



**AN ECO-FRIENDLY AND EFFICIENT METHOD FOR SYNTHESIS OF
3,3'-ARYLMETHYLENE-BIS(4-HYDROXYQUINOLIN-2(1H)-ONES) USING
DIAMMONIUM HYDROGEN PHOSPHATE AS REUSABLE CATALYST**

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Abstract: A simple, efficient and eco-friendly procedure has been developed using diammonium hydrogen phosphate as catalyst for the synthesis of 3,3'-arylmethylene-bis(4-hydroxyquinolin-2(1H)-ones) in aqueous ethanol. The present methodology offers several advantages such as operational simplicity, short reaction time, use of diammonium hydrogen phosphate as a green, non-toxic, inexpensive and reusable catalyst, high yields and environmentally benign reaction conditions.

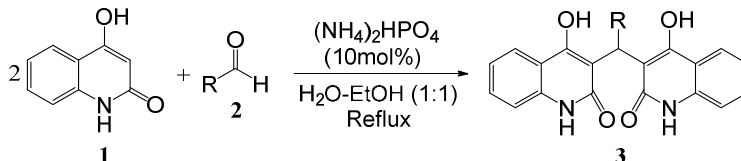
Keywords: Diammonium hydrogen phosphate; 4-Hydroxyquinolin-2(1H)-one; Aromatic aldehyde; 3,3'-Arylmethylene-bis(4-hydroxyquinolin-2(1H)-ones); Multicomponent reaction

Introduction

Quinoline derivatives have shown good antiasthmaticⁱ, antibacterialⁱⁱ, and anti-inflammatoryⁱⁱⁱ activities. The synthesis of quinolinone derivatives has attracted the attention of chemists.^{iv-vi} Synthesis of bis(4-hydroxyquinolin-2(1H)-ones) derivatives has been reported by condensation of aryl aldehyde and 4-hydroxyquinolin-2-one in ethyl alcohol catalyzed by KF/Al₂O₃^{vii} and in ethylene alcohol under microwave irradiation^{viii}. KF/Al₂O₃ gave good results but lack of recyclability and its corrosive nature limits its application. Microwave irradiation promoted reaction does not need catalyst. However, use of special apparatus hinders its industrial applications. Hence, the development of facile and environment friendly methods is still required for green and sustainable chemistry.

Diammonium hydrogen phosphate is a very inexpensive, nontoxic, and commercially available. Recently, the use of diammonium hydrogen phosphate as catalyst for the preparation of tetrahydrobenzo[*b*]pyrans^{ix}, pyrano[2,3-*d*]pyrimidinones^x, 1,8-dioxo-octahydroxanthenes^{xi}, bis(indolyl)methanes^{xii}, dihydropyrimidinones, quinazolinones, azalactones^{xiii} and 3,4-dihydropyrano[*c*]chromenes^{xiv}, has been

reported. Multicomponent reactions (MCRs) are significant tools for sustainable organic synthesis.^{xv} These kinds of reactions profit from avoiding unnecessary separation and purification procedures. Water-ethanol is considered to be relatively environment friendly solvent.^{xvi,xvii} In continuation of our work on the development of environmentally benign synthetic methodologies^{xviii}, we herein report a simple, efficient and eco-friendly multicomponent reaction protocol for synthesis of bis(4-hydroxyquinolin-2(1H)-ones) derivatives from 4-hydroxyquinolin-2(1H)-one and different aromatic aldehydes in the presence of diammonium hydrogen phosphate under reflux in aqueous ethanol (Scheme 1). Separation of the product and recycling of the catalyst were easily achieved four times without any loss of activity.



Scheme 1. Synthesis of 3,3'-arylmethylene-bis(4-hydroxyquinolin-2(1H)-ones) catalyzed by diammonium hydrogen phosphate

Experimental

General

Melting points were measured on a digital melting point apparatus and were uncorrected. Fourier-transform infrared spectra were obtained on a Nexus 470 spectrophotometer. Nuclear magnetic resonance spectra were recorded on a Bruker Avance III 400 with tetramethylsilane as internal standard. All chemicals used were commercial products.

