

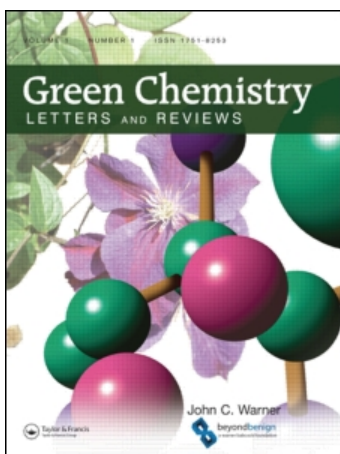
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### An efficient one-pot synthesis of anthraquinone derivatives catalyzed by alum in aqueous media

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## RESEARCH REVIEW

### An efficient one-pot synthesis of anthraquinone derivatives catalyzed by alum in aqueous media

Balaji R. Madje<sup>a</sup>, Kiran F. Shelke<sup>b</sup>, Suryakant B. Sapkal<sup>b</sup>, Gopal K. Kakade<sup>b</sup> and  
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Alum (KAl(SO<sub>4</sub>)<sub>2</sub>·12H<sub>2</sub>O) performs as a novel catalyst for the synthesis of anthraquinone derivatives from phthalic anhydride and substituted benzenes in good to excellent yields (70–96%) using water as a solvent at ambient temperature. Several solvents were examined for this reaction; however, in terms of reaction yield and time, water was found to be the optimum solvent. The remarkable advantages offered by this method are an inexpensive and easily available catalyst, a simple procedure, mild conditions, and much faster (60–120 min) reactions.

**Keywords:** anthraquinone; alum; one-pot synthesis

#### Introduction

Anthraquinones are important members of the organic family. Their structure is observed in some synthetic dyes and in many naturally occurring substances, such as pigments, vitamins, and enzymes (1–3). The quinone compounds occupy an important place among the different classes of anti-tumor agents (4). The hydroxylated 9,10-anthraquinones are widely found in nature and are known to display various pharmacological activities (5). Furthermore, the anthraquinones of the Rubiaceae family exhibit some interesting *in vivo* biological activities, such as anti-microbial (6), anti-fungal (7), hypotensive, analgesic (8), anti-malarial (9,10), anti-oxidant (11), anti-leukemic, and mutagenic functions (12,13).

The synthesis of anthraquinone derivatives currently is of great interest. There are various methods that have been reported for the synthesis of anthraquinones. The most common ones including the intramolecular condensation of aryl and *o*-aroylbenzoic acid produce anthraquinone derivatives using fuming sulfuric acid (14), benzoyl chloride and concentrated sulfuric acid (15,16), benzoyl chloride and zinc chloride (17), and POCl<sub>3</sub>/P<sub>2</sub>O<sub>3</sub>Cl<sub>4</sub> (18). It has been found that Friedel–Crafts reactions between phthalic anhydride and substituted benzenes in the presence of a eutectic mixture of aluminum chloride and sodium chloride (2:1) melt have been used for the preparation of various anthraquinones

(19–21). Other catalysts, such as AlCl<sub>3</sub>/H<sub>2</sub>SO<sub>4</sub> (21), montmorillonite clay and AlCl<sub>3</sub>/NaCl melt (22), montmorillonite K10 clay, and thin layer chromatography (TLC) grade silica gel (23) as heterogeneous catalyst have also been used for this transformation. These methods suffer from some disadvantages, such as long reaction times, use of toxic solvent, the reaction conditions are usually quite severe, some reagents are commercially unavailable, and the desired product was afforded from two steps with low yields. There still remains the need for a simple and efficient process for the synthesis anthraquinones derivatives.

In recent year, organic reactions in aqueous media have received considerable attention. The fact is that water is the inexpensive, most abundant, non-toxic, and environmentally friendly solvent. It exhibits unique reactivity and selectivity, which is different from those in conventional organic solvents (24). In this respect, the development of water-tolerant catalysts has rapidly become an area of intense research. However, there is not any report for the synthesis of anthraquinone derivatives in aqueous media catalyzed by alum. These findings prompted us to investigate the synthesis of anthraquinone derivatives in aqueous media. Alum (KAl(SO<sub>4</sub>)<sub>2</sub>·12H<sub>2</sub>O) was found to be effective in the synthesis of *cis*-isoquinolic acids (25), mono- and di-substituted 2,3-dihydroquinazolin-4(1*H*)-ones (26), dihydropyrimidines via Biginelli reaction (27),

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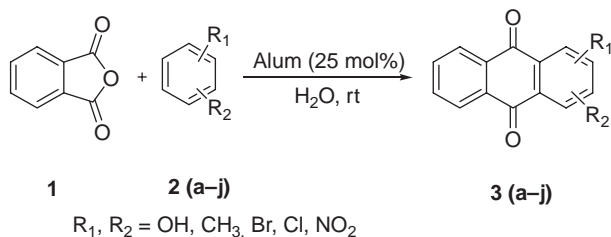
coumarins (28), 1,3,4-oxadiazoles (29), dibenzoxanthenes (30), 1,5-benzodiazepines (30), trisubstituted imidazoles (30) etc. However, there are no examples of the use of alum as a catalyst for the synthesis of anthraquinone derivatives.

