Synthesis of tetraketones in water and under catalyst-free conditions†

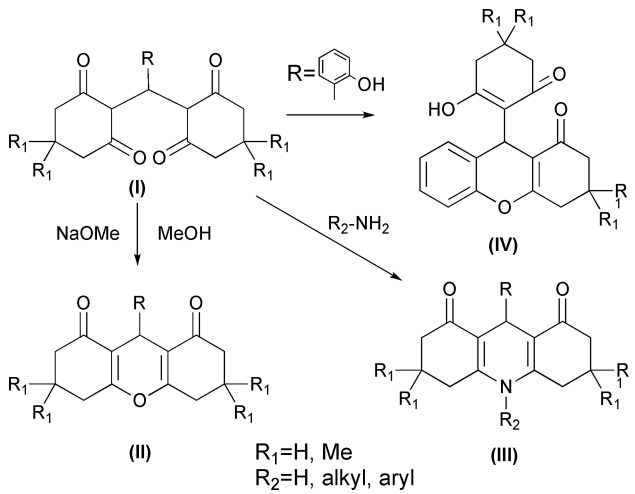
Jian-Jun Yu, Li-Min Wang,* Jin-Qian Liu, Feng-Lou Guo, Ying Liu and Ning Jiao

Received 13th July 2009, Accepted 17th November 2009
First published as an Advance Article on the web 9th December 2009
DOI: 10.1039/b913816a

A simple, environmentally friendly, tandem Knoevenagel condensation and Michael addition procedure is reported. The reactions between cyclic-13-diketones and a variety of aldehydes were carried out in water to afford tetraketones (64–99%). In this green synthetic protocol, the solvent water itself catalysed the reaction by hydrogen bonding, thus avoiding the use of any other catalysts to make the work up procedure easier.

Introduction

Tetraketones (**I**), which have four carbonyl functionalities along with their tautomeric, that is, keto-enol-forms, have some tyrosinase inhibitory properties and some are even better than both the standards kojic acid and L-mimosine.[1] The dimeric intermediate (**I**) is a key intermediate for the preparation of heterocyclic three-ring systems—either xanthendione (**II**), acridindione (**III**),[3] or 4*H*-1-benzopyran (**IV**) derivatives (Scheme 1).[2] Acridindione (**III**) derivatives have been used as electron donors and acceptors[4] and in the photoinitiated polymerization of acrylates and methacrylates.[5] They are also interesting because they have similar properties to those of 1,4-dihydropyridines, which are similar in structure to biologically important compounds such as NADH and NADPH.[6] Recently they have been used as a new class of laser dyes.[3] 4*H*-1-Benzopyrans are an important class of naturally occurring compounds with biological activities.[7,8]



Scheme 1

Tetraketones were synthesized through Knoevenagel condensations and Michael additions of aldehydes with cyclohexane-1,3-diones, dimedones or other types of 1,3-cyclic diketones. They were first reported by Merling in 1894 by synthesizing the cyclohexane-1,3-dione from resorcinol.[9] Vorlander and Kalkow reported the practical synthesis of tetraketones in 1899.[10] Several reports of the attempts to carry out an efficient synthesis of tetraketones have appeared in the literature. Many of these methods involve the use of NaOH,[13] KOH,[2] piperidine[1,11a,11c] and proline[14] as catalyst, the use of cetyltrimethyl ammonium bromide (CTMAB) as surfactant,[12] and the use of aqueous organic solvent as cosolvent.[1,2,3b,11]

In modern organic chemistry, the improvement of reaction efficiency, the avoidance of toxic reagents, the reduction of waste, and the responsible utilization of our resources have become critical objectives.[14,15] By keeping these ideas in mind, a simple and green approach for the synthesis of tetraketones (**I**) has been developed. Pure water as solvent, catalyst free and room temperature conditions are enough to afford the tetraketones in nearly quantitative yields. Most important of all, the purification procedure is just followed by filtration, washing and drying and the water can be reused for the next cycle, so the waste can be reduced effectively.

