A clean method for producing 4-aryl-7,7-dimethyl-5-oxo-3,4,5,6,7,8-hexahydrocoumarin in aqueous media

Tong-Shou Jin*, Ai-Qing Wang, Zhao-Li Cheng, Jian-She Zhang and Tong-Shuang Li

Department of Chemistry, College of Chemistry and Environmental Science, Hebei University, Baoding 071002, P. R. China

A synthesis of 4-aryl-7,7-dimethyl-5-oxo-3,4,5,6,7,8-hexahydrocoumarin from aromatic aldehyde, 5,5-dimethyl-1, 3-cyclohexadion and Meldrum's acid catalysed by hexadecyltrimethylammonium bromide in water is described. This method provides several advantages such as mild reaction conditions, simple work-up procedure and environment friendly.

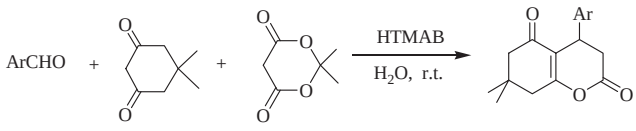
Keywords: coumarin, hexadecyltrimethyl ammonium bromide, aqueous media

Water is an environmentally attractive medium for many organic reactions.[1] It has the advantage of avoiding extensive drying reactants, catalyst and solvent, whilst a unique reactivity and selectivity some times results.[2, 3] Organic reaction in water without using harmful organic solvents are current interest in relation to environmental concerns. However, water as a solvent is not used since many organic materials do not dissolve in water and many reactive intermediates and catalysts are decomposed in water. Phase-transfer catalysis (PTC) or surfactants such as hexadecyltrimethylammonium bromide (HTMAB), tetrabutylammonium bromide (TBAB), 4-dodecylbenesulfonic acid (DBSA), are used to dispense the organic materials in water in the course of synthesis. We have developed novel routes for the synthesis of some heterocyclics compounds catalysed by these PTC or surfactants in water.[4] The aim of this research is to synthesis heterocyclic compounds in aqueous media.

Coumarin and its derivatives are useful compound.[5,6] Many routes have been reported for the synthesis of coumarin and its derivatives, but the synthesis of polyhydrocoumarin have seldom reported.[7] Our interest in organic reaction carried out exclusively in water led us to investigate a simple route to these compounds. Herein we report a highly efficient method for synthesis 4-aryl-7,7-dimethyl-5-oxo-3,4,5,6,7,8-hexahydrocoumarin catalysed by HTMAB in water (Scheme 1).

When the aromatic aldehyde **1**, 5,5-dimethyl-1, 3-cyclohexadion **2** and Meldrum's acid **3** were mixed in water in the presence of HTMAB at room temperature, high yields of products **4** were obtained. The results are summarised in Table 1.

As shown in Table 1, a series of aromatic aldehydes **1** were reacted with **2** and **3** in the presence of HTMAB in water at room temperature, The reaction proceeded smoothly to afford the corresponding product **4** in good yields. No substituents effects on the aromatic ring were observed. Aromatic



1 **2** **3** **4**

Scheme 1

aldehydes containing electron-withdrawing groups (such as nitro group, halide) and electron-donating groups (such as hydroxyl group, alkoxyl group, dimethylamino group) were employed and reacted well to give the corresponding products **4** in good to excellent yields under these reaction conditions. We also found that the reaction cannot be carried out if an aliphatic aldehyde is used.

Taking the reaction of 3-chlorobenzaldehyde as an example, we investigated the effect of the catalyst reagents on the reaction. It was found that the HTMAB plays a crucial role in the success of the reaction in terms of the rate and the yields. For example, the reaction could be carried out in the absence of HTMAB with the mixture (**1c, 2** and **3**) in water at room temperature for 8h, but the yield (41%) was poor. We have also studied the catalyst for this reaction. Some other common PTC or surfactants such as TBAB, DBSA, sodium dodecyl sulfate (SDS) were tested. The results were summarised in Table 2. These data indicated that the HTMAB is the most suitable for this reaction. It is noteworthy that the DBSA cannot catalyse this reaction because the input material **3** decomposed under these acidic condition.

We also found that this catalyst could be reused 5 times for the synthesis of **4c** without significant loss of activity. The results were summarised in Table 3.

The C-2 unit of **3** is more active than **2**,[8] and hence we propose the following mechanism to account for the reaction.

