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Synthesis of 4-Aryl-7,7-dimethyl-5-oxo-3,4,5,6,7,8-hexahydrocoumarins in Water

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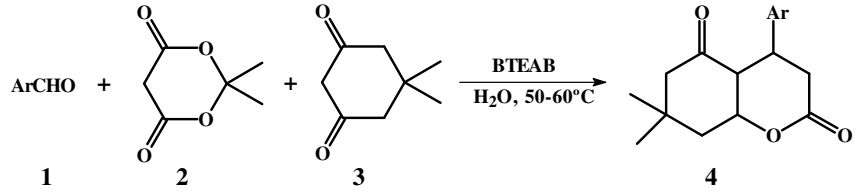
A practical chemistry route to the synthesis of 4-aryl-7,7-dimethyl-5- oxo-3,4,5,6,7,8-hexahydrocoumarins from 5,5-dimethyl-1,3-cyclohexadion, isopropylidene malonate and aromatic aldehydes catalyzed by benzyltriethyl-ammonium bromide (BTEAB) in water is described. This method provides several advantages such as simple work-up procedure, mild reaction conditions and environment friendly. In addition, water was chosen as a green solvent.

Key Words: Synthesis, Coumarin, Aromatic aldehyde, 5,5-Dimethyl-1,3-cyclohexanedione, Isopropylidene malonate, Aqueous media.

INTRODUCTION

Coumarins and its derivatives are very useful compounds. They have been widely used in many chemical technology fields, such as detergent and fluorochrome[1]. They are a kind of medicine intermediates due to their useful biological and pharmacological properties, such as antibacterial, molluscacides, anthelmintic, hypnotic and insecticidal properties[2-4]. Many routes have been reported for the synthesis of coumarin and its derivatives, but the synthesis of polyhydrocoumarins have seldom reported[5,6]. Margaretha[7] has ever reported for the synthesis of 4-aryl-7,7-dimethyl-5-oxo-3,4,5,6,7,8-hexahydrocoumarin with hexahydropyridine as catalyst, but, only a compound was synthesized. More recently, the condensation reaction carried out by microwave irradiation was applied for this purpose to obtain relatively better result[8]. These methods were carried out in the organic solvent. These methods will bring certain pollution to environment. Our interest in organic reaction carried out exclusively in water led us to investigate this compound through a simple route.

We have completed a series of organic synthesize the research of the reaction with water as solvent recently[9-18]. Herein we report a highly efficient and practical method for the synthesis of 4-aryl-7,7-dimethyl-5-oxo-3,4,5,6,7,8-hexahydrocoumarins from 5,5-dimethyl-1,3-cyclohexadion, isopropylidene malonate and aromatic aldehydes catalyzed by benzyl triethyl ammonium bromide (BTEAB) in water (**Scheme-I**).



Scheme-I

EXPERIMENTAL

Liquid aldehydes were distilled before use. IR spectra were recorded on a Bio-Rad FTS-40 spectrometer (KBr). ^{1}H NMR spectra were measured on a Bruker Avance 400 (400 MHz) spectrometer using TMS as internal reference and $CDCl_3$ as solvent.

Procedure of isopropylidene malonate: To a solution of 4.16 g malonic acid in 4.8 mL of acetic anhydride, 0.16 mL sulfuric acid was added with constant stirring and cooling in ice water. 4.0 mL acetone was added after 20 min, the mixture was stirred for 6 h and allowed to stand overnight in the refrigerator and the resulting crystals was filtered off. The crude products were purified by recrystallization by acetone/water, yield 72 %.

General procedure for the synthesis of 4-Aryl-7,7-dimethyl-5-oxo-3,4,5,6,7,8-hexahydro-coumarin: A mixture of an aromatic aldehyde (**1**, 2 mmol), isopropylidene malonate (**2**, 2 mmol) and BTEAB (12 mol %) in water (20 mL) was stirred at room temperature for 0.5 h. Then the 5,5-dimethyl-1,3-cyclohexadion (**3**, 2mmol) was added. The mixture was stirred at 50-60ºC for 4 h. The progress of the reaction was monitored by thin layer chromatograph. After the completion of the reaction, the mixture was cooled to room temperature. The solid was filtered off and washed with H_2O (2 × 20 mL). The crude products were purified by recrystallization by ethanol (95 %) to give **4**. Data of some compounds are shown below:

7,7-Dimethyl-4-phenyl-5-oxo-3,4,5,6,7,8-hexahydrocoumarin (4a): IR (KBr, cm^{-1}): ν_{max} = 3052, 1771, 1658, 1376, 1114, 859; ^{1}H NMR δ = 1.12 (s, 3H, CH_3), 1.14 (s, 3H, CH_3), 2.33 (d, 1H, *J* = 16.4 Hz, 8-H) 2.38 (d, 1H, *J* = 16.4 Hz, 8-H), 2.55 (s, 2H, 6-H), 2.93 (d, 1H, *J* = 12.0 Hz, 3-H), 2.97 (d, 1H, *J* = 12.0 Hz, 3-H), 4.31-4.33 (m, 1H, 4-H), 7.15-7.32 (m, 5H, ArH).

