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Catalyst-free hydroarylation of *in situ* generated *ortho*-Quinone methide (*o*-QM) with electron rich arenes in water

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We report the first C-H hydroarylation of *in situ* generated *ortho*-quinone methides with electron-rich arenes. The reaction takes place in water without any catalyst, and is highly regioselective. Ionic and non-ionic additives provide an increase in reaction rate, yield, and regioselectivity.

Quinone methides are used ubiquitously as reactive intermediates[1] for the synthesis of complex natural products,[2] morden materials,[3] fine chemicals, and pharmaceuticals.[4] In particular, *o*-quinone methides (*o*-QMs) are involved in 1,4 Michael-type additions,[5] aza-Michael reactions,[6] Diels-Alder, and hetero-Diels-Alder cycloadditions.[7] A number of biologically active natural products are also synthesized *via in situ* generated *o*-QMs.[8] Recently, furan annulated heterocycles like furocoumarins and furoquinolones have been synthesized *via* [4+1] cycloaddition of *in situ* generated *o*-QMs and isocyanides.[9] *o*-QMs derived from 4-hydroxycoumarin undergo [4+2] cycloaddition reaction with pentafulvenes to afford pyranocoumarin and pyranopyrone.[10]

Hydroarylation involves direct addition of electron rich aryl C-H bonds to alkenes and alkynes in intermolecular or intramolecular manner and has been considered as one of the most fundamental strategies for the construction of C-C bonds.[11] In Michael-type hydroarylations,[12] electron-poor alkenes such as nitroalkenes and α, β-unsaturated carbonyl compounds react with electron-rich arenes so that a C-H bond is converted into a C-C bond (Fig. 1). However, these reactions require expensive metal catalysts or strong acids in organic solvents. Hence, it is desirable to develop catalyst-free alternatives. Moreover, to the best of our knowledge, the direct C-H hydroarylation of *in situ* generated *o*-QMs with electron rich arenes like *tert*-aryl amines is still unknown.

In continuation of our work on green trasformation,[13] herein we highlight the direct hydroarylation of bioactive heterocycles such as 4-hydroxycoumarins, 4-hydroxypyrones and 2-phenylindoles with *N,N*-dialkylaminoarenes via *in situ* generated *o*-quinone methides in water under catalyst-free conditions (Scheme 1).

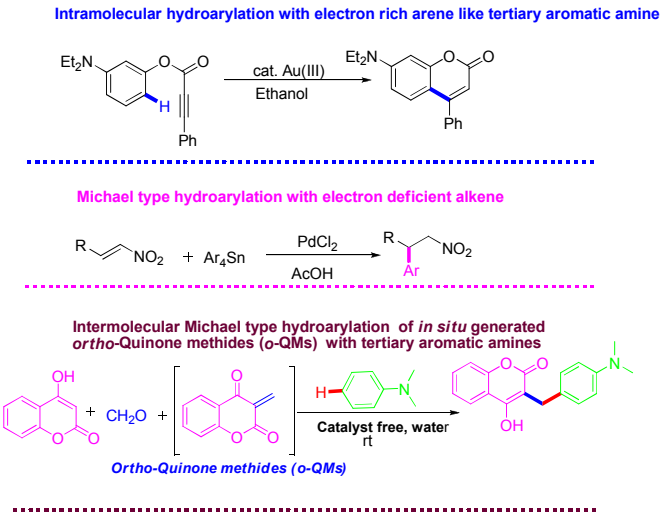
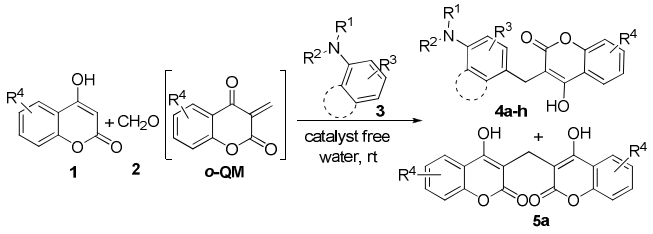


