–85% yield.\textsuperscript{46,47}

As an additional contribution to this field, we report here the synthesis of 3-benzyl-2-hydroxy-1,4-naphthoquinones \textbf{20a}–\textbf{d} from \textit{o}-acetylphenylacetic acids \textbf{16a},\textit{b}, which were obtained by hydrolysis of the respective methyl \textit{o}-acetylphenylacetates \textbf{3c},\textit{d} (Scheme 6). Thus, condensation of \textit{o}-acetylphenylacetic acid (\textbf{16a}) with benzaldehyde (\textbf{7c}) provided the corresponding \(\alpha,\beta\)-unsaturated derivative \textbf{17a} (50%), which, upon catalytic hydrogenation, gave \textit{o}-phenylpropylphenylacetic acid \textbf{18a} in high yield (93%). Subsequent treatment of this ketoacid with \textit{t}-BuOK in \textit{t}-BuOH, resulted in the unreported benzylnaphthoquinone \textbf{20a} in 57% yield.

Reaction of \textbf{17a} with 3,4-dimethoxybenzaldehyde (\textbf{7d}) provided the unknown benzylnaphthoquinone \textbf{20b} in 72% yield.
yield, via compounds 17b and 18b. Reaction of o-acetylphenylacetic acid 16b with benzaldehyde gave the known 3-benzynamphothoquinone 20c, via compounds 17c and 18c. Finally, when 16b reacted with 3,4-dimethoxibenzaldehyde, the known benzynamnaphthoquinone 20d was obtained in 39% yield, via compounds 17d and 18d. This new synthesis of 3-benzyl-2-hydroxy-1,4-naphthoquinones proved to be more efficient than previously reported approaches.42,45

As a whole, we have revisited our general and efficient method for the preparation of methyl o-acetylbenzoates and methyl o-acetylphenylacetic acids. A slight modification consisting of the replacement of the starting o-bromobenzoic acid esters and the o-bromophenylacetic acid esters by the corresponding aryl iodides, allow these ketoacids to be obtained in similar yields and stereoselectivities.

In addition, a new synthetic application of the o-acetylbenzoic acid derived isochroman-1,4-diones, involving transformation into benzo[acridine-6,11,12(5H)-triones,46 and 11H-benzo[b]naphtho[2,3-e]pyran-6,11,12-triones.47 This structural relationship opens an opportunity for a new synthetic approach to these targets, and provides access to libraries of both practically unexplored kind of compounds, for chemical and biological studies.

Work is in progress aimed at the exploration of these promising chemical goals.

Melting points were determined with a Kofler Thermogerate apparatus and are uncorrected. Infrared spectra were recorded, unless otherwise specified, with a Bruker WM-250 apparatus using CDCl3 solutions containing tetramethylsilane (TMS) as internal standard.1H NMR splitting patterns are designated as singlet (s), doublet (d), triplet (t), quartet (q) or quintuplet (p). All first-order splitting patterns were assigned based on the appearance of the multiplet. Splitting patterns that could not be easily interpreted are designated as multiplet (m) or broad (br). Mass spectra were obtained with a HP 5988A mass spectrometer. Elemental analyses were performed with an EA 1108 CHNS Fisons instrument. Thin-layer chromatography (TLC) was performed using Merck GF-254 type 60 silica gel with anhydrous sodium sulphate. and dichloromethane/methanol or EtOAc/hexane mixtures as elu-
tes; the TLC spots were visualised with ultraviolet light or iodine va-
pour. Column chromatography was carried out using Merck type 9385 silica gel. Solutions of extracts in organic solvents were dried with anhydrous sodium sulphate.