7,7-Dimethyl-4-(2-chlorophenyl)-5-oxo-3,4,5,6,7,8-hexahydrocoumarin (4b): IR (KBr, cm^{-1}): ν_{max} = 3065, 1786, 1730, 1648, 1099, 755; ^{1}H NMR δ = 1.17 (s, 3H, CH_3), 1.19 (s, 3H, CH_3), 2.37 (s, 2H, 8-H), 2.59 (d, 1H, *J* = 18.4 Hz, 6-H), 2.53 (d, 1H, *J* = 18.4 Hz, 6-H), 2.95-2.96 (m, 2H, 3-H), 4.77 (s, 1H, 4-H), 6.91-7.42 (m, 4H, ArH).

7,7-Dimethyl-4-(3-chlorophenyl)-5-oxo-3,4,5,6,7,8-hexahydrocoumarin (4c): IR (KBr, cm^{-1}): ν_{max} = 3080, 1780, 1738, 1660, 1114, 972, 798; ^1H NMR δ = 1.13 (s, 3H, CH_3), 1.17 (s, 3H, CH_3), 2.35 (s, 2H, 8-H), 2.57 (s, 2H, 6-H), 2.92 (d, 1H, *J* = 16.4 Hz, 3-H), 2.98 (d, 1H, *J* = 16.4 Hz, 3-H), 4.30 (s, 1H, 4-H), 7.05-7.29 (m, 4H, ArH).

7,7-Dimethyl-4-(4-chlorophenyl)-5-oxo-3,4,5,6,7,8-hexahydrocoumarin (4d): IR (KBr, cm^{-1}): ν_{max} = 3098, 1782, 1695, 1623, 1200, 885; ^1H NMR δ = 0.93 (s, 3H, CH_3), 0.98 (s, 3H, CH_3), 2.31 (d, 1H, *J* = 16.4 Hz, 8-H), 2.33 (d, 1H, *J* = 16.4 Hz, 8-H), 2.58 (s, 2H, 6-H), 2.95-2.98 (m, 2H, 3-H), 4.31 (m, 1H, 4-H), 7.17 (d, 2H, *J* = 8.0 Hz, ArH) 7.35 (d, 2H, *J* = 8.0 Hz, ArH).

7,7-Dimethyl-4-(2,4-dichlorophenyl)-5-oxo-3,4,5,6,7,8-hexahydrocoumarin (4e): IR (KBr, cm^{-1}): ν_{max} = 3088, 1779, 1647, 1656, 1106, 829; ^1H NMR δ = 1.18 (s, 3H, CH_3), 1.20 (s, 3H, CH_3), 2.36 (m, 2H, 8-H), 2.60 (m, 2H, 6-H), 2.93-2.95 (m, 2H, 3-H), 4.70 (s, 1H, 4-H), 6.85-7.45 (m, 3H, ArH).

7,7-Dimethyl-4-(4-nitrophenyl)-5-oxo-3,4,5,6,7,8-hexahydrocoumarin (4f): IR (KBr, cm^{-1}): ν_{max} = 3116, 1783, 1656, 1603, 1354, 1110, 855; ^1H NMR δ = 1.09 (s, 3H, CH_3), 1.17 (s, 3H, CH_3), 2.31 (d, 1H, *J* = 16.8 Hz, 8-H), 2.36 (d, 1H, *J* = 16.8 Hz, 8-H), 2.56 (s, 2H, 6-H), 2.92-3.03 (m, 2H, 3-H), 4.40 (m, 1H, 4-H), 7.34 (d, 2H, *J* = 8.4Hz, ArH) 8.16 (d, 2H, *J* = 8.4 Hz, ArH).

7,7-Dimethyl-4-(4-methoxyphenyl)-5-oxo-3,4,5,6,7,8-hexahydrocoumarin (4g): IR (KBr, cm^{-1}): ν_{max} = 3025, 1777, 1654, 1606, 1376, 1244, 1113, 1034, 969; ^1H NMR δ = 1.11 (s, 3H, CH_3), 1.15 (s, 3H, CH_3), 2.32 (m, 2H, 8-H), 2.53 (s, 2H, 6-H), 2.90-2.92 (m, 2H, 3-H), 3.78 (s, 3H, OCH_3), 4.26 (s, 1H, 4-H), 6.84 (d, 2H, *J* = 8.0 Hz, ArH), 7.05 (d, 2H, *J* = 8.0 Hz, ArH).