Results and discussion

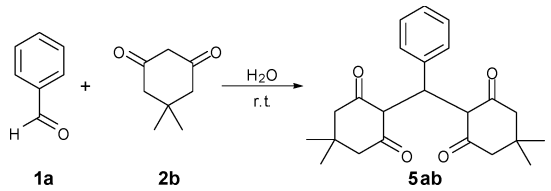
First, the reaction conditions were optimized in the reaction of benzaldehyde and dimedone (Table 1). By comparing the reaction yields of Entries 1 to 5 in Table 1, it was found that 4 h was enough for this reaction. Room temperature gave excellent yields. However, the high temperature decreased the yields (Entries 4, 6 and 7, Table 1). Ethanol and aqueous ethanol were the solvents used mainly for this reaction, however, it is exciting to find that water can also afford the product in good yield even better than ethanol (Entries 4, 8 and 9, Table 1). This may be because the polarity of water is higher than that of ethanol and the effect of ethanol in this reaction is just to increase the solubility of the substrates. Among the various reaction conditions used in Table 1, those indicated in Entry 4 were the most promising conditions.

With the optimal conditions in hand, the range of the substrates was checked. First, the Knoevenagel condensation and Michael addition reaction were carried out by using a series of different aldehydes with cyclohexane-1,3-dione. The results are summarized in Table 2 (Entries 1–14). It was found that both electron-rich and electron-deficient aromatic aldehydes were suitable for this reaction. For benzaldehydes with

Laboratory for Advanced Materials & Institute of Fine Chemicals, East China University of Science and Technology, 130 Meilong Road, Shanghai, 200237, China. E-mail: wanglimin@ecust.edu.cn

† Electronic supplementary information (ESI) available: Experimental and spectra. See DOI: 10.1039/b913816a

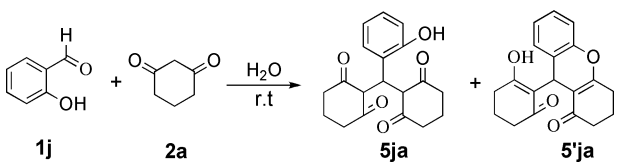
Table 1 Synthesis of tetraketones under various reaction conditions



Entry[a]	Time/h	T/°C	Solvent	Yield (%)[b]
1	0.5	rt	H_2O	64
2	1	rt	H_2O	72
3	2	rt	H_2O	88
4	4	rt	H_2O	96
5	6	rt	H_2O	94
6	4	40	H_2O	90
7	4	60	H_2O	86
8	4	80	H_2O	81
9	4	rt	Ethanol	80
10	4	rt	Ethanol/H_2O = 1 : 1[c]	94

[a] Reaction conditions: benzaldehyde (1 mmol), dimedone (2 mmol), and water (5 mL) at rt. [b] Isolated yield. [c] Aqueous solution of ethanol: ethanol (2.5 mL) and water (2.5 mL).

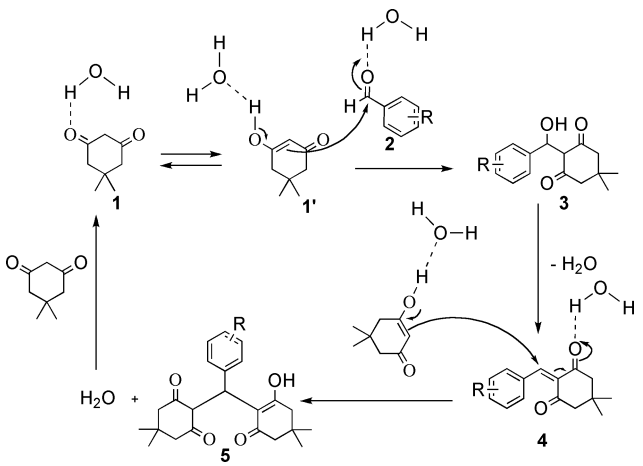
electron-donating groups such as 4-(dimethylamino) benzaldehyde, 4-methoxybenzaldehyde and piperonal, the desired products could be afforded in good yields (Entries 4, 5, 10, Table 2). However, all of the electron-deficient aromatic aldehydes investigated in this way could give excellent yields without obvious steric hindrance effects (Entries 1–3, 6–8, Table 2). A heterocyclic aromatic aldehyde such as 2-furaldehyde could also react with cyclohexane-1,3-dione to afford the tetraketone compound with a yield up to 98% (Entry 11, Table 2). Just as reported previously, when the 2-hydroxybenzaldehyde was used as starting material, the product was totally 2-(1-oxo-2,3,4,9-tetrahydro-1*H*-xanthen-9-yl) cyclohexane-1,3-dione (**5′ja**) instead of the tetraketone (**5ja**) (Scheme 2).



