

## A quick and clean procedure for synthesis of 5-arylmethylene-2,2-dimethyl-1,3-dioxane-4,6-diones in aqueous media

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### Abstract

A quick and efficient procedure for the synthesis of 5-arylmethylene-2,2-dimethyl-1,3-dioxane-4,6-diones uses the condensation reaction of isopropylidene malonate and aromatic aldehydes using hexadecyltrimethylammonium bromide (HTMAB) as catalyst in water. This method provides several advantages such as neutral conditions, short reaction time, high yields, and is environmentally friendly. The isopropylidene malonate has been prepared similarly.

**Keywords:** 5-Arylmethylene-2,2-dimethyl-1,3-dioxane-4,6-diones, isopropylidene malonate, aromatic aldehydes, green synthesis

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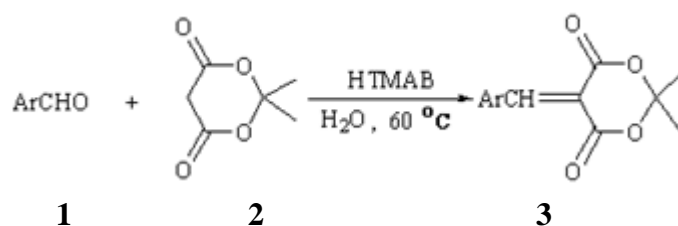
### Introduction

In recent years, the preparation of 5-arylmethylene-2,2-dimethyl-1,3-dioxane-4,6-diones has attracted strong interest owing to the broad spectrum of their properties: these compounds can be employed as intermediates for a series of natural products and heterocyclic compounds.<sup>1,2</sup> Several conventional syntheses of 5-arylmethylene-2,2-dimethyl-1,3-dioxane-4,6-diones use the condensation reaction of isopropylidene malonate and aromatic aldehydes in organic solvents<sup>3</sup> or use microwave irradiation<sup>4,5</sup> or grinding.<sup>6</sup> However, although each of the above methods has its own merits, they are plagued by the limitations of low yield, use of toxic organic solvents, and the requirements of excess of reagents/catalysts, special apparatus, and harsh reaction conditions. Consequently, there is scope for further development of mild conditions, increasing the variation of the substituents in the components, and better yields. More recently, some methods have been reported as giving relatively better results.<sup>7-9</sup>

With the increasing environmental concerns and regulatory constraints faced in the chemical and pharmaceutical industries, development of environmentally benign organic reactions has become a crucial and demanding research area in modern organic chemical research.<sup>10</sup> In 1980, Breslow discovered that the Diels-Alder reaction performed in water can be

subject to huge accelerations.<sup>11,12</sup> This observation led to increased interest from synthetic organic chemists in organic reactions in water. Therefore, more and more chemists are devoted to the research on 'green synthesis' which means that the reagents, solvents and catalysts are environmentally friendly. Recently, organic reactions in water without the use of harmful organic solvents have attracted much attention, because water is a cheap, safe and environmentally benign solvent.<sup>13-18</sup>

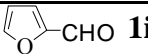
We have recently completed a series of organic syntheses using water as solvent.<sup>19-26</sup> In our investigations to develop a quick synthetic method in water using HTMAB as catalyst, we examined the synthesis of 5-arylmethylene-2,2-dimethyl-1,3-dioxane-4,6-diones in water, which is a green solvent (Scheme 1).



### Scheme 1

In a typical general procedure, a solution of an aromatic aldehyde **1** and isopropylidene malonate **2** in water was heated in the presence of a catalytic amount of HTMAB, and the corresponding 5-arylmethylene-2,2-dimethyl-1,3-dioxane-4,6-diones **3** were obtained in good to excellent yields. The results are summarized in Table 1.