7,7-Dimethyl-4-(3,4-dioxymethylenephenyl)-5-oxo-3,4,5,6,7,8-hexahydrocoumarin (4h): IR (KBr, cm^{-1}): ν_{max} = 3071, 1786, 7653, 1495, 1236, 1203, 1183, 859; ^1H NMR δ = 1.08 (s, 3H, CH_3), 1.11 (s, 3H, CH_3), 2.19 (d, 1H, *J* = 16.0 Hz, 8-H) 2.34 (d, 1H, *J* = 16.0 Hz, 8-H), 2.49 (s, 2H, 6-H), 2.85-2.86 (m, 2H, 3-H), 4.21 (s, 1H, 4-H), 5.82 (m, 2H, OCH_2O), 6.92-7.05 (m, 3H, ArH).

7,7-Dimethyl-4-(4-hydroxyphenyl)-5-oxo-3,4,5,6,7,8-hexahydrocoumarin (4i): IR (KBr, cm^{-1}): ν_{max} = 3256, 3024, 1788, 1630, 1093, 839; ^1H NMR δ = 1.12 (s, 3H, CH_3), 1.17 (s, 3H, CH_3), 2.34 (s, 2H, 8-H), 2.55 (s, 2H, 6-H), 2.91-2.93 (m, 2H, 3-H), 4.25-4.26 (m, 1H, 4-H), 6.70 (d, 2H, *J* = 8.4 Hz, ArH), 7.0 (d, 2H, *J* = 8.4 Hz, ArH).

7,7-Dimethyl-4-(4-hydroxy-3-methoxyphenyl)-5-oxo-3,4,5,6,7,8-hexahydrocoumarin (4j): IR (KBr, cm^{-1}): ν_{max} = 3250, 3016, 1770, 1655, 1105, 849; ^1H NMR δ = 1.05 (s, 3H, CH_3), 1.11 (s, 3H, CH_3), 2.28 (m, 2H,

8-H), 2.48 (s, 2H, 6-H), 2.86-2.87 (m, 2H, 3-H), 4.17-4.20 (m, 1H, 4-H), 6.59-6.78 (m, 3H, ArH), 6.85 (s, 1H, OH).

7,7-Dimethyl-4-(4-dimethylaminophenyl)-5-oxo-3,4,5,6,7,8-hexahydrocoumarin (4k): IR (KBr, cm^{-1}): ν_{max} = 3016, 1791, 1703, 1640, 1129, 879; ^1H NMR δ = 0.93 (s, 3H, CH_3), 1.13 (s, 3H, CH_3), 2.09 (d, 1H, *J* = 16.4 Hz, 8-H), 2.24 (d, 1H, *J* = 16.4 Hz, 8-H), 2.38 (s, 2H, 6-H), 2.60-2.66 (m, 2H, 3-H), 2.95 (s, 6H, 2N-CH_3), 4.07-4.27 (m, 1H, 4-H), 6.74-7.15 (m, 4H, ArH).

RESULTS AND DISCUSSION

In a typical general experimental procedure, a solution of an aromatic aldehyde (**1**), isopropylidene malonate (**2**) and 5,5-dimethyl-1,3-cyclohexadion (**3**) in water was heated in 50-60ºC in the presence of a catalytic amount of BTEAB (12 mol %) for a certain period of time required to complete the reaction, resulting in the formation of 4-aryl-7,7-dimethyl-5-oxo-3,4,5,6,7,8-hexahydrocoumarins. The reaction mixture was filtered off and washed with H_2O and filtrate was recycled to reuse. The crude product was purified by recrystallization from ethanol to afford the pure products **4**. The results are presented in Table-1.

