SHORT PAPER

J. Chem. Research (S),
2003, 674–675

Three-component processes for the synthesis of 4-aryl-7,7-dimethyl- 5-oxo-3,4,5,6,7,8-hexahydrocoumarin in aqueous media

Daqing Shi[a,b]*, Jing Chen[a], Qiya Zhuang[a] and Hongwen Hu[b]

[a]*Department of Chemistry, Xuzhou Normal University, Xuzhou, 221116, P. R China*

[b]*Department of Chemistry, Nanjing University, Nanjing, 210093, P. R. China*

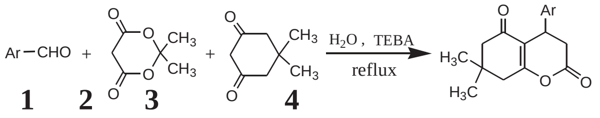
The reaction of an aromatic aldehyde, isopropylidene malonate and 5,5-dimethyl- 1,3-cyclohexanedione in water in the presence of triethylbenzylammonium chloride (TEBA) as catalyst affords a one-pot synthesis of 4-aryl-7,7-dimethyl-5-oxo-3,4,5,6,7,8-hexahydrocoumarin.

Keywords: hexahydrocoumarin, water, synthesis

The need to reduce the amount of toxic waste and byproducts arising from chemical processes requires increasing emphasis on the use of less toxic and environmentally compatible materials in the design of new synthetic methods.[1]

One of the tools used to combine economic aspects with the environmental ones is the multicomponent reaction strategy. This process consists of two or more synthetic steps which are carried out without isolation of any intermediate thus reducing time, saving money, energy and raw materials.[2]

Coumarin and coumarin derivatives are natural compounds and are important chemicals in perfume, cosmetic and pharmaceutical industrial production.[3] Hexahydrocoumarins are general prepared by reaction of isopropylidene malonate, an aldehyde and 5,5-dimethyl-1,3- cyclohexanedione in an organic solvent (i.e. ethanol) and in the presence of organic bases like piperidine.[4] Based on our previous studies on the use of water as solvent for carrying out carbon-carbon forming reactions under heterogeneous catalysis,[5] we now report the three-component reaction of aromatic aldehydes **1**, isopropylidene malonate **2** and 5,5-dimethyl-1,3-cyclohexamedione **3** in water at reflux and in the presence of a catalytic amount of triethylbenzylammonium chloride (TEBA) for 6 h, allowing the one-pot formation of 4-aryl-7,7-dimethyl-5-oxo-3,4,5,6,7,8-hexahydrocomarins **4** in 77–96% overall yields (Scheme 1).



Scheme 1

Table 1 summarises our results on the three-component reaction of a number of substrates. Structures of the products were established on the basis of spectroscopic data, particularly ^{1}H NMR analysis, and were further confirmed by the X-ray crystal structure analysis of the product **4e**[6] (Fig.1). Selected bond lengths and angles are shown in Table 2.

In summary, the three-component conversion of aromatic aldehydes, isoproprylidene malonate and 5,5-dimethyl-1,3-cyclohexadione to 4-aryl-7,7-dimethyl-5-oxo-3,4,5,6,7,8-hexahydrocoumarins has been efficiently performed in water as a solvent and by using a catalytic amount of TEBA. The easy purification of products simply by crystalllisation, the use of water as solvent combined with the exploitation of the multicomponent strategy open to this process suggest good prospects for its industrial applicability.

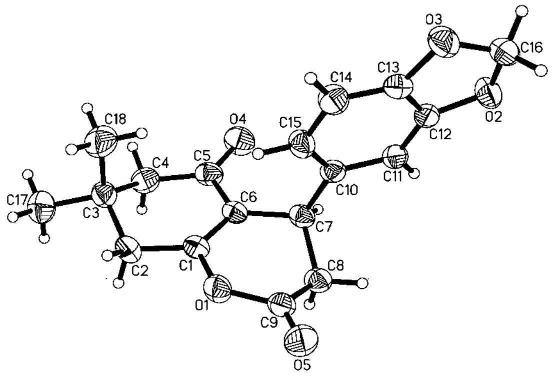


Fig.1 The X-ray crystal structure of compound **4e**.