Methyl 2-Acetylbenzoates and Methyl 2-(2-Acetylphenyl)acacetates

3. General Procedure

In a sealed tube fitted with Teflon screw cap, solutions of 1c, 1d, 1g and 1h (1.2 mmol), BVE (0.09 mmol), Pd(OAc)2 (7.5%), PPh3 (0.18 mmol) and Et3N (0.90 mL) in anhydrous and deoxygenated CH3CN (2.5 mL), were heated to 100 °C for 4 h. The respective reaction mixture was filtered through Celite, washed with CH2Cl2, and the filtrates were evaporated by rotary-evaporation. The crude products were purified by flash chromatography using EtOAc/hexane mixtures (9:1, 1:1, 0:1) as eluent. The compounds were recrystallized from suitable solvents, before analyses. In some cases, the products were obtained as mixtures of diastereomers, which were separated by column chromatography.

**Scheme 6** Synthesis of 3-benzyl-2-hydroxy-1,4-naphthoquinones 20a–d from o-acetylphenylacetic acids 16a,b
were washed with distilled water (25 mL). The organic phases were dried with anhydrous Na2SO4 and concentrated to dryness. The residues were dissolved in a mixture of 10% THF/H2O (40 mL, 1:1) and the solution was stirred for 2 h at r.t., the solvent was evaporated and the residues were extracted with CH2Cl2 (3 × 40 mL). The combined organic layers were washed with 10% aqueous NaHCO3, dried over anhydrous Na2SO4, and the solvent evaporated off. The residues were purified by column chromatography (EtOAc/hexane, 2:3, to give 3a–d.

Methyl 2-Acetylbenzoate (3a)00

Yield: 182 mg (90%); colourless oil.

IR: 1710 (C=O) cm–1.

1H NMR (CDCl3): 2.53 (s, 3 H, CH3), 3.70 (s, 3 H, OCH3), 4.00 (s, 3 H, CH2), 7.32–7.67 (m, 3 H, 3 × Ar-H), 7.77–7.95 (m, 2 H, 2 × Ar-H).

13C NMR (CDCl3, CD3OD): 28.5 (CH3), 40.2 (CH3), 51.8 (OCH3), 56.0 (OCH3), 103.2 (CH), 129.6 (CH), 132.0 (CH), 147.5 (Ar-OCH3), 172.2 (C=O), 199.1 (C=O).

MS: m/z (%) = 239 (21) [M+], 223 (100).

3-Bromomethyl-3-hydroxy-3-methyl-3-isobenzofuran-1-ones 4; General Procedure

Bromine (1.2 mL, 23.4 mmol) was added dropwise, under stirring, to solutions of lactols 3a and 3b (23.4 mmol) in a mixture of AcOH/toluene (1:2, 90 mL) heated at 60 °C. The reaction mixtures were stirred for 30 minutes, evaporated to dryness, and the residues were crystallised from CHCl3 to afford 4a and 4b, respectively.

Methyl 2-(2-Acetylphenyl)acetate (3c)

Yield: 186 mg (90%); colourless oil.

IR: 1725 (C=O), 1695 (C=O) cm–1.

1H NMR (CDCl3): 3.84 (s, 2 H, CH2), 3.93 (s, 3 H, OCH3), 4.00 (s, 3 H, CH2), 5.34 (br s, 1 H, OH), 7.07–7.20 (m, 2 H, 2 × Ar-H), 7.63–7.82 (m, 2 H, 2 × Ar-H).

13C NMR (CDCl3): 28.5 (CH3), 56.8 (OCH3), 56.9 (OCH3), 103.6 (CH), 125.8 (CH), 130.1 (CH), 147.5 (Ar-OCH3), 172.3 (C=O), 199.1 (C=O).

MS: m/z (%) = 245 (77) [M + H]+, 243 (80) [M + H]+, 227 (98), 225 (100).


3-Hydroxy-3-methyl-3H-isobenzofuran-1-one (5a)

Yield: 1.60 g (90%); white solid; mp 132–134 °C (CHCl3).

IR (NaCl): 3378 (OH), 1719 (C=O) cm–1.

