



Green Synthesis of Henna (*Lawsonia inermis* L.) Based Scaffolds

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Expedient aqueous synthesis of 3,3-arylmethylenebis(2-hydroxy naphthalene-1,4-diones) by condensation reaction of aromatic aldehyde and 2-hydroxy-1,4-naphthoquinone under reflux and microwave irradiation using lemon juice as a catalyst has been studied. The green protocol described herein avoid severe reaction conditions and prove to be effective in terms of good yields, operational simplicity, easy work up and short reaction time. The antimicrobial properties of the synthesized compound can be explored and is expected to be comparable to parent compound Lawsone, which is known to impart red-orange colour.

Keywords: *Lawsonia inermis*, Lemon juice, Microwave synthesis, Aqueous media.

INTRODUCTION

Quinone cores are common in nature and play important physiological roles in animals and plants [1]. These are important in biological systems and have industrial applications as dyes or drugs [2]. Conventionally it has been extracted from the leaves of Heena plant (*Lawsonia inermis* L. Family Lythraceae) because of their biological features, commercial applications and use as intermediates in the synthesis of heterocycles, naphthoquinones are an interesting class of chemicals among quinones [3]. Naphthoquinones have many physiological roles e.g. ubiquinone, plastoquinone and K vitamins are biochemical systems' functional ingredients [4-6]. They are usually yellow or brown in colour, and play important roles as dyes in pigmentation [4]. Some of the naturally occurring naphthoquinones shows broad range of biological activities such as antimicrobial properties, cytotoxic and phytotoxic effects [6].

Naphthoquinone derivatives are important heterocycles possessing a broad spectrum of biological activities [7] and also find applications in various other fields. Considering the importance of naphthoquinone scaffolds, development of new simple methods for the synthesis of naphthoquinone scaffolds is an interesting challenge.

Moreover, microwave assisted organic synthesis (MAOS) is using new technologies as a showpiece in the organic process, medicinal and combinatorial chemistry [8-11]. Therefore, many

academic and industrial research groups are using MAOS as a useful technique for optimization of reactions and efficient synthesis of new chemical entities [8].

Because of the wide utility of naphthoquinone-based scaffolds there has been significant impetus in developing newer synthetic routes for these structural motifs. Recent reports on the synthesis of 3,3-arylmethylenebis(2-hydroxy naphthalene-1,4-diones) employed harsh conditions, expensive catalyst and long reaction times [12]. Consequently, there is scope for developing improved and environmentally benign methodology for the synthesis of these naphthoquinone derivatives.

Herein a new and convenient protocol for the synthesis of 3,3-arylmethylenebis(2-hydroxy naphthalene-1,4-diones) via condensation of aromatic aldehyde and 2-hydroxy-1,4-naphthoquinone under reflux and microwave irradiation is reported.

EXPERIMENTAL

All the chemicals were acquired from Sigma-Aldrich, India and used exactly as such. Merck's silica gel 60 F₂₅₄ (pre-coated aluminium plates) was utilized to track the reaction's development. The melting points were calculated using a Tropical Labequip instrument and are uncorrected. The values are reported as ν_{\max} cm⁻¹ for IR (KBr) spectra obtained on a Perkin-Elmer FTIR spectrophotometer. Analytikjena Specord 250 Spectrophotometer was used to measure absorbance. The

^1H & ^{13}C NMR spectra were acquired at 400 MHz on a Jeol JNM ECX-400P with TMS as an internal standard on a Jeol JNM ECX-400P.

Synthesis of 3,3-arylmethylenebis(2-hydroxynaphthalene-1,4-dione)

Conventional method: A mixture of aldehyde (1.0 mmol), 2-hydroxy-1,4-naphthoquinone (2.0 mmol), lemon juice (1.0 mL) and 10 mL of EtOH-H₂O (1:1, v/v) was stirred magnetically under reflux in a 50 mL round-bottomed flask for a suitable time (Table-1). The reaction mixture was allowed to cool to room temperature after completion of the reaction, which was monitored using TLC with petroleum ether:ethyl acetate (60:40, v/v) as the eluent. The resulting precipitate was collected by filtration at the pump and rinsed with water followed by ethanol to yield pure 3,3-arylmethylenebis(2-hydroxynaphthalene-1,4-dione) derivatives.