Experimental

Melting points are uncorrected. IR spectra were recorded on a FT IR-8101 spectrometer in KBr with absorptions in cm^{-1}. ^{1}H NMR spectra were determined on an Invona-400 spectrometer using $CDCl_3$ solutions. Chemical shifts are expressed in ppm downfield from internal tetramethylsilane. Microanalyses were carried out on a Perkin-Elmer 2400 II elemental analyzer. X-ray diffraction was recorded on a Siemens P4 diffactometer.

General procedure for the synthesis of hexahydrocumarins **4:** A mixture of the aromatic aldehyde **1** (5 mmol), isopropylidene malonate **2**[7] (5 mmol), 5,5-dimethyl-1,3-cyclohexamedione **3** (5 mmol) and TEBA (0.1 g) in H_2O (10 ml) was refluxed for 6 h, then cooled to room temperature. The crystalline powder formed was collected by filtration, washed with water and recrystallised from ethanol to give pure **4**.

4a: M.p. 169–170 °C; IR (KBr) *v*: 2964, 1773, 1655, 1491, 1419, 1372, 1311, 1183, 1163, 1109, 1036, 1010, 970, 860, 829 cm^{-1}; ^{1}H NMR δ: 1.09 (3H, s, CH_3), 1.15 (3H, s, CH_3), 2.32 (2H, s, C_8-H), 2.53 (2H, s, C_6-H), 2.87–2.94 (2H, m, C_3-H), 4.26–4.28 (1H, m, C_4-H), 7.08–7.27 (4H, m, ArH); Anal. calcd for $C_{17}H_{17}ClO_3$: C 66.99, H 5.62; found C 67.08, H 5.47%.

4b: M.p. 167–168 °C; IR (KBr) *v*: 2965, 1770, 1655, 1601, 1509, 1470, 1418, 1376, 1220, 1183, 1158, 1112, 1037, 971, 862, 842 cm^{-1}; ^{1}H NMR δ: 1.09 (3H, s, CH_3), 1.15 (3H, s, CH_3), 2.32 (2H, s, C_8-H), 2.53 (2H, s, C_6-H), 2.88–2.97 (2H, m, C_3-H), 4.28–4.29 (1H, m, C_4-H), 6.95–7.14 (4H, m, ArH); Anal. calcd for $C_{17}H_{17}FO_3$: C 70.82, H 5.94; found C 70.93, H 5.71%.

4c: M.p. 176–177 °C; IR (KBr) *v*: 2960, 1788, 1652, 1616, 1523, 1375, 1315, 1236, 1161, 1104, 1036, 1006, 855, 811 cm^{-1}; ^{1}H NMR δ: 1.10 (3H, s, CH_3), 1.14 (3H, s, CH_3), 2.30 (2H, s, C_8-H), 2.51 (2H, s, C_6-H), 2.80–2.95 (8H, m, $(CH_3)_2N$+C_3-H), 4.10–4.28 (1H, m, C_4-H), 6.64–7.03 (4H, m, ArH); Anal. calcd for $C_{19}H_{23}NO_3$: C 72.81, H 7.33, N 4.46; found C 73.01, H 7.17, N 4.58%.

---

* To receive any correspondence.

† This is a Short Paper, there is therefore no corresponding material in *J Chem. Research (M).*

Table 1 The synthesis of 4-aryl-7,7-dimethyl-5-oxo-3,4,5,6,7,8-hexahydrocoumarin in aqueous media

Entry	Ar	Yield/%		Entry	Ar	Yield/%	
		A[a]	B[b]			A[a]	B[b]
4a	4-ClC_6H_4	86	82	**4e**	3,4-$OCH_2OC_6H_3$	96	85
4b	4-FC_6H_4	92	-	**4f**	2,4-$(CH_3O)_2C_6H_3$	84	-
4c	4-$(CH_3)_2NC_6H_4$	77	66	**4g**	4-HO-3-$CH_3OC_6H_3$	90	75
4d	2,4-$Cl_2C_6H_3$	94	-				

a: Method A: cat. TEBA in water at reflux for 6h.
b: Method B: in EtOH, under microwave irradiation for 3-5 min.