Table 1 Synthesis of hexahydrocoumarins catalysed by HTMAB in aqueous media

				M.p. / °C	
Entry	Ar	Product	Yields[a]/%	Found	Reported[7]
1	C_6H_5 1a	4a	86	99–101	
2	2-ClC_6H_4 1b	4b	89	134–135	
3	3-ClC_6H_4 1c	4c	92	116–118	
4	4-ClC_6H_4 1d	4d	90	160–161	156–158
5	2,4-$Cl_2C_6H_4$ 1e	4e	82	162–164	
6	4-$NO_2C_6H_4$ 1f	4f	79	140–141	
7	4-HOC_6H_4 1g	4g	75	223–224	
8	4-HO-3-$CH_3OC_6H_3$ 1h	4h	64	160–163	158–160
9	4-$CH_3OC_6H_4$ 1i	4i	73	126–127	128–130
10	4-$Me_2NC_6H_4$ 1j	4j	59	138–140	136–138
11	3,4-$OCH_2OC_6H_3$ 1k	4k	89	139–140	130–132

[a]Isolated yield.

* Correspondence. E-mail: orgsyn@mail.bhu.edu.cn

Table 2 The reaction in the presence of various catalysts in water

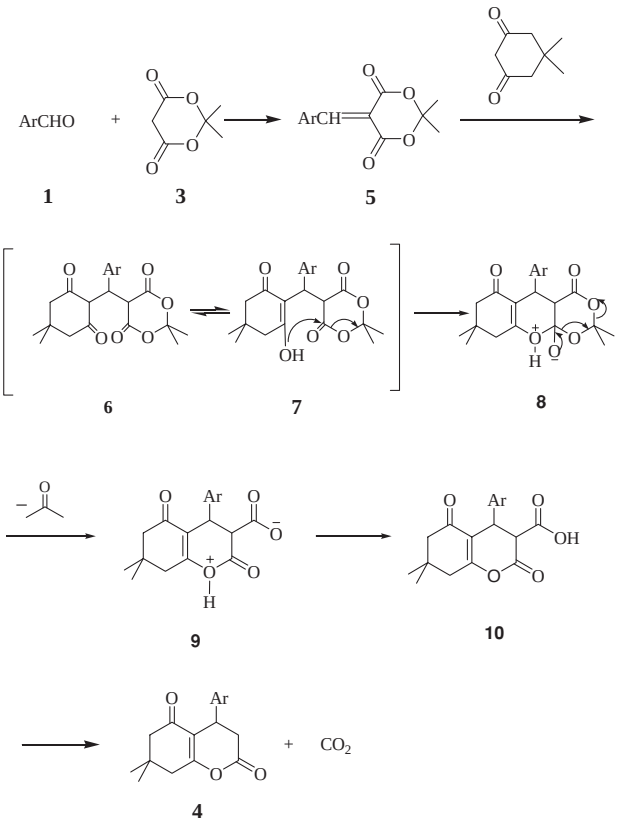
Catalyst	TBAB	DBSA	SDS	HTMAB
Yield/%	86	0	68	92

Table 3 Reuse of the catalyst for synthesis of **4c**

Times	1	2	3	4	5
Yield/%	92	89	86	82	79

One molecule of aromatic aldehyde **1** was firstly condensed with Meldrum's acid **3** through a fast Knoevenagel reaction to afford the arylidenedimethyldioxanedione **5**. Then the active methylene of **2** was reacted with the electrophilic C=C double bond of **5** giving the intermediate **6** followed by formation of **7** by a Michael addition. Then intermediate **7** was cyclised by the nucleophilic attack of OH group on the carbonyl (C=O) moiety and the elimination of one molecule of acetone and carbon dioxide to give the product **4** (Scheme 2)**.** In this process, HTMAB could promote these reactions as an emulsifier. The products have been identified by ^{1}H NMR, and IR analyses.

In summary, a procedure for the preparation of 4-aryl-7, 7-dimethyl-5-oxo-3,4,5,6,7,8- hexahydrocoumarin catalysed by HTMAB in aqueous media has 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 is a clean and environmentally desirable system. No harmful organic solvents are used. In addition, high temperature is not needed.



Scheme 2

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. Melting points are uncorrected.

General coupling procedure: A mixture of an aromatic aldehyde (**1**, 2mmol), meldrum's acid (**3**, 2mmol) and HTMAB (50mg) in water (20 ml) was stirred at room temperature for 30min. Then the 5,5-dimethyl-1,3-cyclohexadione (**2**, 2mmol) was added. The mixture was warmed to 30–35 °C slowly and stirred for 6–8h. After the reaction is finished, the solid was filtered off and washed with H_2O (2×20ml). The crude products were purified by recrystallisation by ethanol (95%) to give **4**.