Fig. 1 Hydroarylation of alkene and alkyne



Scheme 1. Synthesis of 3-Substituted 4-hydroxycoumarin

The heterocycles such as coumarins, pyrones and indoles are key structural units in many natural products, and wide range of pharmaceuticals[14] like Warfarin,[15] Phenprocoumon,[16] 5-MeO-DMT,[17] and PNU-96988.[18]

Various methods have been reported for the preparation of 3-substituted coumarin, pyrone and 2-phenylindole using several metal, Lewis and Brønsted acid catalysts.[19] Recently, G. Palmisano *et al.* have reported Ultrasound-enhanced synthesis of 3-Arylcoumarin *via* sequential Knoevenagel-reductive Michael addition with Hantzsch 1,4-dihydropyridine.[20]

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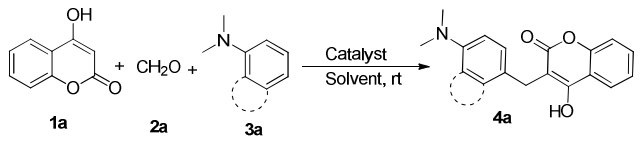
We have interested to develop 3-substituted heterocycles *via* direct hydroarylation with electron-rich arenes. In the preliminary study, various catalysts and solvents were tested for the C-H hydroarylation of *in situ* generated *o*-quinone methides (*o*-QMs) derived from 4-hydroxycoumarin and formaldehyde with tertiary aryl amines at room temperature. The results of optimization of reaction conditions are shown in Table 1.

Table 1 Optimization of the reaction conditions[a]



Entry	Catalyst (20 mol %)	Solvent	Yield **4a** (%)[e]	Yield **5a** (%)[e]
1	Acetic acid	Ethanol	Trace	85
2	Boric acid	Ethanol	Trace	70
3	PTSA	Ethanol	Trace	84
4	TFA	Ethanol	Trace	85
5	$ZnCl_2$	Ethanol	Trace	76
6	$CuSO_4$	Ethanol	Trace	71
7	Copper triflate	Ethanol	Trace	74
8	Zinc triflate	Ethanol	Trace	76
9	*L*-Proline	Ethanol	25	70
10	Catalyst free	Ethanol	40	60
11[b]	Catalyst free	Ethanol	20	70
12[c]	Catalyst free	CH_3CN	10	80
13[c]	Catalyst free	DCM	Trace	90
14[c]	Catalyst free	THF	Trace	85
15[d]	Catalyst free	Water	72	20

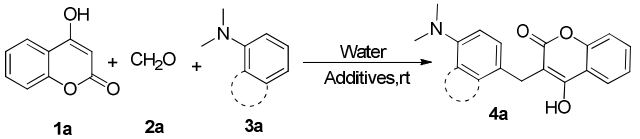
[a] Reaction conditions: 4-hydroxycoumarin (1 mmol), formaldehyde (2 mmol) and *N,N*-dialkylaniline (1 mmol) in 5 mL of solvent at room temperature for 8 h. [b] Refluxed. [c] At room temperature for 12 h. [d] At room temperture for 6 h. [e] Isolated yields.

Firstly, the reaction was carried out in ethanol at room temperature in the presence of catalytic amounts of some Brønsted acids: acetic acid, *p*-toluenesulfonic acid (PTSA), boric acid, and trifluoroacetic acid (TFA). Unfortunately, under these conditions the major isolated product was dimer **5a** instead of the desired product **4a** (Table 1, entries 1 to 4). The same result was obtained using Lewis acids such as $ZnCl_2$, $CuSO_4$, copper triflate, and zinc triflate (Table 1, entries 5 to 8).