### Results and discussion

As a continuation of our research devoted to the development of green organic chemistry by performing organic transformations with water as the reaction medium (31–37), herein, we have developed an efficient and green methodology for the synthesis of anthraquinone derivatives from phthalic anhydride and substituted benzene using alum (25 mol%) as an inexpensive catalyst in water, which makes use of milder conditions over the reported procedure as depicted in Scheme 1; the methodology developed is simple with good to excellent yields of products.

We first compared the catalyst effect on different solvents for the synthesis of 2-methylantraquinone as summarized in Table 1. In a typical experiment, the reaction of phthalic anhydride **1** and toluene **2g** in water was carried out in the presence of alum ( $\text{KAl}(\text{SO}_4)_2 \cdot 12\text{H}_2\text{O}$ ) to afford the corresponding 2-methylantraquinone **3g** in 92% yield. The reaction proceeded rapidly at ambient temperature with 25 mol% of catalyst (which is highly water soluble). The reaction was completed within 60 min (Table 1, entry 10) and no remarkable change in the yield of product was observed up to 90 min (Table 1, entry 11). We kept the catalyst constant and used different solvents, such as  $\text{CH}_2\text{Cl}_2$ ,  $\text{CH}_3\text{CN}$ , THF,  $\text{CHCl}_3$ , DMSO, DMF, MeOH, EtOH, and dioxane; all of which afforded a very low yield of product (Table 1, entries 1–9). Varying the amount of catalyst did not improve the yield (Table 1, entries 12–15). These results suggest that water is the best solvent for the synthesis of 2-methylantraquinone; it may be due to the greater solubility of the catalyst in water compared with organic solvent.

With optimal conditions in hand, we then reacted various benzene derivatives with phthalic anhydride



Scheme 1. Alum as a catalyst for the synthesis of anthraquinone derivatives.

Table 1. Solvent effect for synthesis of 3-methylantraquinone **3g**<sup>a</sup>.

Entry	Solvent	Catalyst (mol%)	Time (min)	Yield (%) <sup>b</sup>
1	$\text{CH}_2\text{Cl}_2$	25	150	30
2	$\text{CH}_3\text{CN}$	25	150	40
3	THF	25	120	35
4	$\text{CHCl}_3$	25	120	50
5	DMSO	25	100	45
6	DMF	25	100	45
7	MeOH	25	90	35
8	EtOH	25	60	40
9	Dioxane	25	90	45
10	$\text{H}_2\text{O}$	25	60	92
11	$\text{H}_2\text{O}$	25	90	92
12	$\text{H}_2\text{O}$	10	90	45
13	$\text{H}_2\text{O}$	15	90	65
14	$\text{H}_2\text{O}$	20	90	70
15	$\text{H}_2\text{O}$	30	90	92

<sup>a</sup>Reaction condition: **1** (1 mmol) and **2g** (1.1 mmol) at room temperature.

<sup>b</sup>Isolated yield.