TABLE-1
SYNTHESIS OF HEXAHYDROCOUMARINS CATALYZED BY BTEAB IN WATER

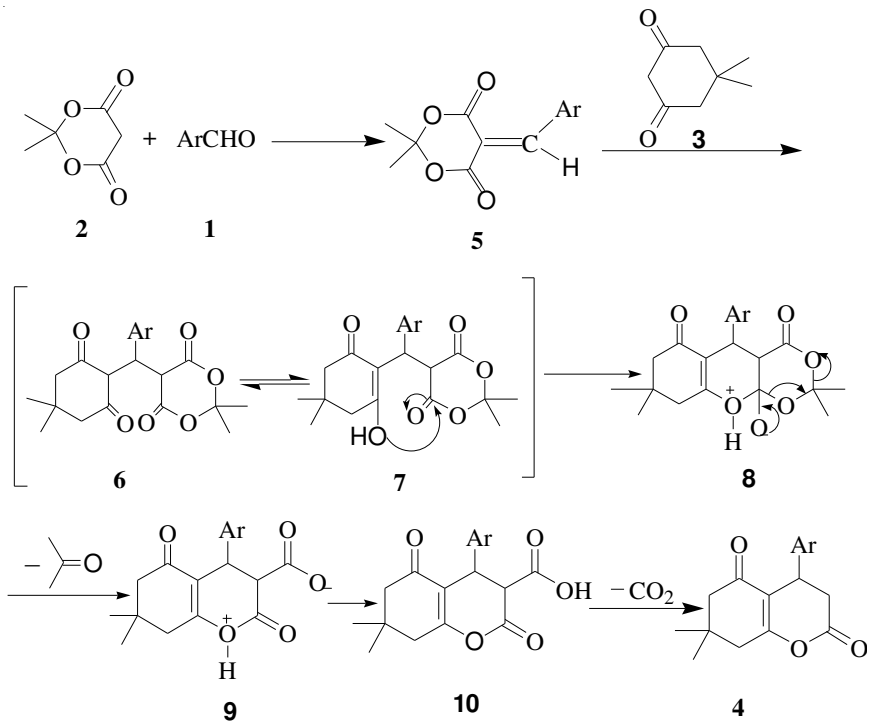
Ar	Product	Yield[a] (%)	m.p. (ºC)	
			Found	Reported[8,19]
C_6H_5 **1a**	**4a**	86	98-100	99-101
2-ClC_6H_4 **1b**	**4b**	92	134-135	134-135
3-ClC_6H_4 **1c**	**4c**	94	116-118	116-118
4-ClC_6H_4 **1d**	**4d**	92	158-160	156-158
2,4-$Cl_2C_6H_3$ **1e**	**4e**	93	162-164	162-164
4-$NO_2C_6H_4$ **1f**	**4f**	90	140-142	140-141
4-$CH_3OC_6H_4$ **1g**	**4g**	88	126-128	128-130
3,4-$OCH_2OC_6H_3$ **1h**	**4h**	89	132-134	130-132
4-HOC_6H_4 **1i**	**4i**	76	222-224	223-224
4-HO-3-$CH_3OC_6H_3$ **1j**	**4j**	72	160-162	158-160
4-$Me_2NC_6H_4$ **1k**	**4k**	66	138-140	136-138

[a]Isolated yield.

As shown in Table-1, a series of aromatic aldehyde **1** were reacted with **2** and **3** in the presence of BTEAB in water at 50-60ºC, the reaction proceed to afford the corresponding product **4** in good to excellent yields.

It is found that the temperature have certain influence to reaction. At room temperature the conversion reaction can be carried out, but time needs to be longer. If temperature over 60ºC, isopropylidene malonate and products will be a partial hydrolysis. Therefore, the reaction temperature controls in the 50-60ºC.

The catalyst plays a crucial role in the success of the reaction in terms of the rate and the yields. For example, 3-chlorobenzaldehyde reacted with isopropylidene malonate and 5,5-dimethyl-1,3-cyclo-hexadion in water in 50-60ºC in the presence of 3 mol % BTEAB to give the product **4c** in modest yield (74 %) after 4 h of reaction time. Increasing of the catalyst to 5, 8, 12 and 15 mol % results in accelerating the reaction yields to 82, 90, 94 and 94 %, respectively. The use of 12 mol % BTEAB in water in 50-60ºC is sufficient to push the reaction forward. Higher amounts of the catalyst did not improve the results to a greater extent. Thus, 12 mol % BTEAB was chosen as a quantitative catalyst for these reactions.



2 **1** **5** **3** **6** **7** **8** **9** **10** **4**

Scheme-II

Based on the reference[20], the C-2 unit of **2** is more active than **3**, the possible mechanism to account for the reaction has been proposed (**Scheme-II**). One molecule of aromatic aldehyde (**1**) was first condensed with isopropylidene malonate (**2**) through a fast Knoevenagel reaction to afford

the arylidenedi-methyldioxanedione (**5**). Then the active methylene of **3** was reacted with the electrophilic C=C double bond of **5** giving the intermediate **6**, followed formation of **7** by the tautomerization. Then the intermediate **7** was cyclized by the nucleophilic attack of OH group on the carbonyl (C=O) moiety and eliminate one molecule of acetone and carbon dioxide to give the products (**7** → **8** → **9** → **10** → **4**) (**Scheme-II**). In this process, BTEAB could promote these reactions as an emulsifier.

Conclusion

In summary, a procedure for the synthesis of 4-aryl-7,7-dimethyl-5-oxo-3,4,5,6,7,8- hexahydrocoumarins catalyzed by BTEAB in water have been developed. This is a one-pot three-component condensation in water. It is noteworthy that the experimental procedure is very simple and strict anhydrous conditions are not required. Water solution is a clean and environmentally desirable system. No harmful organic solvents are used. In addition, high temperature is not needed. This report has proposed and demonstrated a new useful and attractive process for the synthesis of these compounds.

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