We also screened organocatalysts such as *L*-proline, which gave only 25% yield for the desired **4a** (Table 1, entry 9). It is surprising that an enhanced yield of **4a** was observed under catalyst-free condition (Table 1, entry 10). On the contrary, decreased yield of **4a** was obtained under reflux without any catalyst (Table 1, entry 11). When reactions were performed in different solvents such as acetonitrile, dichloromethane, and tetrahydrofuran under catalyst-free conditions, the reaction was completed in 12 h with prevalent formation of **5a.** (Table 1, entries 12, 13 and 14). On the contrary, compound **4a** was formed in good yield when the transformation was performed in aqueous medium under catalyst-free condition (Table 1, entry 15).

Water was thus chosen for further investigations since it is readily available, environmentally benign, safe, cheap, non-flammable and non toxic. Furthermore, water displays unique reactivity[21] and selectivity[22] that cannot be obtained in conventional organic solvents.

Table 2 Study of hydrophobic effect of ionic and non-ionic additives on intermolecular hydroarylation of *o*-QMs with arenes in water[a]



Entry	Solvent	Time (h)	Yield **4a** (%)[c]	Yield **5a** (%)[c]
1	H_2O	6	72	20
2[b]	H_2O	4	50	40
3	1 M aq. LiCl	3.5	74	10
4	1.5 M aq. LiCl	2.2	78	5
5	2 M aq. LiCl	1.5	79	traces
6	2.5 M aq. LiCl	1.2	81	-
7[b]	2.5 M aq. LiCl	1.0	40	50
8	0.5 M aq. Glucose	4.5	74	10
9	1 M aq. Glucose	3	76	10
10	2.5 M aq. Glucose	3	75	12
11	2.5 M aq. NaCl	4.5	70	22
12	2 M aq. Urea	7	60	35

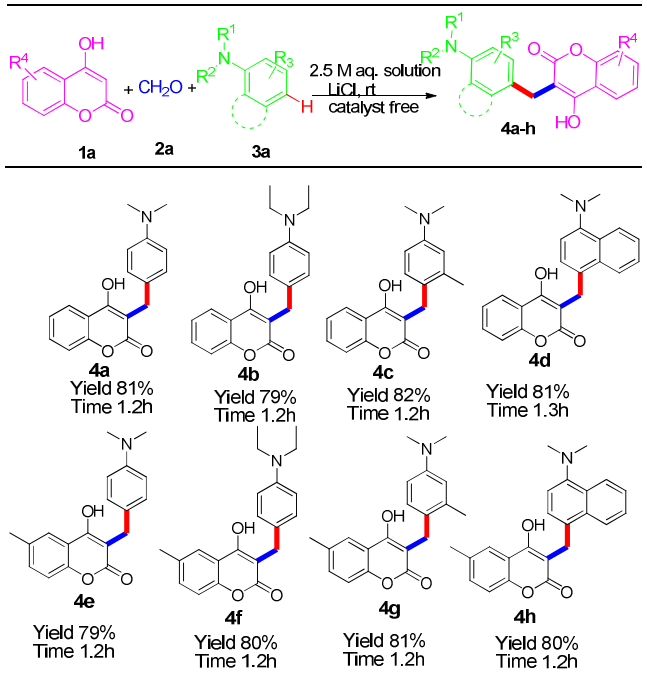
[a] Reaction conditions: 4-hydroxycoumarin (1 mmol), formaldehyde (2 mmol) and *N,N*-dialkylaniline, (1 mmol) in 5 mL of solvent at room temperature. [b] Refluxed. [c] Isolated yields.

We carried out the same reaction in water using ionic and non-ionic additives to study the effect of hydrophobicity on the reaction. The yield of the desired product **4a** increased significantly when reaction was carried out in water in the presence of pro-hydrophobic additives like LiCl, glucose and NaCl.[23] The use of different concentrations of pro-hydrophobic additives have been studied and results are given in Table 2.