1H NMR (CDCl3): 2.58 (s, 3 H, CH3), 3.85 (d, J = 4.4 Hz, 2 H, CH2), 5.34 (br s, 1 H, OH), 7.07–7.20 (m, 2 H, 2 × Ar-H), 7.63–7.82 (m, 2 H, 2 × Ar-H).

13C NMR (CDCl3, CD3OD): 29.7 (CH3), 52.4 (OCH3), 126.4 (CH), 128.8 (C), 147.5 (Ar-OCH3), 172.0 (C=O), 199.1 (C=O).

MS: m/z (%) = 211 (29) [M+H]+, 209 (100).

Anal. Calc for C9H7BrO3: C, 44.47; H, 2.90; Br, 32.87. Found: C, 44.15; H, 2.65; Br, 32.4.

3-Bromomethyl-3-hydroxy-3-methyl-3H-isobenzofuran-1-ones 5; General Procedure

20% Aqueous H2SO4 (10 mL) was added to solutions of 4a and 4b (23.4 mmol) in dioxane (18 mL) and the reaction mixtures were heated at reflux for 2 h. The mixtures were allowed to cool to r.t., poured into water (20 mL) and extracted with CH2Cl2 (5 × 20 mL). The combined organic layers were washed with water (2 × 20 mL), dried with anhydrous Na2SO4 and concentrated to dryness, to give 5a and 5b, respectively.

Isochroman-1,4-diones 6; General Procedure

Bromine (1.2 mL, 23.4 mmol) was added dropwise, under stirring, to solutions of lactones 4a and 4b (23.4 mmol) in a mixture of AcOH/toluene (1:2, 90 mL) heated at 60 °C. The reaction mixtures were stirred for 30 minutes, evaporated to dryness and the residues were crystallised from CHCl3 to afford 6a and 6b, respectively.

Isochroman-1,4-dione (6a)00

Yield: 3.40 g (98%); white solid; mp 147–148 °C (CHCl3).

IR (NaCl): 1725 (C=O), 1695 (C=O) cm–1.

1H NMR (CDCl3): 7.82–7.95 (m, 2 H, 2 × Ar-H), 8.06–8.10 (m, 1 H, Ar-H), 8.25–8.29 (m, 1 H, Ar-H).

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3-(2-Bromobenzylidene)isochroman-1,4-dione (8a)
MS: 131.7 (C), 134.6 (CH), 135.8 (CH), 161.4 (C=O), 189.4 (C=O).
IR (NaCl): 1763 (C=O) cm–1.
Yield: 284 g (75%); yellow solid; mp 227–229 °C (MeOH).

3-(2-Carbomethoxybenzylidene)isochromane-1,4-dione (11)
To give

13C NMR (CDCl3): δ = 7.96 (d, J= 7.5 Hz, 1 H, Ar-H), 7.81–7.91 (m, 3 H, H-C= and 2 × H-Ar), 139.4 (CH-Ar), 149.6 (C = CH), 160.4 (CO), 166.3 (CO), 189.3 (CO).

Yield: 342 mg (85%); yellow solid; mp 289–290 °C (MeOH).

3-Benzylidene-isochromane-1,4-diones 8; General Procedure

NH2OAc (209 mg, 2.71 mmol) was added to a solution of 6a and 6b (1.23 mmol) and the respective aldehyde (1.23 mmol) in AcOH (5 ml), and the resulting solutions were heated at 60 °C for 6 h. The reaction mixtures were allowed to cool to r.t., water (10 ml) was then added and the precipitated solids were washed with water and dried, to give 8a, 8b or 12.