Table 2 Selected bond lengths and angles

Bond	Length/Å	Bond	Length/Å
O(1)–C(9)	1.381(2)	C(3)–C(4)	1.529(2)
O(1)–C(1)	1.3864(18)	C(4)–C(5)	1.506(2)
O(2)–C(12)	1.3784(19)	C(5)–C(6)	1.461(2)
O(2)–C(16)	1.426(2)	C(6)–C(7)	1.499(2)
O(3)–C(13)	1.382(2)	C(7)–C(10)	1.530(2)
O(3)–C(16)	1.422(2)	C(7)–C(8)	1.539(2)
O(4)–C(5)	1.2264(19)	C(8)–C(9)	1.485(2)
O(5)–C(9)	1.192(2)	C(10)–C(15)	1.382(2)
C(1)–C(6)	1.341(2)	C(10)–C(11)	1.401(2)
C(1)–C(2)	1.482(2)	C(11)–C(12)	1.361(2)
C(2)–C(3)	1.529(2)	C(12)–C(13)	1.375(2)
C(3)–C(18)	1.523(3)	C(13)–C(14)	1.357(2)
C(3)–C(17)	1.525(2)	C(14)–C(15)	1.395(2)
Angle	**(°)**	**Angle**	**(°)**
C(9)–O(1)–C(1)	120.18(12)	C(6)–C(7)–C(8)	107.43(13)
C(12)–O(2)–C(16)	105.65(13)	C(6)–C(7)–C(10)	115.02(13)
C(13)–O(3)–C(16)	105.47(13)	C(6)–C(7)–C(8)	107.43(13)
C(6)–C(1)–O(1)	122.06(14)	C(10)–C(7)–C(8)	110.91(13)
C(6)–C(1)–C(2)	126.44(15)	C(9)–C(8)–C(7)	112.28(14)
O(1)–C(1)–C(2)	111.48(13)	O(5)–C(9)–O(1)	116.87(15)
C(1)–C(2)–C(3)	113.28(14)	O(5)–C(9)–C(8)	126.67(17)
C(18)–C(3)–C(17)	108.95(16)	O(1)–C(9)–C(8)	116.40(15)
C(18)–C(3)–C(4)	109.42(16)	C(15)–C(10)–C(11)	119.43(15)
C(17)–C(3)–C(4)	110.61(15)	C(15)–C(10)–C(7)	122.52(14)
C(18)–C(3)–C(2)	110.57(16)	C(11)–C(10)–C(7)	118.02(14)
C(17)–C(3)–C(2)	109.29(15)	C(12)–C(11)–C(10)	117.66(15)
C(4)–C(3)–C(2)	108.00(14)	C(11)–C(12)–C(13)	122.35(15)
C(5)–C(4)–C(3)	114.06(15)	C(11)–C(12)–O(2)	128.05(15)
O(4)–C(5)–C(6)	120.57(17)	C(13)–C(12)–O(2)	109.57(15)
O(4)–C(5)–C(4)	121.93(17)	C(14)–C(13)–C(12)	121.28(16)
C(6)–C(5)–C(4)	117.48(14)	C(14)–C(13)–O(3)	128.78(16)
C(1)–C(6)–C(5)	118.22(15)	C(12)–C(13)–O(3)	109.92(14)
C(1)–C(6)–C(7)	120.98(15)	C(13)–C(14)–C(15)	117.36(16)
C(5)–C(6)–C(7)	120.74(14)	C(10)–C(15)–C(14)	121.90(16)
C(6)–C(7)–C(10)	115.02(13)	O(3)–C(16)–O(2)	108.29(13)

4d: M.p. 173–174 ˚C; IR (KBr) *v*: 2964, 2874, 1775, 1676, 1656, 1585, 1559, 1468, 1421, 1370, 1307, 1181, 1101, 1045, 968, 858, 834 cm^{-1}; ^1H NMR δ: 1.18 (6H, s, 2×CH_3), 2.34 (2H, s, C_8-H), 2.60 (2H, s, C_6-H), 2.91–2.93 (2H, m, C_3-H), 4.58–4.68 (1H, m, C_4-H), 6.83–7.43 (3H, m, ArH); Anal. calcd for $C_{17}H_{16}Cl_2O_3$: C 60.19, H 4.75; found C 60.43, H 4.53%.

4e: M.p. 154–155 ˚C; IR (KBr) *v*: 2959, 2899, 1787, 1653, 1488, 1442, 1422, 1363, 1292, 1236, 1111, 1033, 972, 935, 883, 858, 801, 767 cm^{-1}; ^1H NMR δ: 1.11 (3H, s, CH_3), 1.14 (3H, s, CH_3), 2.32 (2H, s, C_8-H), 2.53 (2H, s, C_6-H), 2.85–2.94 (2H, m, C_3-H), 4.21–4.22 (1H, m, C_4-H), 5.92 (2H, s, OCH_2O), 6.58–6.72 (3H, m, ArH); Anal. calcd for $C_{18}H_{18}O_5$: C 68.77, H 5.77; found C 68.92, H 5.58%.