Microwave irradiation method: In a 50 mL round bottomed flask, aldehyde (1.0 mmol), 2-hydroxy-1,4-naphthoquinone (2.0 mmol) and lemon juice (1 mL) were mixed thoroughly. The loaded round bottomed was then placed in the microwave reactor and heated at 150 W and 70 °C for 7-10 min (Table-1). After cooling to room temperature, the mixture was quenched with 5 mL of water. The resulting precipitate was collected by filtration at the pump and rinsed with water followed by ethanol to yield pure 3,3-arylmethylenebis(2-hydroxynaphthalene-1,4-dione) derivatives.

3,3-(4-Methoxyphenyl)methylenebis(2-hydroxynaphthalene-1,4-dione) (IIIa): Orange solid; m.p.: 221-222 °C (Lit. 220-222 °C) [12]; ^1H NMR (400 MHz, DMSO-*d*₆): δ 8.11 (d, $J = 7.6$ Hz, 4H, Ar), 7.78-7.67 (m, 6H, Ar), 7.06-7.01

(m, 2H, Ar), 5.97 (s, 1H, ArCH), 4.15 (bs, OH, overlap with DMSO), 3.68 (s, 3H, OCH₃); IR (KBr, ν_{max} , cm⁻¹): 3356, 1668, 1300.

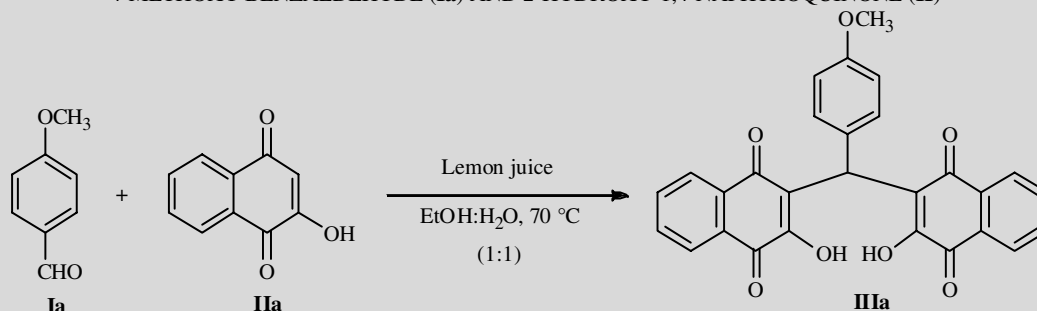
3,3-Phenylmethylenebis(2-hydroxynaphthalene-1,4-dione) (IIIb): Orange solid; m.p.: 202-203 °C (Lit. 202-204 °C) [12]; ^1H NMR (400 MHz, DMSO-*d*₆): δ 8.10-7.98 (m, 4H, Ar), 7.79-7.69 (m, 4H, Ar), 7.37 (d, $J = 7.7$, 2H, Ar), 7.33 (d, $J = 8.4$ Hz, 2H, Ar), 7.30 (s, 1H, Ar), 6.03 (s, 1H, ArCH), 4.32 (bs, OH, overlap with DMSO); IR (KBr, ν_{max} , cm⁻¹): 3332, 1656, 1282.