Typical procedure for the synthesis of 3,3'-arylmethylene-bis(4-hydroxyquinolin-2(1H)-ones) derivatives

A mixture of 4-hydroxyquinolin-2(1H)-one (4 mmol), aldehyde (2 mmol) and diammonium hydrogen phosphate (0.2 mmol) in water-ethanol (1:1, 10 mL) was stirred at reflux temperature. After completion of the reaction confirmed by thin layer chromatography, the reaction mixture was cooled to room temperature. The precipitated solid was filtered, washed with water-ethanol (1:1) and crystallized from dimethylformamide-water to afford 3,3'-arylmethylene-bis(4-hydroxyquinolin-2(1H)-ones) derivatives. The products obtained are all known compounds and were identified by comparing of their physical and spectra data with the reported ones^{vii, viii}.

3,3'-(2,4-Dichlorophenyl)methylene-bis(4-hydroxyquinolin-2(1H)-ones) (3a)

IR (KBr) ν : 3077, 1643, 1596, 1549, 1454, 1476, 1411, 1331, 1255, 1164, 1114, 886, 767 cm^{-1} . ^1H NMR (DMSO- d_6) δ : 6.48 (s, 1H, CH), 7.33 (d, $J=8.0$ Hz, 1H, Ar-H), 7.41 (d, $J=8.0$ Hz, 1H, Ar-H), 7.44-7.49 (m, 2H, Ar-H), 7.51-7.58 (m, 3H, Ar-H), 7.65 (d, $J=7.6$ Hz, 2H, Ar-H), 7.82 (d, $J=8.0$ Hz, 2H, Ar-H), 12.24 (s, 2H, 2NH), 12.74 (s, 1H, OH), 13.11 (s, 1H, OH).

3,3'-(3-Nitrophenyl)methylene-bis(4-hydroxyquinolin-2(1H)-ones) (3b)

IR (KBr) ν : 3059, 1639, 1597, 1529, 1465, 1378, 1335, 1259, 1094, 809, 798 cm^{-1} . ^1H NMR (DMSO- d_6) δ : 6.35 (s, 1H, CH), 7.35-7.38 (m, 2H, Ar-H), 7.49 (d, $J=8.0$ Hz, 2H, Ar-H), 7.58-7.69 (m, 4H, Ar-H), 7.92 (s, 1H, Ar-H), 8.04 (d, $J=7.6$ Hz, 2H, Ar-H), 8.15 (d, $J=7.6$ Hz, 1H, Ar-H), 12.35 (s, 2H, 2NH), 12.97 (s, 2H, 2OH).

3,3'-(4-Chlorophenyl)methylene-bis(4-hydroxyquinolin-2(1H)-ones) (3c)

IR (KBr) ν : 3073, 1645, 1611, 1493, 1392, 1326, 1211, 1148, 1092, 898, 836, 771

cm⁻¹. ¹H NMR (DMSO-d₆) δ: 6.21(s, 1H, CH), 7.17 (d, *J*=8.4 Hz, 2H, Ar-H), 7.33-7.36 (m, 4H, Ar-H), 7.49 (d, *J*=8.4 Hz, Ar-H, 2H), 7.64-7.67 (m, 2H, Ar-H), 7.99 (s, 2H, Ar-H), 12.27 (s, 2H, 2NH), 12.74 (s, 1H, OH), 13.15 (s, 1H, OH).

3,3'-(2-Chlorophenyl)methylene-bis(4-hydroxyquinolin-2(1H)-ones) (3d)

IR (KBr) v: 3079, 1641, 1594, 1505, 1406, 1338, 1276, 1158, 1277, 1046, 846, 759 cm⁻¹. ¹H NMR (DMSO-d₆) δ: 6.41(s, 1H, CH), 7.32-7.47 (m, 8H, Ar-H), 7.61 (d, *J*=7.6 Hz, 2H, Ar-H), 7.98 (d, *J*=8.0 Hz, 2H, Ar-H), 12.17 (s, 2H, 2NH), 12.78 (s, 1H, OH), 13.09 (s, 1H, OH), 13.18 (s, 1H, OH).