3-(2-Bromobenzylidene)isochroman-1,4-dione (8a)
Yield: 988 mg (81%); yellow solid; mp 130–132 °C (MeOH).
IR (NaCl): 1746 (C=O) cm–1.
1H NMR (CDCl3): δ = 7.19–7.29 (m, 1 H, Ar-H), 7.38–7.46 (m, 1 H, Ar-H), 7.58–7.69 (m, 2 H, =CH, Ar-H), 7.86–7.93 (m, 2 H, =CH, Ar-H), 8.24–8.36 (m, 3 H, 3 × Ar-H).
13C NMR (CDCl3): δ = 118.1 (CH), 126.6 (C), 126.7 (C), 126.9 (CH), 127.7 (CH), 130.6 (CH), 131.2 (CH), 131.5 (C), 132.5 (CH), 133.1 (C), 133.2 (CH), 135.2 (2 × CH), 145.4 (C), 157.8 (C=O), 176.6 (C=O).
MS: m/z(%) = 328 (44) [M]+, 330 (39) [M]+, 249 (100).

3-(2-Bromo-4,5-dimethoxyphenyl)-3-hydroxy-6,7-dimethoxy-1,4-naphthoquinone (10b)
Yield: 170 mg (85%); red solid; mp 222–224 °C (MeOH).

3-(2-Carbomethoxybenzoyl)-1H-isochromene-1-one (14)
Yield: 690 mg (70%); red solid; mp 139–141 °C (MeOH/CH2Cl2).
IR (NaCl): 1765 (C=O) cm–1.
1H NMR (CDCl3): δ = 3.79 (s, 3 H, CH3), 7.33 (s, 1 H, Ar-H), 7.41–7.49 (m, 1 H, H-Ar), 7.55–7.72 (m, 4 H, H-C= and 3 × Ar-H), 7.77 (t, J = 7.5 Hz, 1 H, Ar-H), 8.07 (d, J = 7.7 Hz, 1 H, Ar-H), 8.31 (d, J = 7.7 Hz, 1 H, Ar-H).
13C NMR (CDCl3): δ = 52.6 (CH), 110.5 (CH-C), 122.7 (C-Ar), 127.9 (CH-Ar), 128.1 (CH-Ar), 129.4 (C-Ar), 130.0 (C-Ar), 130.5 (CH-Ar), 131.8 (CH-Ar), 133.2 (CH-Ar), 133.2 (CH), 133.5 (C-Ar), 139.4 (CH-Ar), 149.6 (C = CH), 160.4 (CO), 166.3 (CO), 189.3 (CO).
MS: m/z(%) = 309 (65) [M + H]+, 174 (100) [M-C8H7O2].
was added until pH 3.0. The suspensions were extracted with CHCl₃ (3 × 20 mL). The combined extracts were washed with water (15 mL), dried with anhydrous Na₂SO₄ and concentrated to dryness under vacuum, to give residues that were purified by recrystallization, to afford compounds 17a or 17b.

2-(2-Acetylphenyl)acetic Acid (16a)

Yield: 255 mg (92%); mp 172–173 °C (MeOH).

Methyl 2-(2-Cinnamoylphenyl)acetate (17a)

ent, to provide

\[ \text{Methyl 2-(2-Cinnamoylphenyl)acetate (17a)} \]


Yield: 255 mg (92%); mp 135 °C (MeOH).

Methyl 2-(2-(3-Phenylpropanoyl)phenyl)acetates 18; General Procedure

1H NMR (CDCl₃): δ = 2.97–3.06 (m, 2 H, CH₂), 3.23–3.31 (m, 2 H, CH₂), 2.90 (s, 3 H, CH₃), 3.45 (s, 3 H, OCH₃), 3.86 (s, 2 H, CH₂), 7.15–7.38 (m, 7 H, Ar-H), 7.44 (d, J = 7.4 Hz, 1 H, Ar-H). MS: m/z (%) = 280 (6); 220 (100).


Methyl (E)-2-[2-(3-(3,4-dimethoxyphenyl)acryloyl)phenyl]acetate (17b)

Yield: 363 mg (95%); colourless oil.

IR (NaCl): 1734 (C=O), 1655 (C=O).% = 340 (13) [M⁺], 281 (100).

Yield: 255 mg (98%); mp 172–173 °C (MeOH).

Methyl 2-(2-Cinnamoyl-4,5-dimethoxyphenyl)acetate (17c)

Yield: 184 mg (87%); colourless oil.