3,3-(4-Chlorophenyl)methylenebis(2-hydroxynaphthalene-1,4-dione) (IIIc): Yellow solid; m.p.: 183-184 °C (Lit. 180-182 °C) [12]; ^1H NMR (400 MHz, DMSO-*d*₆): δ 7.99-7.93 (m, 4H, Ar), 7.87-7.62 (m, 4H, Ar), 7.54-7.45 (m, 4H, Ar), 6.05 (s, 1H, ArCH), 3.77 (bs, OH, overlap with DMSO); ^{13}C NMR (100 MHz, DMSO-*d*₆): δ 183.90, 181.66, 157.17, 146.67, 135.18, 133.63, 132.62, 130.40, 129.32, 126.55, 126.12, 124.95, 122.65, 38.01; IR (KBr, ν_{max} , cm⁻¹): 3342, 1655, 1278.

3,3-(4-Bromophenyl)methylenebis(2-hydroxynaphthalene-1,4-dione) (III d): Yellow solid; m.p.: 212-214 °C (Lit. 216-218 °C) [12]. ^1H NMR (400 MHz, DMSO-*d*₆): δ 8.01-7.99 (m, 4H, Ar), 7.80-7.78 (m, 4H, Ar), 7.40-7.37 (m, 2H, Ar), 7.28-7.24 (m, 2H, Ar), 5.99 (s, 1H, ArCH), 4.10 (bs, OH, overlap with DMSO). IR (KBr, ν_{max} , cm⁻¹): 3336, 1660, 1272.

3,3-(4-Methylphenyl)methylenebis(2-hydroxynaphthalene-1,4-dione) (IIIe): Yellow solid; m.p.: 172-174 °C (Lit. 170-172 °C) [12]. ^1H NMR (400 MHz, DMSO-*d*₆): δ 8.12-8.09 (m, 4H, Ar), 8.01 (m, 1H, Ar), 7.80-7.69 (m, 6H, Ar), 7.08 (d, $J = 8.8$ Hz, 1H, Ar), 6.05 (s, 1H, ArCH), 4.20 (bs, OH, overlap with DMSO), 2.20 (s, 3H, CH₃). IR (KBr, ν_{max} , cm⁻¹): 3347, 1661, 1298.

TABLE-1
EFFECT OF DIFFERENT MEDIA AND CATALYST ON THE CONDENSATION OF 4-METHOXY BENZALDEHYDE (Ia) AND 2-HYDROXY-1,4-NAPHTHOQUINONE (II)^a



S. No.	Catalyst	Loading (mL)	Temperature (°C)	Reaction media ^d	Time	(%) Yield (IIIa)
1	None	–	70	Water	24 h	– ^b
2	None	–	70	Ethanol	24 h	– ^b
2	HCl	0.5	70	Ethanol	5 h	– ^c
3	Acetic acid	0.5	70	Ethanol	5 h	– ^c
4	Tomato juice	1 mL	70	Ethanol:water	50 min	85
5	Mosambi	1 mL	70	Ethanol:water	40 min	80
6	Coconut	1 mL	70	Ethanol:water	70 min	86
7	Lemon Juice	1 mL	70	Ethanol:water	40 min	93
8	Lemon Juice	2 mL	70	Ethanol:water	40 min	93
9	Lemon Juice	0.5 mL	70	Ethanol:water	70 min	88
10	Lemon Juice	0.5 mL	40	Ethanol:water	3h	70

^aMolar ratio 4-methoxybenzaldehyde:2-hydroxy-1,4-naphthoquinone (1:2); ^bIncomplete reaction; ^cSluggish and incomplete reactions; ^dSolvent (10 mL)