Scheme 2 The Knoevenagel condensation, Michael addition and dehydration reaction of salicylaldehyde and 1,3-cyclohexanedione.

Besides cyclic-1,3-diketones (cyclohexane-1,3-dione and dimedione), heterocyclo-1,3-diones and cyclopent-1,3-diones were also investigated in these conditions. 4-Hydroxy-6-methylpyran-2-one, spirolactone and 2,2-tetramethylene-4,6-dioxo-1,3-dioxane were used to react with benzaldehyde and afforded the target products in good yields (Entries 16–18, Table 2). Cyclopent-1,3-dione was first reported to take part in this reaction and the yield was excellent (Entry 19, Table 2). More importantly, 1,3-indandione also gave a good result under these conditions (Entry 20, Table 2). However, under these conditions, dimethyl malonate and acetylacetone gave no reaction or just a Knoevenagel condensation product, respectively (Entry 21, 22 Table 2).

As well as its action as a solvent, water also helps in the enolization of **1** by making hydrogen bonds with the OH of **1′** and, thus, it increases the nucleophilic character of the methylene carbon (C-2) of **1**. Meanwhile, it also increases the electrophilic character of the carbonyl carbon of **2** by forming hydrogen bonds with the carbonyl oxygen of aldehyde **2**.[15a] After the Knoevenagel condensation reaction, the intermediate **4** is afforded. By the nucleophilic attacking of **1′**, **4** is transformed to the tetraketone **5** (Scheme 3).



Scheme 3 Plausible mechanism for the Knoevenagel condensation and Michael addition leading to tetraketones.

The reaction procedure is very simple (Fig. 1). After the benzaldehyde and 1,3-cyclohexanedione were added to water, a nearly homogeneous system was formed at the beginning of the reaction (Fig. 1(a)). After the reaction was completed, the product precipitated (Fig. 1(b)). The product could be afforded after filtration, washing and drying.

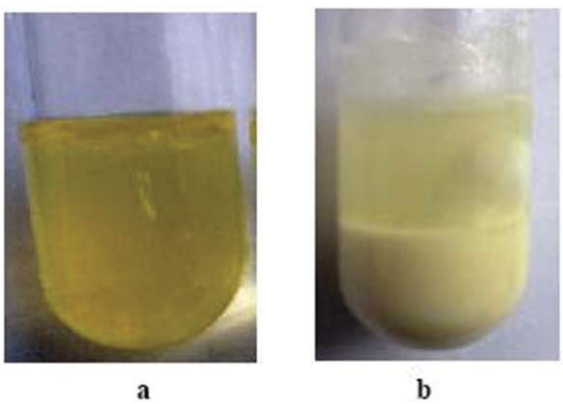
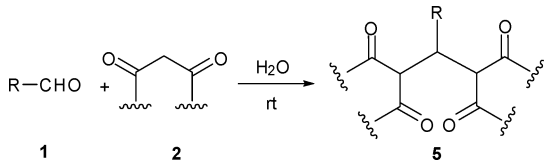


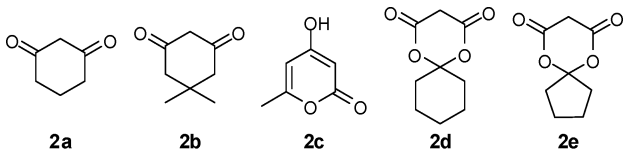
Fig. 1 The phenomenon of the reaction between benzaldehyde and 1,3-cyclohexanediones. (**a**) The homogeneous phase at the beginning of the reaction. (**b**) The product precipitated after reaction completion.