Increasing the concentration of LiCl resulted in increased yield of the desired products **4a**.The best result was obtained using a 2.5 M aq. solution of LiCl, with an exclusive formation of **4a** (Table 2, entry 6). Likewise, aq. glucose (non-ionic hydrophobic additive) afforded better results at high concentrations, ranging from 0.5 M to 2.5 M[24] (Table 2, entries 8, 9 and 10). No significant improvement was gained in the yield of **4a** when we employed 2.5 M aq. NaCl as well as 2.0 M aq. urea solution (Table 2, entries 11 and 12 respectively). The reaction was also performed at various temperatures and best results were obtained at room temperature, as dimerized product **5a** prevailed under reflux (Table 2, entry 7).

To explore the scope and limitations of this protocol, we investigated the reaction of 4-hydroxycoumarin with formaldehyde and tertiary aromatic amines **4a-h** under optimized reaction conditions (Table 3).

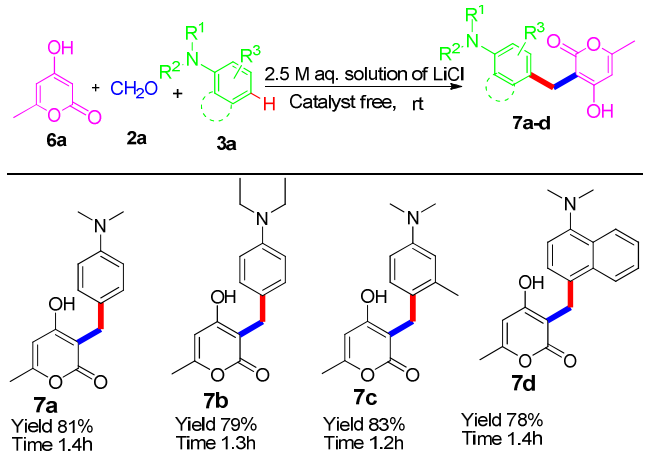
Table 3 Intermolecular Hydroarylation of coumarins *o*-QMs with tertiary aromatic amines [a,b]



[a] Reaction conditions: 4-hydroxycoumarin (1 mmol), formaldehyde (2 mmol) and *N,N*-dialkylaniline (1 mmol) in 5 mL of 2.5 M aq. solution of LiCl at room temperature under catalyst-free condition. [b]Isolated yield.

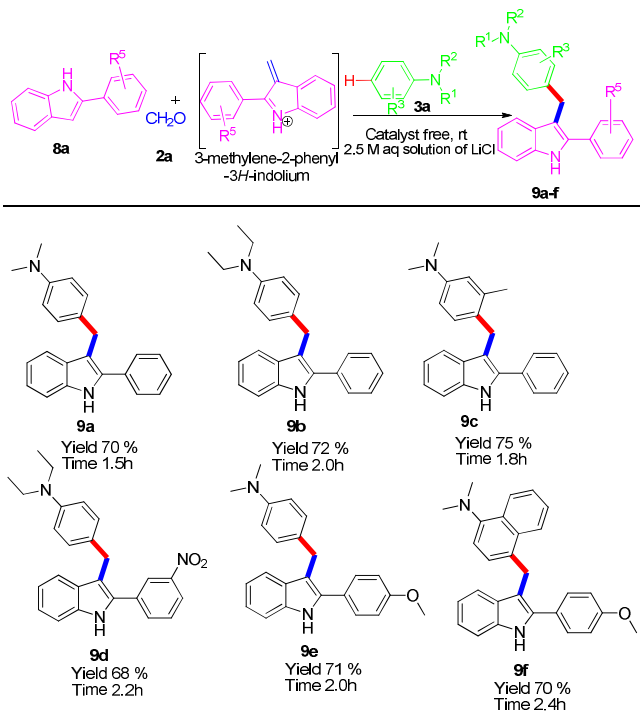
We also synthesized a chemical library of C3-alkylated 4-hydroxypyrones **7a-d** and C3-alkylated 2-phenylindoles **9a-f** in good to excellent yields (Table 4 and 5). It is notable that in all the cases we obtained exclusively para substituted products.