TABLE-2
SYNTHESIS OF 3,3-ARYLMETHYLENEBIS(2-HYDROXYNAPHTHALENE-1,4-DIONE) (III) USING LEMON JUICE AS CATALYST^a

S. No.	Aromatic aldehyde	Product	Method A ^b		Method B ^c	
			Time (min)	Yield (%)	Time (min)	Yield (%)
1	4-OCH ₃ C ₆ H ₅ (Ia)	IIIa	40	93	7	93
2	C ₆ H ₅ (Ib)	IIIb	45	90	8	88
3	4-ClC ₆ H ₄ (Ic)	IIIc	45	89	8	89
4	4-BrC ₆ H ₄ (Id)	IIId	40	91	9	88
5	4-CH ₃ C ₆ H ₄ (Ie)	IIIe	35	90	8	92
6	2-ClC ₆ H ₄ (If)	IIIf	40	88	10	90
7	4-F ₃ CC ₆ H ₄ (Ig)	IIIg	50	89	10	92
8	4-FC ₆ H ₄ (Ih)	IIIh	50	92	9	91
9	2-BrC ₆ H ₄ (Ii)	IIIi	45	90	9	88
10	2-CH ₃ OC ₆ H ₄ (Ij)	IIIj	40	92	8	88
11	3-ClC ₆ H ₄ (Ik)	IIIk	35	90	10	90

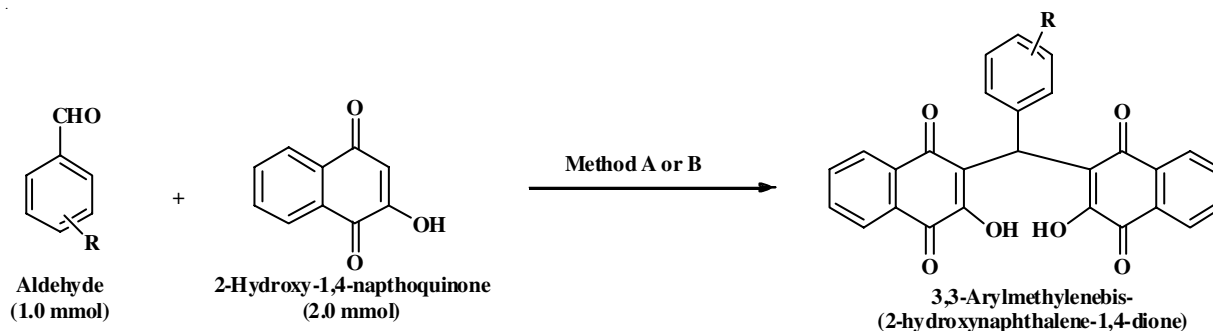
^aAromatic aldehyde: 2-Hydroxy-1,4-naphthoquinone (1:2 molar ratio); ^bMethod A: Lemon juice (1 mL); H₂O: EtOH (1:1), 70 °C; ^cMethod B: Lemon juice (1 mL); Microwave irradiation.

3,3-(2-Chlorophenyl)methylenebis(2-hydroxynaphthalene-1,4-dione) (IIIf): Yellow solid; m.p.: 218-220 °C (Lit. 215-217 °C) [12]. ¹H NMR (400 MHz, DMSO-*d*₆): δ 8.12-8.08 (m, 4H, Ar), 7.78-7.67 (m, 4H, Ar), 7.37 (dd, *J*_{1,2} = 2.0 Hz, *J*_{1,3} = 7.2 Hz, 1H, Ar), 7.21-7.17 (m, 3H, Ar), 5.97 (s, 1H, ArCH), 4.16 (bs, OH, overlap with DMSO). IR (KBr, ν_{max}, cm⁻¹): 3325, 1653, 1280.

3,3-(4-Trifluoromethylphenyl)methylenebis(2-hydroxynaphthalene-1,4-dione) (IIIg): Yellow solid; Yield: 91%; m.p.:

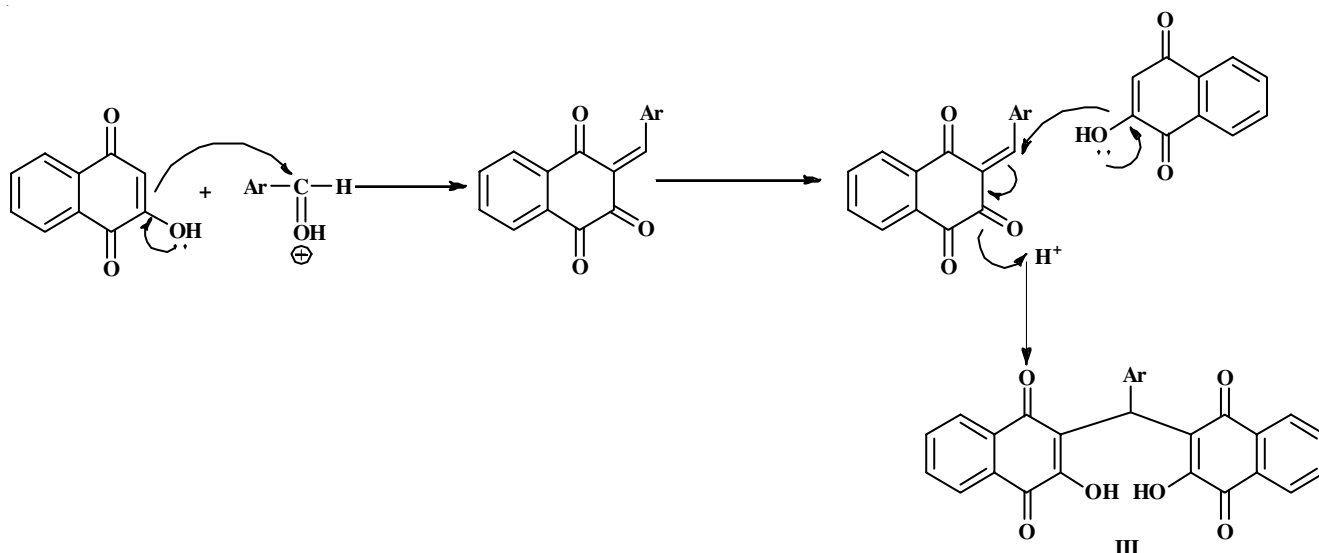
188-190 °C. ¹H NMR (400 MHz, DMSO-*d*₆): δ 7.99-7.97 (m, 2H, Ar), 7.93 (d, *J* = 7.3 Hz, 2H, Ar), 7.87-7.63 (m, 4H, Ar), 7.54 (d, *J* = 7.8 Hz, 2H, Ar), 7.46-7.45 (m, 2H, Ar), 6.06 (s, 1H, ArCH), 4.44 (bs, OH, overlap with DMSO). IR (KBr, ν_{max}, cm⁻¹): 3340, 1651, 1300.

3,3-(4-Fluorophenyl)methylenebis(2-hydroxynaphthalene-1,4-dione) (IIIh): Yellow solid; m.p.: 192-194 °C (Lit. 193-195 °C) [12]. ¹H NMR (400 MHz, DMSO-*d*₆): δ 8.10 (d, *J* = 7.8 Hz, 4H, Ar), 7.78-7.68 (m, 4H, Ar), 7.25-7.24 (m, 2H, Ar), 7.00-



Method A: Lemon juice (1 mL); H₂O:EtOH (1:1), 70 °C; Method B: Lemon juice (1 mL); Microwave irradiation

Scheme-I



Scheme-II: Probable mechanism for the formation of 3,3-arylmethylenebis(2-hydroxynaphthalene-1,4-dione)

6.95 (m, 2H, Ar), 7.46-7.45 (m, 2H, Ar), 6.09 (s, 1H, ArCH), 4.34 (bs, OH, overlap with DMSO). IR (KBr, ν_{\max} , cm^{-1}): 3345, 1673, 1298.