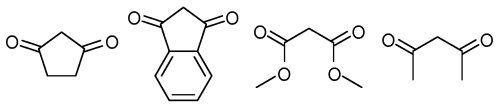
Conclusions

In summary, we report an effective, green and mild method for the synthesis of tetraketones. To the best of our knowledge, it is the first example of using water as a solvent without catalyst, surfactant or ionic liquid. This process provides an

Table 2 The synthesis of tetraketones **5** in water







Entry[a]	R-CHO (**1**)	1,3-cyclic diketones (**2**)	Time/h	Yield (%)[b]	Mp (lit.)/°C
1	4-Br-C_6H_4 (**1b**)	**2a**	4	91	225–227 (240–241)[16]
2	3-Br-C_6H_4 (**1c**)	**2a**	4	96	206–208 (248–249)[17]
3	2-Br-C_6H_4 (**1d**)	**2a**	4	85	241–243 (199–200)[1]
4	4-MeO-C_6H_4 (**1e**)	**2a**	4	93	190–191 (199–201)[1]
5	4-(NMe_2)-C_6H_4 (**1f**)	**2a**	4	70[c]	142 (150)[11a]
6	4-NO_2-C_6H_4 (**1g**)	**2a**	1/2	91	210–212 (218)[11a]
7	3-NO_2-C_6H_4 (**1h**)	**2a**	1/2	99	204–205 (209–211)[1]
8	2-NO_2-C_6H_4 (**1i**)	**2a**	4	90	204–206 (212–213)[11a]
9	2-OH- C_6H_4 (**1j**)	**2a**	4	90[d]	228–230 (234)[18]
10	3,4-OCH_2O–C_6H_3 (**1k**)	**2a**	4	80	204–206 (212)[11a]
11	2-Furyl (**1l**)	**2a**	4	98	142–144 (146)[11a]
12	H (**1m**)	**2a**	4	96	130–132 (134)[11a]
13	n-Pr (**1n**)	**2a**	4	64	97–98 (97–98)[11a]
14	C_6H_5 (**1a**)	**2a**	4	94	207–208 (217–218)[1]
15	C_6H_5 (**1a**)	**2b**	1/2	96	194–195 (190–192)[3b]
16	C_6H_5 (**1a**)	**2c**	4	85	167–169 (176)[13]
17	C_6H_5 (**1a**)	**2d**	4	80	115–117
18	C_6H_5 (**1a**)	**2e**	4	95	157–159
19	C_6H_5 (**1a**)	**2f**	4	85	222–223
20	C_6H_5 (**1a**)	**2g**	4	95	156–158 (162)[19]
21	C_6H_5 (**1a**)	**2h**	4	trace	/
22	C_6H_5 (**1a**)	**2i**	4	trace	/

[a] Reaction conditions: benzaldehyde (1 mmol), dimedone (2 mmol), and water (5 mL) at rt. [b] Isolated yield. [c] The product was recrystallized from ethanol. [d] The 4*H*-benzopyran derivative (**5′ja**) was afforded.

opportunity to avoid organic solvents and resource consumption compared to the traditional reaction system. The simplicity of the methodology, ease of the product isolation and mild conditions could make this process available on an industrial scale.

Experimental

General

Melting points were determined with an X-4 apparatus and were uncorrected. ^{1}H (400 MHz) and ^{13}C (100 MHz) NMR spectra were recorded on a Bruker Avance 400 spectrometer in $CDCl_3$ using TMS as internal reference. Mass (EI) spectra were recorded on a Micromass GCTTM mass spectrometer. All chemicals used were reagent grade and were used as received without further purification.