**Table 1.** Synthesis of 5-arylmethylene-2,2-dimethyl-1,3-dioxane-4,6-diones in water

Entry	ArCHO	Product	Yield (%) <sup>a</sup>	Mp (°C)	
				Found <sup>b</sup>	Reported
1	C <sub>6</sub> H <sub>5</sub> CHO <b>1a</b>	<b>3a</b>	87	80-82	76-78 <sup>5</sup>
2	4-CH <sub>3</sub> C <sub>6</sub> H <sub>4</sub> CHO <b>1b</b>	<b>3b</b>	84	117-119	116-118 <sup>3</sup>
3	4-CH <sub>3</sub> OC <sub>6</sub> H <sub>4</sub> CHO <b>1c</b>	<b>3c</b>	83	125-127	123-125 <sup>5</sup>
4	3,4-(OCH <sub>2</sub> O)C <sub>6</sub> H <sub>3</sub> CHO <b>1d</b>	<b>3d</b>	82	168-169	167-169 <sup>3</sup>
5	4-HOC <sub>6</sub> H <sub>4</sub> CHO <b>1e</b>	<b>3e</b>	87	192-193	192-194 <sup>3</sup>
6	4-(CH <sub>3</sub> ) <sub>2</sub> NC <sub>6</sub> H <sub>4</sub> CHO <b>1f</b>	<b>3f</b>	92	166-168	162-164 <sup>3</sup>
7	4-ClC <sub>6</sub> H <sub>4</sub> CHO <b>1g</b>	<b>3g</b>	88	160-161	158-160 <sup>3</sup>
8	4-NO <sub>2</sub> C <sub>6</sub> H <sub>4</sub> CHO <b>1h</b>	<b>3h</b>	90	203-204	203-204.5 <sup>6</sup>
9	 CHO <b>1i</b>	<b>3i</b>	75	93-95	90-92 <sup>5</sup>

<sup>a</sup> Isolated yield; <sup>b</sup> After recrystallization.

From the results in Table 1, benzaldehyde and aromatic aldehydes with electron-withdrawing groups (-Cl, -NO<sub>2</sub>) and electron-donating groups (-CH<sub>3</sub>, -OCH<sub>3</sub>, -OCH<sub>2</sub>O-, -OH, -N(CH<sub>3</sub>)<sub>2</sub>) have all provided good results. We found that the temperature has some influence on the reaction: we can also carry out this conversion at room temperature, but the time needs to be longer. At temperatures over 60 °C, the isopropylidene malonate and products are partially hydrolyzed. Therefore, 60 °C seems to be the best reaction temperature.

The catalyst (HTMAB) plays a crucial role in the success of the reaction in terms of the time and the yields. For example, 4-dimethylaminobenzaldehyde reacted with isopropylidene malonate in the presence of 0 mol. % HTMAB to give the product **3f** in quantitative yield (66%) after 30 minutes reaction at 60 °C. Increasing the catalyst to 5, 10, and 15 mol. % results in improved reaction yields to 76%, 92% and 92% respectively. Use of just 10 mol. % HTMAB is sufficient to push the reaction forward. Higher amounts of the catalyst did not improve the results to a great extent. Reactions carried out in the absence of HTMAB are more difficult and the reaction time is too long. Thus, 10 mol. % HTMAB was chosen as a quantitative catalyst for these reactions. In addition, it must be pointed out that all of these reactions were carried out in water.

To find the optimum reaction time, the reaction was carried out in the presence of HTMAB for 20, 30, 45, 60 and 90 minutes, resulting in the isolation of **3f** in 75%, 92%, 89%, 86% and 70% yield, respectively. The reason for this variation is probably hydrolytic decomposition of 5-arylmethylene-2,2-dimethyl-1,3-dioxane-4,6-diones. Therefore, 30 minutes was chosen as the best condition for the reactions.

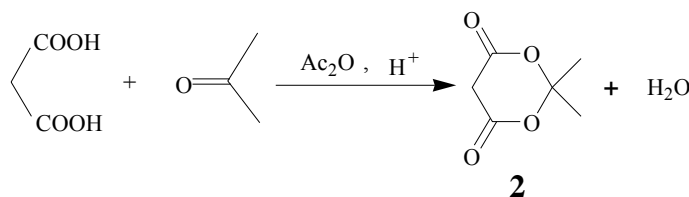
In summary, a quick and efficient procedure for the synthesis of 5-arylmethylene-2,2-dimethyl-1,3-dioxane-4,6-diones through the reaction of aromatic aldehydes and isopropylidene malonate using a catalytic amount of HTMAB as catalyst is reported. In addition, these reactions attest to the unique property of water as a reaction medium. This procedure offers several advantages including mild reaction conditions, cleaner reaction, short reaction time, high yields of products, as well as a simple experimental and isolated procedure, which makes it a useful and attractive process for the synthesis of these compounds. Mostly important, water has been chosen as a, “green” solvent for these reactions.

## Experimental Section

**General Procedures.** All liquid reagents were distilled before use. IR spectra were recorded on Bio-Rad FTS-40 spectrometer (KBr). <sup>1</sup>H NMR spectra were measured on a Bruker AVANCE 400 (400 MHz) spectrometer using TMS as internal standard and CDCl<sub>3</sub> as solvent. Elemental analyses were determined using a Perkin-Elmer 2400 II elemental analyzer.