3,3'-(4-Bromophenyl)methylene-bis(4-hydroxyquinolin-2(1H)-ones) (3e)

IR (KBr) v: 3078, 1641, 1589, 1473, 1405, 1328, 1269, 1157, 1276, 1037, 846, 749 cm⁻¹. ¹H NMR (DMSO-d₆) δ: 6.17 (s, 1H, CH), 7.09 (d, *J*=8.0 Hz, 2H, Ar-H), 7.35 (d, *J*=8.0 Hz, 2H, Ar-H), 7.39-7.48 (m, 4H, Ar-H), 7.65 (d, *J*=7.6 Hz, 2H, Ar-H), 7.99 (d, *J*=8.0 Hz, 2H, Ar-H), 12.29 (s, 2H, 2NH), 12.78 (s, 1H, OH), 13.16 (s, 1H, OH).

3,3'-(4-Fluorophenyl)methylene-bis(4-hydroxyquinolin-2(1H)-ones)(3f)

IR (KBr) v: 3078, 1649, 1606, 1508, 1396, 1327, 1228, 1157, 1276, 1033, 854, 758 cm⁻¹. ¹H NMR (DMSO-d₆) δ: 6.19 (s, 1H, CH), 7.07-7.17 (m, 4H, Ar-H), 7.35 (d, *J*=8.0 Hz, 2H, Ar-H), 7.35-7.48 (m, 2H, Ar-H), 7.61 (d, *J*=7.6 Hz, 2H, Ar-H), 7.98 (d, *J*=8.0 Hz, 2H, Ar-H), 12.27 (s, 2H, 2NH), 12.78 (s, 1H, OH), 13.06 (s, 1H, OH).

3,3'-(4-Methoxyphenyl)methylene-bis(4-hydroxyquinolin-2(1H)-ones) (3g)

IR (KBr) v: 3075, 1653, 1612, 1519, 1485, 1418, 1345, 1225, 1191, 1135, 1049, 876, 775 cm⁻¹. ¹H NMR (DMSO-d₆) δ: 3.75(s, 3H, CH₃O), 6.16 (s, 1H, CH), 6.86 (d, *J*=8.4 Hz, 2H, Ar-H), 7.05 (d, *J*=8.4 Hz, 2H, Ar-H), 7.32-7.35 (m, 2H, Ar-H), 7.47 (d, *J*=8.0 Hz, 2H, Ar-H), 7.62-7.66 (m, 2H, Ar-H), 7.99 (s, 2H, Ar-H), 12.25 (s, 2H, 2NH), 12.71 (s, 1H, OH), 13.17 (s, 1H, OH).

3,3'-(4-Dimethylaminophenyl)methylene-bis(4-hydroxyquinolin-2(1H)-ones) (3h)

IR (KBr) v: 3072, 1653, 1611, 1527, 1485, 1341, 1330, 1293, 1226, 1157, 1125, 973, 865, 774 cm⁻¹. ¹H NMR (DMSO-d₆) δ: 2.87(s, 6H, 2CH₃), 6.13 (s, 1H, CH), 6.67 (d, *J*=8.8 Hz, 2H, Ar-H), 6.95 (d, *J*=8.8 Hz, 2H, Ar-H), 7.31-7.35 (m, 2H, Ar-H), 7.47 (d, *J*=8.0 Hz, 2H, Ar-H), 7.61-7.65 (m, 2H, Ar-H), 7.97 (s, 2H, Ar-H), 12.15 (s, 1H, NH), 12.26 (s, 1H, NH), 12.68 (s, 1H, OH), 13.17 (s, 1H, OH).