Data of compounds are shown below:

4a, *7,7-dimethyl-4-phenyl-5-oxo-3,4,5,6,7,8-hexahydrocoumarin*: IR (KBr): ν_{max} 3052, 1771, 1658, 1376, 1114, 859 cm^{-1}; ^{1}H NMR δ_H 1.16 (3H, s, CH_3), 1.24(3H, s, CH_3), 2.33(1H, d, *J*=16.4Hz, 8-H) 2.38(1H, d, *J*=16.4Hz, 8-H), 2.55(2H, s, 6-H), 2.95(2H, d, 3-H), 4.32(1H, br.s, 4-H), 7.16–7.30 (5H, m, ArH). Anal. Calcd for $C_{17}H_{18}O_3$: C, 75.53; H, 6.71. Found: C, 75.38; H, 6.99.

4b, *7,7-dimethyl-4-(2-chlorophenyl)-5-oxo-3,4,5,6,7,8-hexahydrocoumarin*: IR (KBr): ν_{max} 3065, 1786, 1730, 1648, 1099, 755 cm^{-1}; ^{1}H NMR δ_H 1.17(3H, s, CH_3), 1.19(3H, s, CH_3), 2.37(2H, s, 8-H), 2.59(1H, d, *J*=18.4Hz, 6-H), 2.65(1H, d, *J*=18.4Hz, 6-H), 2.96(2H, br.s, 3-H), 4.77(1H, br.s, 4-H), 6.91–7.42 (4H, m, ArH); Anal. Calcd for $C_{17}H_{17}O_3Cl$: C, 67.00; H, 5.62. Found: C, 66.69; H, 5.77.

4c, *7,7-dimethyl-4-(3-chlorophenyl)-5-oxo-3,4,5,6,7,8-hexahydrocoumarin*: IR (KBr): ν_{max} 3080, 1780, 1738, 1660, 1114, 972, 798 cm^{-1}; ^{1}H NMR δ_H 1.13(3H,s, CH_3), 1.17(3H,s, CH_3), 2.35(2H, s, 8-H), 2.57(2H, s, 6-H), 2.95(2H, d, 3-H), 4.30(1H, br.s, 4-H), 7.05–7.29(4H, m, ArH); Anal. Calcd for $C_{17}H_{17}O_3Cl$: C, 67.00; H, 5.62. Found: C, 66.71; H, 5.97.

4d, *7,7-dimethyl-4-(4-chlorophenyl)-5-oxo-3,4,5,6,7,8-hexahydrocoumarin*: IR (KBr): ν_{max} 3098, 1782, 1695, 1623, 1200, 885 cm^{-1}; ^{1}H NMR δ_H 0.93(3H, s, CH_3), 0.98(3H, s, CH_3), 2.31(1H, d, *J*=16.4Hz, 8-H), 2.33(1H, d, *J*=16.4Hz, 8-H), 2.58(2H, s, 6-H), 2.96(2H, br.s, 3-H), 4.31(1H, br.s, 4-H), 7.17(2H, d, *J*=8.0Hz, ArH) 7.35(2H, d, *J*=8.0Hz, ArH).

4e, *7,7-dimethyl-4-(2,4-dichlorophenyl)-5-oxo-3,4,5,6,7,8-hexahydrocoumarin*: IR (KBr): ν_{max} 3088, 1779, 1647, 1656, 1106, 829 cm^{-1}; ^{1}H NMR δ_H 1.18(3H,s, CH_3), 1.20(3H,s, CH_3), 2.36(2H, m, 8-H), 2.60(2H, m, 6-H), 2.94(2H, d, 3-H), 4.70(1H, br.s, 4-H), 6.85–7.45 (3H, m, ArH); Anal. Calcd for $C_{17}H_{16}O_3Cl_2$: C, 60.19; H, 4.75. Found: C, 60.20; H, 4.97.

4f, *7,7-dimethyl-4-(4-nitrophenyl)-5-oxo-3,4,5,6,7,8-hexahydrocoumarin*: IR (KBr): ν_{max} 3116, 1783, 1656, 1603, 1354, 1110, 855 cm^{-1}; ^{1}H NMR δ_H 1.09(3H, s, CH_3), 1.17(3H, s, CH_3), 2.31(1H, d, *J*=16.8Hz, 8-H), 2.36(1H, d, *J*=16.8Hz, 8-H), 2.56(2H, s, 6-H), 2.95(2H, d, 3-H), 4.40 (1H, br.s, 4-H), 7.34(2H, d, *J*=8.4Hz, ArH) 8.16(2H, d, *J*=8.4Hz, ArH); Anal. Calcd for $C_{17}H_{17}O_5N$: C, 64.75; H, 5.43; N, 4.44. Found: C, 65.01; H, 5.85; N, 4.12.