4f: M.p. 145–146 ˚C; IR (KBr) *v*: 2962, 1788, 1644, 1614, 1583, 1505, 1471, 1377, 1288, 1212, 1164, 1130, 1086, 1036, 919, 853, 790 cm^{-1}; ^1H NMR δ: 1.06 (3H, s, CH_3), 1.12 (3H, s, CH_3), 2.37 (2H, s, C_8-H), 2.48 (2H, s, C_6-H), 2.79–2.89 (2H, m, C_3-H), 3.71 (3H, s, CH_3O), 3.76 (3H, s, CH_3O), 4.28–4.30 (1H, m, C_4-H), 6.37–7.06 (3H, m, ArH); Anal. calcd for $C_{19}H_{22}O_5$: C 69.07, H 6.71; found C 69.35, H 6.48%.

4g: M.p. 186–187 ˚C; IR (KBr) *v*: 3347, 2959, 2872, 1786, 1652, 1512, 1462, 1378, 1282, 1258, 1146, 1106, 1038, 846 cm^{-1}; ^1H NMR δ: 1.10 (3H, s, CH_3), 1.15 (3H, s, CH_3), 2.32 (2H, s, C_8-H), 2.52 (2H, s, C_6-H), 2.89–2.96 (2H, m, C_3-H), 3.85 (3H, s, CH_3O), 4.20–4.25 (1H, m, C_4-H), 5.56 (1H, s, OH), 6.60–6.82 (3H, m, ArH); Anal. calcd for $C_{18}H_{20}O_5$: C 68.34, H 6.37; found C 68.51, H 6.43%.

We are grateful to the "Surpassing Project" Foundation of Jiangsu Province for financial support.

Received 20 May 2003; accepted 26 August 2003
Paper 03/1925

References

1 J. Amato, *Science*, 1993, **259**: 1538; D.L. Illman, *Chem. Eng. News*, 1993, **71**:5; D.L. Illman, *Chem. Eng. News*, 1994, **72**:22.
2 N. Hall, *Science*, 1994, **266**:32; A. Domling, E. Herdtweck and I. Ugi, *Acta Chem. Scand.*, 1998, **52**:107.
3 T.O. Soine, *J. Pharm. Sci.*, 1964, **53**:231.
4 P. Margaretha, *Tetrahedron Lett.*, 1970, **17**:1449; Y. Gao, S.J. Tu, Z.s. Lu, D.Z. Niu and B.W. Sun, *Chin. J. Org. Chem.* 2001, **21**:599.
5 D.Q. Shi, S. Zhang, Q.Y. Zhuang, X.S. Wang, S.J. Tu and H.W. Hu, *Chin. J. Org. Chem*. 2003(in press); D.Q. Shi, Q.Y. Zhaung, J. Chen, X.S. Wang, S.J. Tu and H.W. Hu, *Chin. J. Org. Chem.* 2003 (in press).
6 Crystal data for **4e**: $C_{18}H_{18}O_5$, M = 314.32, colorless block crystals, 0.54×0.48×0.24 mm, Triclinic, space group P-1, a = 6.963(1), b = 8.957(2), c = 13.594(3) Å, α = 90.16(2)°, β = 103.11(2)°, γ = 109.60(2)°, V = 775.0(3) $Å^3$, Z = 2, Dc = 1.347 $g.cm^{-3}$, μ = 0.098 mm^{-1}, F (000) = 332. Intensity data were collected on a Siemens P4 diffractometer with graphite-monochromated Mo$K\alpha$ radiation (λ = 0.71069 Å) using ω scan mode with 1.54° <θ<25.00°, 2731 unique reflections were measured. Refinement of positions and anisotropic thermal parameters for all non-hydrogen atoms converged to R = 0.0382 and wR = 0.0949. Crystallographic data (excluding structure factors) for the structure reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication No. CCDC-217032
7 D. Davidson and S.A. Bernhard, *J. Am. Chem. Soc.*, 1948, **70**, 3426.