IR (NaCl): 1734 (C=O), 1655 (C=O).

MS: m/z (%) = 238 (13) [M⁺], 185 (39), 173 (100).


Methyl 2-(2-Cinnamoyl-4,5-dimethoxyphenyl)acetate (17c)

Yield: 184 mg (87%); colourless oil.

IR (NaCl): 1734 (C=O), 1655 (C=O).

MS: m/z (%) = 238 (13) [M⁺], 185 (39), 173 (100).


Methyl 2-(2-Cinnamoyl-4,5-dimethoxyphenyl)acetate (17d)

Yield: 255 mg (93%); colourless oil.

IR (NaCl): 1735 (C=O), 1656 (C=O), 1632 (C=O) cm⁻¹.

MS: m/z (%) = 340 (22) [M⁺], 281 (26), 164 (24), 151 (100).


Methyl 2-(2-Cinnamoyl-4,5-dimethoxyphenyl)acetate (17d)

Yield: 184 mg (87%); colourless oil.

IR (NaCl): 1734 (C=O), 1655 (C=O).

MS: m/z (%) = 238 (13) [M⁺], 185 (39), 173 (100).


Methyl 2-(2-(3-(3,4-dimethoxyphenyl)acryloyl)phenyl)acetate (17b)

Yield: 363 mg (95%); colourless oil.

IR (NaCl): 1734 (C=O), 1656 (C=O), 1632 (C=O) cm⁻¹.

MS: m/z (%) = 280 (6); 220 (100).

Anal. Calcd for C_{22}H_{26}O_{7}: C, 65.66; H, 6.51. Found: C, 65.65; H, 6.66.

**Methyl 2-(2-(3,4-Dimethoxyphenyl)propanoyl)phenylacetate (18b)**

Yield: 328, mg (87%); colourless oil.

IR (NaCl): 3312 (OH), 1652 (C=O), 1640 (C=O) cm⁻¹.

HRMS (ESI): m/z (%) = 342 (100) [M⁺], 293 (93), 138 (53).

HRMS (ESI): m/z [M + H⁺] calcd for C_{19}H_{17}O_{5}: 325.1071; found: 325.1084.

2-Benzyl-3-hydroxynaphthalene-1,4-dione (20a)

Yield: 65 mg (57%); orange solid; mp 148–150 °C (MeOH/EtO).

IR (NaCl): 1735 (C=O), 1671 (C=O) cm⁻¹.

HRMS (ESI): m/z [M + H⁺] calcd for C_{17}H_{13}O_{3}: 265.0859; found: 265.0843.

2-(3,4-Dimethoxybenzy1)-3-hydroxynaphthalene-1,4-dione (20b)

Yield: 56 mg (72%); red solid; mp 160–162 °C (MeOH).

IR (NaCl): 1742 (C=O), 1672 (C=O) cm⁻¹.

HRMS (ESI): m/z (%) = 384 (55) [M⁺], 353 (46), 138 (100).

HRMS (ESI): m/z [M + H⁺] calcd for C_{19}H_{17}O_{5}: 325.1071; found: 325.1085.

2-Benzyl-3-hydroxy-6,7-dimethoxynaphthalene-1,4-dione (20c)

Yield: 43 mg (54%); red solid; mp 148 °C (decomp).

IR (NaCl): 3341 (OH), 1638 (C=O) cm⁻¹.

HRMS (ESI): m/z [M + H⁺] calcd for C_{19}H_{17}O_{5}: 325.1071; found: 325.1058.

2-(3,4-Dimethoxybenzyl)-3-hydroxynaphthalene-1,4-dione (20d)

Yield: 43 mg (39%); red solid; mp 180 °C (MeOH).

IR (NaCl): 3312 (OH), 1652 (C=O), 1646 (C=O) cm⁻¹.

HRMS (ESI): m/z (%) = 384 (55) [M⁺], 353 (46), 138 (100).

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