Experimental procedure for the synthesis of compound 5aa

In a 20 mL flask was placed benzaldehyde (1 mmol/106 mg), cyclohexane-1,3-dione (2 mmol/224 mg) and water (5 mL). The resulting yellow solution was stirred at room temperature for 4 h (TLC monitored/R_f: 0.6 (CH_2Cl_2–EtOAc, 4 : 1), white precipitate was formed and the resultant precipitates were filtered, washed by cold water and dried in vacuum affording 2,2′-(phenylmethylene) dicyclohexane-1,3-dione (**5aa**) as white solid. 0.294 g, yield: 94%.^{1}HNMR ($CDCl_3$, 400 MHz): δ 1.99-2.09 (4H, m, H-5/H-5′), 2.35-2.52 (4H, m, H-4/H-4′), 2.54-2.70(4H, m, H-6/H-6′), 5.48 (1H, s, H-7), 7.12 (2H, d, J = 8.0 Hz, H-2/H-6), 7.18 (1H, t, J = 7.2 Hz, H-4), 7.27 (2H, t, J = 7.8 Hz, H-3/H-5), 12.36 (2H, br s, -OH); ^{13}CNMR ($CDCl_3$, 100 MHz): δ 20.1(C-5/C-5′), 32.9 (C-4/C-4′), 33.0 (C-7), 33.5 (C-6/C-6′), 116.4 (C-2/C-2′), 125.8 (C-4), 126.5 (C-2/C-6), 128.1 (C-3/C-5), 137.8 (C-1), 190.7 (-COH), 192.1 (CO); EIMS: m/z 312.1 (M^+, 45).

Experimental procedure for the synthesis of compound 5fa

In a 20 mL flask was placed 4-(dimethylamino) benzaldehyde (1 mmol/149 mg), cyclohexane-1,3-dione (2 mmol/224 mg) and water (5 mL). The red solution was stirred at room temperature for 4 h (TLC monitored/R_f: 0.3 (CH_2Cl_2–EtOAc, 4 : 1), red precipitate was formed and the resultant precipitates were filtered to afford the raw product. Recrystallization from ethanol afforded the pure product 2,2′-((4-(dimethylamino) phenyl)methylene)dicyclohexane-1,3-dione (**5fa**) 0.246 g. Red solid; Yield: 94%. ^{1}HNMR ($CDCl_3$, 400 MHz): δ 1.98-2.07 (4H, m, H-5/H-5′), 2.30-2.50 (4H, m, H-4/H-4′), 2.52-2.68 (4H, m, H- 6/H-6′), 2.91(6H, s, -N(CH_3)$_2$), 5.42 (1H, s, H-7), 6.67 (2H, d, J = 8.8 Hz, H-3/H-5),6.96 (2H, d, J = 8.4 Hz, H-2/H-6), 12.38 (2H, br s, -OH); ^{13}CNMR ($CDCl_3$, 100 MHz): δ 20.1(C-5/C-5′), 32.0 (C-4/C-4′), 33.0 (C-7), 33.5 (C-6/C-6′), 40.7 (-N(CH_3)$_2$), 112.7 (C-2/C-2′), 116.8 (C-2/C-6), 125.5 (C-3/C-5), 127.2 (C-1), 148.8(C-4), 190.8 (-COH), 191.9 (CO); EIMS: m/z 355.2 (M+, 10).

Experimental procedure for the synthesis of compound 5ja′

In a 20 mL flask was placed salicylaldehyde (1 mmol/122 mg), cyclohexane-1,3-dione (2 mmol/224 mg) and water (5 mL). The yellow solution was stirred at room temperature for 4 h (TLC monitored/R_f: 0.45 (CH_2Cl_2–EtOAc, 4 : 1). A creamy white solid was formed and the resultant precipitates were filtered, washed by cold water and dried in vacuum affording 2-(1-oxo-2,3,4,9-tetrahydro-1*H*-xanthen-9-yl) cyclohexane-1,3-dione (**5′ja**) as creamy white solid. 0.278 g, yield: 90%. ^{1}HNMR ($CDCl_3$, 400 MHz): δ 1.71-2.82 (12H, m, 6CH_2), 4.65 (1H, s, CH), 7.00-7.05 (3H, m, ArH), 7.13-7.20 (1H, m, ArH), 10.85 (b, 1H, OH); ^{13}CNMR ($CDCl_3$, 100 MHz): δ 20.7, 20.8, 25.8, 25.9, 27.7, 37.1, 112.4, 115.7, 124.7, 126.2, 127.3, 128.9, 150.0, 167.1, 196.5; EIMS: m/z 310.2 (M^+, 34).