**General procedure for isopropylidene malonate**<sup>27</sup>

To a solution of 4.16 g malonic acid in 4.8 mL of acetic anhydride, 0.16 mL sulfuric acid was added while stirring and cooling in ice water. Acetone (4.0 mL) was added after 20 minutes, the mixture was stirred for 6 hours, and was then allowed to stand overnight in the refrigerator, and the resulting crystals filtered off. The crude products were purified by recrystallization from acetone/water to give the pure products **2** (Scheme 2). **2**: Yield 72%, m.p. 95-96 °C (lit.<sup>27</sup> 94-95 °C). <sup>1</sup>H NMR (CDCl<sub>3</sub>): δ<sub>H</sub> = 1.76 (s, 6H, 2×CH<sub>3</sub>), 3.60 (s, 2H, CH<sub>2</sub>) ppm. Anal. Calcd. for C<sub>6</sub>H<sub>8</sub>O<sub>4</sub>: C 50.00, H 5.59; Found C 50.09, H 5.52 %.



Scheme 2

### General procedure for the synthesis of 5 – arylmethylene - 2,2 – dimethyl - 1,3 – dioxane - 4,6 - diones

A mixture of the aromatic aldehyde (**1**, 1 mmol), isopropylidene malonate (**2**, 1 mmol) and HTMAB (10 mol. %) in water (20 mL) was stirred at 60 °C. The progress of the reaction was monitored by thin layer chromatograph (TLC). After completion of the reactions (about 30 min), the mixture was cooled to room temperature, the solid was filtered off and washed with H<sub>2</sub>O (40 mL). The crude products were purified by recrystallization from ethanol (95%) to give **3**.

The data for some compounds are as follows:

**5-Benzylidene-2,2-dimethyl-1,3-dioxane-4,6-diones (3a)**. IR (KBr): ν<sub>max</sub> = 3100, 3000, 1765, 1730, 1605, 1580, 1370, 1232, 818 cm<sup>-1</sup>. <sup>1</sup>H NMR (CDCl<sub>3</sub>): δ 1.70 (s, 6H, 2×CH<sub>3</sub>), 6.90-6.92 (t, 1H, *J* = 8.0 Hz, ArH), 7.05 (t, 2H, *J* = 8.0 Hz, ArH), 7.14-7.16 (d, 2H, *J* = 8.0 Hz, ArH), 8.36 (s, 1H, CH) ppm. Anal. Calcd. for C<sub>13</sub>H<sub>12</sub>O<sub>4</sub>: C 67.23, H 5.21. Found: C, 67.14; H, 5.18.

**2,2-Dimethyl-5-(4-methylbenzylidene)-1,3-dioxane-4,6-diones (3b)**. IR (KBr): ν<sub>max</sub> = 3000, 1770, 1730, 1600, 1380, 1275, 1190, 1175, 820 cm<sup>-1</sup>. <sup>1</sup>H NMR (CDCl<sub>3</sub>): δ 1.79 (s, 6H, 2×CH<sub>3</sub>), 2.43 (s, 3H, CH<sub>3</sub>), 7.28 (d, 2H, *J*=8.4 Hz, ArH), 8.01 (d, 2H, *J*=8.4 Hz, ArH), 8.38 (s, 1H, CH) ppm. Anal. Calcd. for C<sub>14</sub>H<sub>14</sub>O<sub>4</sub>: C 68.28, H 5.73. Found: C, 68.34, H 5.68.

**5-(4-Methoxybenzylidene)-2,2-dimethyl-1,3-dioxane-4,6-diones (3c)**. IR (KBr): ν<sub>max</sub> = 3000, 1750, 1550, 1300, 1270, 1180, 830 cm<sup>-1</sup>. <sup>1</sup>H NMR (CDCl<sub>3</sub>): δ 1.73 (s, 6H, 2×CH<sub>3</sub>), 3.88 (s, 3H, OCH<sub>3</sub>), 7.08-7.10 (d, 2H, *J*=8.0 Hz, ArH), 8.12-8.14 (d, 2H, *J*=8.0 Hz, ArH), 8.31 (s, 1H, CH) ppm. Anal. Calcd. for C<sub>14</sub>H<sub>14</sub>O<sub>5</sub>: C 64.12, H 5.34. Found: C 64.24, H 5.22.