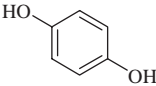
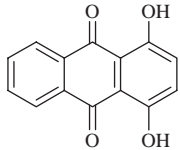
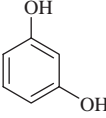
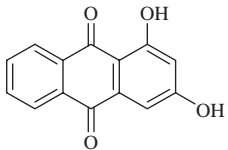
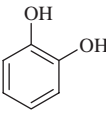
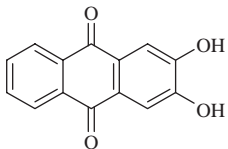
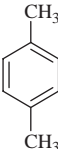
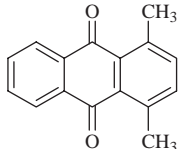
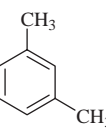
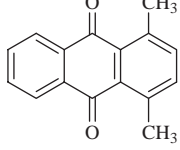
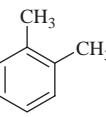
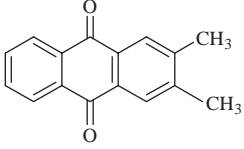
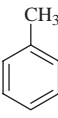
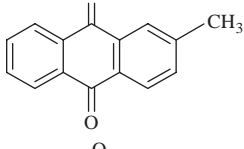
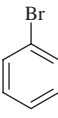
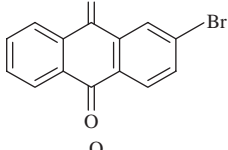
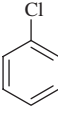
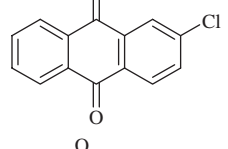
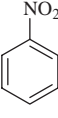
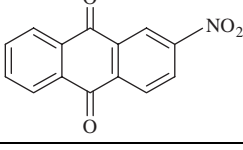
to give the corresponding anthraquinone derivatives in good to excellent yields (Table 2, entries **3 (a–j)**). In a similar fashion, a variety of substituted benzene with electron donating substituents reacts well under the reaction conditions giving the corresponding anthraquinone derivatives with high yields in short reaction time (Table 2, entry **3 (a–g)**). In contrast, by using substituted benzene with electron withdrawing groups, the corresponding anthraquinone derivatives were produced slowly, and the reaction required long reaction time (Table 2, entry **3 (h–j)**).

All the reactions were completed within 60–120 min. The obtained yields of anthraquinone derivatives were 70–96%. The structures of the products were confirmed by IR,  $^1\text{H}$  NMR, mass spectrometry, and elemental analysis.

### Experimental

Reactions were monitored by TLC (silica, 80:20 ethyl acetate:hexane). IR spectra were recorded on Perkin–Elmer FTIR spectrophotometer in KBr disc.  $^1\text{H}$  NMR spectra were recorded on a 400 MHz Varian–Mercury Plus spectrometer and are reported as parts per million (ppm) downfield from tetramethylsilane as internal standard. The following abbreviations are used: singlet (s), doublet (d), triplet (t), multiplet (m), and broad (br). Mass spectra were taken with a Waters Micromass-Quattro-II mass spectrometer. All chemicals were obtained from commercial suppliers and were used without purification.

Table 2. Synthesis of anthraquinone derivatives from phthalic anhydride with substituted benzenes in the presence of alum in water.

Entry	Benzene	Product	Time (min)	Yield (%) <sup>a</sup>	MP (°C) (31–37)
3a			60	96	194–196
3b			60	95	266–268
3c			60	96	260–262
3d			90	94	134–136
3e			90	96	158–160
3f			90	94	148–150
3g			60	92	176–178
3h			120	80	205–206
3i			120	85	210–212
3j			120	70	230–232

<sup>a</sup>Isolated yield based on benzene derivative.

### General procedures

Phthalic anhydride (1 mmol), substituted benzene (1.1 mmol), and water (5 mL) were mixed in a 25-mL single-neck round-bottom flask, and to this alum 25 mol% was added. The reaction mixture was stirred at room temperature for the appropriate time (Table 2, entries **3** (a–j)) and the progress of the reaction was monitored by TLC. After completion of the reaction, the mixture was extracted with ethyl acetate (2 × 10 mL). The combined organic layer was dried over anhydrous Na<sub>2</sub>SO<sub>4</sub> and evaporated under reduced pressure; the crude material was purified by column chromatography over silica gel to afford products **3** (a–j) with high purity.

### The spectral data of some representative anthraquinone derivatives

#### 2-Methylantraquinone (**3g**)

C<sub>15</sub>H<sub>10</sub>O<sub>2</sub>, yellow solid; IR (KBr, cm<sup>-1</sup>): 2950, 2900, 1669, 1593, 1326, and 1291; <sup>1</sup>H NMR (400 MHz, CDDL<sub>3</sub>): δ2.4–2.8 (3H, s) and 7–8.5 (7H, m); EIMS (*m/z*, %): 222 [M + 1].

#### 2-Chloroanthraquinone (**3i**)

C<sub>14</sub>H<sub>7</sub>ClO<sub>2</sub>, pale yellow; IR (KBr, cm<sup>-1</sup>): 1680, 1582, 1300, and 1280; <sup>1</sup>H NMR (400 MHz, CDDL<sub>3</sub>): δ7.42–7.98 (7H, m); EIMS (*m/z*, %): 245 [M + 1].

### Conclusion

In conclusion, we have developed an efficient and convenient green synthesis for the preparation of anthraquinone derivatives from commercially available phthalic anhydride and substituted benzene using the inexpensive, non-toxic, and easily available alum catalyst. The method offers several advantages including high yield of products, short reaction times, and ease of work up procedure.

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