Results and Discussion

To optimize the reaction conditions, the reaction of 2,4-dichlorobenzaldehyde and 4-hydroxyquinolin-2(1H)-one was used as a model reaction. The reaction was examined in various solvents using 10 mol% diammonium hydrogen phosphate as catalyst. The best results were obtained when H₂O-EtOH (1:1) was used as a solvent at reflux (Table 1, entry 3). In order to determine the optimal amount of diammonium hydrogen phosphate, model reaction was carried out at reflux in H₂O-EtOH (1:1). The product was not obtained even after reflux for 6 h in the absence of the catalyst (Table 1, entry 6) indicating that the catalyst is necessary for the reaction. The optimal amount of diammonium hydrogen phosphate was 10 mol % (based on 2,4-dichlorobenzaldehyde). Extra amounts of the catalyst did not improve the yields.

To explore the generality and scope of the catalyst, we extended our study using diammonium hydrogen phosphate (10 mol %) in H₂O-EtOH (1:1) with different aromatic aldehydes to prepare a series of 3,3'-arylmethylene-bis(4-hydroxyquinolin-2(1H)-ones) derivatives (Table 2). Various aromatic aldehydes containing electron-withdrawing substituents, electron-donating

substituents were utilized successfully in the reaction, and gave the corresponding products in high yields and in short reaction times. The method has ability to tolerate a variety of functional groups such as bromo, chloro, nitro and methoxy.

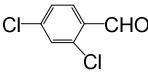
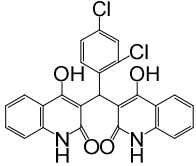
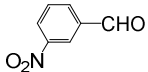
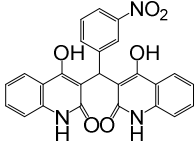
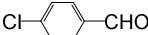
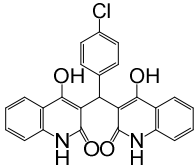
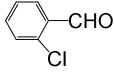
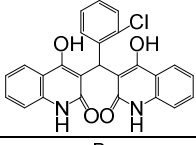
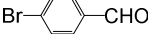
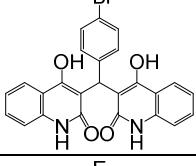
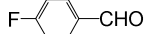
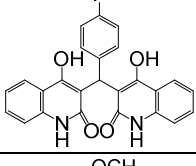
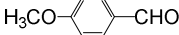
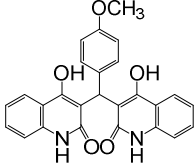
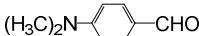
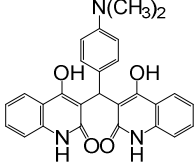
Table 1. Condensation of 4-hydroxyquinolin-2(1H)-one with 2,4-dichlorobenzaldehyde catalyzed by diammonium hydrogen phosphate ^a

Entry	Solvent	Catalyst loading (mol%)	Time (min)	Yield ^b (%)
1	H ₂ O	10	210	Trace
2	EtOH	10	60	82
3	H ₂ O-EtOH (1:1)	10	45	82
4	H ₂ O-EtOH (1:3)	10	120	52
5	H ₂ O-EtOH (3:1)	10	120	56
6	H ₂ O-EtOH (1:1)	0	360	0
7	H ₂ O-EtOH (1:1)	5	120	68
8	H ₂ O-EtOH (1:1)	20	45	82

^a Reaction conditions: 2,4-dichlorobenzaldehyde (2 mmol), 4-hydroxyquinolin-2(1H)-one (4 mmol), solvent (10 mL).

^b Isolated yields.