Table 4 Synthesis of C-3-alkylated 4-hydroxypyrone derivatives [a,b]



[a] Reaction conditions: 4-hydroxypyrone (1 mmol), formaldehyde (2 mmol) and *N, N*-dialkylaniline (1 mmol) in 5 mL of 2.5 M aq. solution of LiCl at room temperature under catalyst-free condition. [b] Isolated yield.

Table 5 Hydroarylation of *in situ* generated 3-methylene-2-phenyl-3H-indolium with tert-aryl amines [a,b]



[a] Reaction conditions: 2-phenylindole (1 mmol), formaldehyde (2 mmol) and *N, N*-dialkylaniline (1 mmol) in 5 mL of 2.5 M aq. solution of LiCl at room temperature under catalyst-free condition. [b]Isolated yield.

One of the possibly reason of regioselectivity is the steric hindrance of *N*-alkyl group and ortho hydrogen of *N,N*-dialkylanilines, which provides para selectivity. Similar results were reported by Jørgensen *et.al* for the synthesis of optically active aromatic mandelic acid esters by the reaction of glyoxylate with *N,N*-dialkylanilines.[25]

Conclusions

In summary, we have developed a novel green process for intermolecular hydroarylation of *in situ* generated *o*-quinone methides (*o*-QMs) with electron rich arenes in aqueous medium under catalyst-free condition at room temperature. The reaction is efficient and highly regioselective. We hope this protocol will be beneficial for the green synthesis of other bioactive agents.

Experimental

General procedure for the preparation of C3-alkylated 4-hydroxycoumarins (4a-h). 4-Hydroxycoumarin (1 mmol), formaldehyde (2 mmol) and *N,N*-dimethylaniline (1 mmol) in 5 mL of 2.5 M aq. solution of LiCl were taken in a round-bottom flask equipped with a magnetic stirrer. The reaction mixture was then stirred at room temperature for an appropriate time as given in Table 3 and the progress of the reaction was monitored by TLC. After completion of the reaction, the reaction mixture was extracted with ethyl acetate. Evaporation of the solvent gave a crude product

which was purified by column chromatography (silica gel, ethyl acetate:hexane).

General procedure for the synthesis of C3-alkylated 4-hydroxypyrones (7a-d). 4-Hydroxypyrone (1 mmol), formaldehyde (2 mmol) and *N,N*-dimethylaniline (1 mmol) in 5 mL of 2.5 M aq. solution of LiCl were taken in a round-bottom flask equipped with a magnetic stirrer. The reaction mixture was then stirred at room temperature for an appropriate time as given in Table 4 and the progress of the reaction was monitored by TLC. After completion of the reaction, the reaction mixture was extracted with ethyl acetate. Evaporation of the solvent gave a crude product which was purified by column chromatography (silica gel, ethyl acetate:hexane).

General procedure for the preparation of C3-alkylated 2-phenylindole (9a-f). 2-phenylindole (1 mmol), formaldehyde (2 mmol) and *N,N*-dimethylaniline (1 mmol) in 5 mL of 2.5 M aq. solution of LiCl were taken in a round-bottom flask equipped with a magnetic stirrer. The reaction mixture was then stirred at room temperature for an appropriate time as given in Table 5 and the progress of the reaction was monitored by TLC. After completion of the reaction, the reaction mixture was extracted with ethyl acetate. Evaporation of the solvent gave a crude product which was purified by column chromatography (silica gel, ethyl acetate:hexane).

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Notes and references

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Graphical Abstract

Catalyst-free hydroarylation of *in situ* generated *ortho*-Quinone methide (*o*-QM) with electron rich arenes in water

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We report the first C-H hydroarylation of *in situ* generated *ortho*-quinone methides with electron-rich arenes. The reaction takes place in water without any catalyst, and is highly regioselective. Ionic and non-ionic additives provide an increase in reaction rate, yield, and regioselectivity.