**2,2-Dimethyl-5-(3,4-dioxymethylenebenzylidene)-1,3-dioxane-4,6-diones (3d)**. IR (KBr): ν<sub>max</sub> = 3125, 1740, 1710, 1560, 1450, 1265, 1180, 790 cm<sup>-1</sup>. <sup>1</sup>H NMR (CDCl<sub>3</sub>): δ 1.78 (s, 6H, 2×CH<sub>3</sub>), 6.11 (s, 2H, OCH<sub>2</sub>O), 6.91 (d, 1H, *J*=8.4 Hz, ArH), 7.52-7.60 (d, 1H, *J*=8.4 Hz, ArH), 8.02-8.10

(s, 1H, ArH), 8.27 (s, 1H, CH) ppm. Anal. Calcd. for  $C_{14}H_{12}O_6$ : C 60.86, H 4.34. Found: C 60.94, H 4.28.

**5-(4-Hydroxybenzylidene)-2,2-dimethyl-1,3-dioxane-4,6-diones (3e).** IR (KBr):  $\nu_{max}$  3270, 1750, 1690, 1590, 1450, 1270, 1200, 1800, 840  $cm^{-1}$ .  $^1H$  NMR ( $CDCl_3$ ):  $\delta$  1.76 (s, 6H,  $2\times CH_3$ ), 6.94 (d, 2H,  $J=8.4$  Hz, ArH), 8.14 (d, 2H,  $J=8.4$  Hz, ArH), 8.29 (s, 1H, CH), 10.94 (s, 1H, OH) ppm. Anal. Calcd. for  $C_{13}H_{12}O_5$ : C 62.90, H 4.83. Found: C 62.82, H 4.89.

**2,2-Dimethyl-5-(4-dimethylaminobenzylidene)-1,3-dioxane-4,6-diones (3f).** IR (KBr):  $\nu_{max}$  3075, 1730, 1700, 1620, 1510, 1370, 1290, 1160, 1130, 820  $cm^{-1}$ .  $^1H$  NMR ( $CDCl_3$ ):  $\delta$  1.75 (s, 6H,  $2\times CH_3$ ), 2.49 [s, 6H,  $(CH_3)_2N$ ], 6.70 (d, 2H,  $J = 9.5$  Hz, ArH), 8.20-8.30 (m, 3H, ArH and CH) ppm. Anal. Calcd. for  $C_{15}H_{17}NO_4$ : C 65.44, H 6.22, N 5.09. Found: C 65.56, H 6.14, N 5.12.

**5-(4-Chlorobenzylidene)-2,2-dimethyl-1,3-dioxane-4,6-diones (3g).** IR (KBr):  $\nu_{max}$  3000, 1770, 1740, 1380, 1320, 1200, 1020, 820  $cm^{-1}$ .  $^1H$  NMR ( $CDCl_3$ ):  $\delta$  1.80 (s, 6H,  $2\times CH_3$ ), 7.45 (d, 2H,  $J=8.6$  Hz, ArH), 8.03 (d, 2H,  $J=8.6$  Hz, ArH), 8.36 (s, 1H, CH) ppm. Anal. Calcd. for  $C_{13}H_{11}ClO_4$ : C 58.54, H 4.13. Found: C 58.62, H 4.09.

**2,2-Dimethyl-5-(4-nitrobenzylidene)-1,3-dioxane-4,6-diones (3h).** IR (KBr):  $\nu_{max}$  3000, 1758, 1728, 1600, 1367, 1231, 830  $cm^{-1}$ .  $^1H$  NMR ( $CDCl_3$ ):  $\delta$  1.85 (s, 6H,  $2\times CH_3$ ), 7.35-7.68 (m, 4H, ArH), 8.38 (s, 1H, CH). Anal. Calcd. for  $C_{13}H_{11}NO_6$ : C 56.32, H 4.00, N 5.52. Found C: 56.24, H 3.95, N 5.58 %.

**5-(2-Furylmethylene)-2,2-dimethyl-1,3-dioxane-4,6-diones (3i).** IR (KBr):  $\nu_{max}= 3020, 1770, 1720, 1620, 1390, 770$   $cm^{-1}$ .  $^1H$  NMR ( $CDCl_3$ ):  $\delta$  1.75 (s, 6H,  $2\times CH_3$ ), 6.20-6.48 (m, 3H, =CH), 8.39 (s, 1H, CH) ppm. Anal. Calcd. for  $C_{11}H_{10}NO_5$ : C 59.46, H 4.54. Found C, 59.41; H, 4.47.

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