Acknowledgements

This work was financially supported by the Natural Science Foundation of China (NO. 20672035).

References

1 K. M. Khan, G. M. Maharvi, M. T. H. Khan, A. J. Shaikh, S. Perveen, S. Begun and M. I. Choudhary, *Bioorg. Med. Chem.*, 2006, **14**, 344.
2 B. A. Marco, T. A. Manuel, P. M. Itzia, M. M. Francisco, E. Georgina, M. Elies and E. Enrique, *J. Chem. Crystallogr.*, 1999, **29**, 759.
3 (*a*) P. Shanmugasundaram, K. J. Prabahar and V. T. Ramakrishnan, *J. Heterocycl. Chem.*, 1993, **30**, 1003; (*b*) N. Srividya, P. Ramamurthy, P. Shanmugasundaram and V. T. Ramakrishnan, *J. Org. Chem.*, 1996, **61**, 5083.
4 (*a*) H. J. Timpe, S. Ulrich and S. Ali, *J. Photochem. Photobiol., A*, 1991, **61**, 77; (*b*) H. J. Timpe, S. Ulrich and J. P. Fouassier, *J. Photochem. Photobiol., A*, 1993, **73**, 139; (*c*) S. Ulrich, H. J. Timpe, J. P. Fouassier and F. M. Savary, *J. Photochem. Photobiol., A*, 1993, **74**, 165.
5 H. J. Timpe, S. Ulrich, C. Decker and J. P. Fouassier, *Macromolecules*, 1993, **26**, 4560.
6 F. T. McNamara, J. W. Nieft, J. F. Ambrose and E. S. Huyser, *J. Org. Chem.*, 1977, **42**, 988.
7 G. P. Ellis, Ed. *Chromenes, Chromanones and Chromones*, Wiley, New York, 1977.
8 (*a*) I. Yavari, M. A. Abbasinejad, A. Alizadeh and Z. Hossaini, *Tetrahedron*, 2003, **59**, 1289; (*b*) I. Yavari, H. Djahaniani and F. Nasiri, *Tetrahedron*, 2003, **59**, 9409; (*c*) H. Miao and Z. Yang, *Org. Lett.*, 2000, **2**, 1765; (*d*) P. Kumar and M. S. Bodas, *Org. Lett.*, 2000, **2**, 3821.
9 Merling, *Annalen.*, 1894, **278**, 28.
10 Vorlander and Kalkow, *Justus Liebigs Annalen der Chemie.*, 1899, **309**, 380.
11 (*a*) F. E. King and D. G. I. Felton, *J. Chem. Soc.*, 1948, **13**, 1371; (*b*) H. Stetter, *Angew. Chem.*, 1955, **67**, 769; (*c*) E. C. Horning and M. G. Horning, *J. Org. Chem.*, 1946, **11**, 95.
12 Z. J. Ren, W. G. Cao, W. Q. Tong and X. P. Jing, *Synth. Commun.*, 2002, **32**, 1947.
13 G. Cravotto, A. Demetri, G. M. Nano, G. Palmmisano, A. Penoni and S. Tagliapietra, *Eur. J. Org. Chem.*, 2003, 4438.
14 D. B. Ramachary and M. Kishor, *J. Org. Chem.*, 2007, **72**, 5056.
15 (*a*) L. D. S. Yadav, S. Singh and V. K. Rai, *Green Chem.*, 2009, **11**, 878–882; (*b*) W. Leitner, *Green Chem.*, 2009, **11**, 603.
16 N. G. Kozlov, K. N. Gusak and A. V. Tkachev, *Chem. Heterocycl. Compd.*, 2007, **43**, 740.
17 K. N. Gusak, A. B. Tereshko, N. G. Kozlov and N. I. Shakailo, *Russ. J. Gen. Chem.*, 2000, **70**, 1893.
18 N. G. Kozlov, K. N. Gusak and Russ, *J. Org. Chem.*, 1999, **35**, 402.
19 L. B. Rosine, L. Claude and J. G. Jean, *J. Med. Chem.*, 1975, **18**, 85.