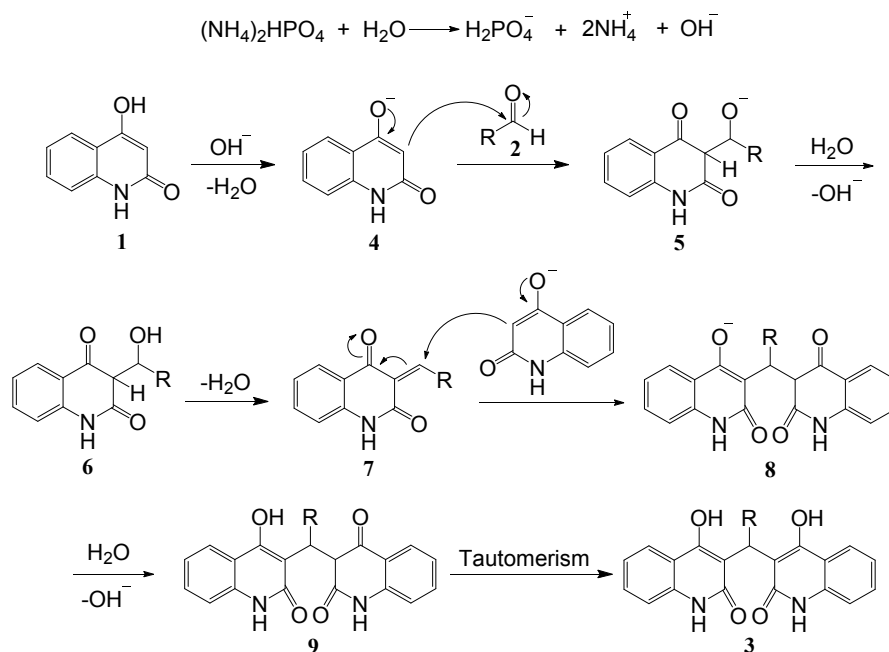
Table 2. Synthesis of 3,3'-arylmethylene-bis(4-hydroxyquinolin-2(1H)-ones) catalyzed by diammonium hydrogen phosphate ^a

Entry	Aldehyde	Product	Time (min)	Yield ^b (%)
1			45	82
2			120	91
3			20	88
4			90	90
5			20	87
6			25	95
7			60	85
8			120	75

^a Reaction conditions: 4-hydroxyquinolin-2(1H)-one (4 mmol), aldehyde (2 mmol), diammonium hydrogen phosphate (10 mol %), H₂O-EtOH (1:1, 10 mL), reflux.

^b Isolated yields.

A plausible mechanism for the synthesis of 3,3'-arylmethylene-bis(4-hydroxyquinolin-2(1H)-ones) in the presence of diammonium hydrogen phosphate is exhibited in Scheme 2. The transformation involves a Knoevenagel condensation of 4-hydroxyquinolin-2(1H)-one with the aldehyde followed by a Michael addition with another molecule of 4-hydroxyquinolin-2(1H)-one.



Scheme 2. Plausible mechanism for the synthesis of 3,3'-arylmethylene-bis(4-hydroxyquinolin-2(1H)-ones)

Table 3. Reusability of catalyst^a

Run	Time (min)	Yield ^b (%)
1	20	88
2	20	88
3	20	89
4	20	87
5	20	86

^a Reaction conditions: 4-hydroxyquinolin-2(1H)-one (4 mmol), 4-chlorobenzaldehyde (2 mmol), diammonium hydrogen phosphate (10 mol %), H₂O-EtOH (1:1, 10 mL), reflux.

^b Isolated yields.

The reusability of the catalyst was tested upon the reaction of 4-hydroxyquinolin-2(1H)-one (4 mmol) and 4-chlorobenzaldehyde (2 mmol). After completion of the reaction confirmed by thin layer chromatography, the reaction mixture was cooled to room temperature and filtered to separate the products from the catalyst. The filtrate (consisting of water-ethanol, diammonium hydrogen phosphate and some other residual reactants or by-products) was reused directly in the next run without any treatment. As can be seen from Table 3, the catalyst aqueous-ethanol

solutions could be reused at least four times without any loss of activity.

Conclusion

In conclusion, we have reported a simple, efficient and green protocol for the synthesis of 3,3'-arylmethylene-bis(4-hydroxyquinolin-2(1H)-ones) in aqueous ethanol. The method offers several advantages such as operational simplicity, short reaction time, the use of diammonium hydrogen phosphate, as a green, non-toxic, inexpensive and reusable catalyst, high yields and environmentally benign reaction conditions.

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