4g, *7,7-dimethyl-4-(4-hydroxyphenyl)-5-oxo-3,4,5,6,7,8-hexahydrocoumarin*: IR (KBr): ν_{max} 3256, 3024, 1788, 1630, 1093, 839 m^{-1}; ^{1}H NMR δ_H 1.12(3H, s, CH_3), 1.17(3H, s, CH_3), 2.34(2H, s, 8-H), 2.55(2H, s, 6-H), 2.92(2H, d, 3-H), 4.25 (1H, br.s, 4-H), 6.70(2H, d, *J*=8.4Hz, ArH), 7.0 (2H, d, *J*=8.4Hz, ArH). Anal. Calcd for $C_{17}H_{18}O_4$: C, 71.31; H,6.34. Found: C, 75.59; H, 6.45.

4h, *7,7-dimethyl-4-(4-hydroxy-3-methoxyphenyl)-5-oxo-3,4,5,6,7,8-hexahydrocoumarin*: IR (KBr): ν_{max} 3250, 3016, 1770, 1655, 1105, 849cm^{-1}; ^{1}H NMR δ_H 1.05(3H, s, CH_3), 1.11(3H, s, CH_3), 2.28(2H, m, 8-H), 2.48(2H, s, 6-H), 2.87(2H, d, 3-H), 4.188 (1H,br.s, 4-H), 6.59–6.78(3H, m, ArH), 6.85(1H, s, OH).

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

4j, *7-dimethyl-4-(4-dimethylaminophenyl)-5-oxo-3,4,5,6,7,8-hexahydrocoumarin*: IR (KBr): ν_{max} 3016, 1791, 1703, 1640, 1129, 879 cm^{-1}; ^{1}H NMR δ_H 0.93(3H, s, CH_3), 1.13(3H, s, CH_3), 2.09(1H, d, *J*=16.4Hz, 8-H), 2.24(1H, d, *J*=16.4Hz, 8-H), 2.38(2H, s, 6-H), 2.63(2H, d, 3-H), 2.95(6H, s, 2N-CH_3), 4.17 (1H, t, 4-H), 6.74–7.15 (4H, m, ArH)

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

This project was supported by the National Natural Science Foundation of China (29872011 and 29572039), Educational Ministry of China, Educational Department of Hebei Province (990104), Science and Technology Commission of Hebei Province.

Received 7 May 2004; accepted 22 June 2004
Paper 04/2516

References

1 P.T. Anastas and T.C. Williamson, Green Chemistry. *Designing Chemistry for the Environment*, Symposium at the 208th National Meeting of the American Chemical Society; American Chemical Society: Washington DC, 1996.
2 C.J. Li and T.H. Chan, *Organic Reaction in Aqueous Media*, John Wiley & Sons Inc: New York, 1997.
3 (a) R. Breslow, U. Maitra and D. Rideout, Tetrahedron Lett.,1983, **24**, 1901; (b) S.D. Copley and J.R.Knowles, *J. Am. Chem. Soc.*, 1987, **109**, 5008.
4 (a) T.S. Jin, J.C. Xiao, S.J. Wang, T.S. Li and X.R. Song, *Synlett*, 2003, 2001; (b) T.S. Jin, A.Q. Wang, X. Wang, J.S. Zhang and T.S. Li, *Synlett*, 2004, 871; (c) T.S. Jin, J.S. Zhang, J.C. Xiao, A.Q. Wang and T.S. Li, *Synlett*, 2004, 866.
5 J.I. Kroschwitz and M. Howe-Grant. *Encyclopedia of Chemical Technology* Vol. 7, 4th edn, John Wiley & Sons Inc: New York, 1999**,** 650.
6 (a) G.M. Cingolani, F. Gualtieri and M. Pigini, *J. Med. Chem.*,1969, **12**, 531; (b) A. Schonberg and N. Latif, *J. Am. Chem. Soc.*,1954, **76**, 6208; (c) A. Mitra, S.K. Misras and A. Patra, *Synth. Commun.*,1980, **10**, 915.
7 (a) P. Margaretha, *Tetrahedron Lett.*, 1970, **17**, 1449; (b) Y. Gao, S.J. Tu, Z.S. Lu, D.Z. Niu and B.W. Sun, *Chin. J. of Org. Chem.*, 2001, **21**, 599
8 S. Margartta, O. Estael and V. Yamila, *Tetrahedron*, 1999, **55**, 875.