3,3-(2-Bromophenyl)methylenebis(2-hydroxynaphthalene-1,4-dione) (IIIi): Yellow solid; m.p.: 210-212 °C. ^1H NMR (400 MHz, DMSO- d_6): δ 7.99 (d, $J = 7.3$ Hz, 2H, Ar), 7.92 (d, $J = 7.3$ Hz, 2H, Ar), 7.86-7.75 (m, 4H, Ar), 7.51 (d, $J = 7.8$ Hz, 1H, Ar), 7.32 (d, $J = 7.3$ Hz, 1H, Ar), 7.22-7.18 (m, 1H, Ar), 7.12-7.08 (m, 1H, Ar), 6.02 (s, 1H, ArCH), 3.98 (bs, OH, overlap with DMSO). IR (KBr, ν_{\max} , cm^{-1}): 3330, 1672, 1254

3,3-(2-Methoxyphenyl)methylenebis(2-hydroxynaphthalene-1,4-dione) (IIIj): Yellow solid; m.p.: 212-214 °C (Lit. 214-216 °C) [12]. ^1H NMR (400 MHz, DMSO- d_6): δ 8.12 (d, $J = 7.9$ Hz, 4H, Ar), 7.76-7.65 (m, 6H, Ar), 7.01-6.99 (m, 2H, Ar), 6.01 (s, 1H, ArCH), 4.11 (bs, OH, overlap with DMSO), 3.65 (s, 3H, OCH_3). IR (KBr, ν_{\max} , cm^{-1}): 3354, 1670, 1270.

3,3-(3-Chlorophenyl)methylenebis(2-hydroxynaphthalene-1,4-dione) (IIIk): Yellow solid; m.p.: 222-224 °C (231-233 °C) [12]. ^1H NMR (400 MHz, DMSO- d_6): δ 8.11 (d, $J = 8.1$ Hz, 4H, Ar), 7.67-7.60 (m, 6H, Ar), 7.10-6.99 (m, 2H, Ar), 6.03 (s, 1H, ArCH), 4.02 (bs, OH, overlap with DMSO), 3.65 (s, 3H, OCH_3). IR (KBr, ν_{\max} , cm^{-1}): 3424, 1672, 1270.

RESULTS AND DISCUSSION

After the preliminary experimentation, the optimum reaction conditions for the synthesis of 3,3-aryl-methylenebis(2-hydroxynaphthalene-1,4-diones) (IIIa) was performed by the condensation of 4-methoxybenzaldehyde (Ia) (1.0 mmol) and 2-hydroxy-1,4-naphthoquinone (II) (2.0 mmol) in the presence of lemon juice (1 mL) as catalyst and water:ethanol (1:1) as solvent at 70 °C. The reactions were carried out both at room temperature and at higher temperatures in the presence of catalyst like HCl, acetic acid, tomato juice, mosambi juice, coconut water and lemon juice. The details of reactions carried out for optimization are listed in Table-2.

Further, the effect of the microwave irradiation was also investigated on this condensation reaction. The reaction of 2-hydroxy-1,4-naphthoquinone (II) and 4-methoxybenzaldehyde (Ia) was attempted at 70 °C at 150 W power and 1 mL of lemon juice. The reaction was found to complete after 7 min with a yield of 93% of compound IIIa. Reaction at higher temperature (150 °C) did not affect the yield or reaction time whereas reaction at lower of temperature (40 °C) affects the yield of compound IIIa significantly. Similar results were obtained on changing the power from 150 W to 200 W and 50 W. It can be concluded from the results that 1 mL lemon juice under microwave irradiation (150 W, 70 °C) catalyzes the condensation reaction 2-hydroxy-1,4-naphthoquinone (II) and 4-methoxybenzaldehyde (Ia) efficiently to afford the corresponding xanthene derivative IIIa in high yield (Scheme-I). The optimized protocols were extended to other aromatic aldehydes also.

A probable mechanism for the formation of 3,3-arylmethylenebis(2-hydroxynaphthalene-1,4-dione) from the condensation of aromatic aldehyde and 2-hydroxy-1,4-naphthoquinone is shown in Scheme-II.

Conclusion

An efficient synthetic approaches was devised for the synthesis of 3,3-arylmethylenebis(2-hydroxynaphthalene-1,4-dione) derivatives. The condensation has been proficiently performed in water as a “green” solvent using lemon juice as catalyst. The advantages of this method include operational simplicity, high yields and easy availability of the catalyst.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interests regarding the publication of this article.

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