

Solvent-free synthesis of xanthenediones and acridinediones

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Abstract

In the absence of any solvent, the reactions of various aromatic aldehydes with 5,5-dimethyl-1,3-cyclohexanedione catalyzed by methanesulfonic acid under thermal heating conditions smoothly afforded 9-aryl-3,3,6,6-tetramethyl-tetrahydroxanthene-1,8-diones in nearly quantitative yields. Under the same melting conditions, rapid and efficient synthesis of 9-aryl-3,3,6,6-tetramethyl-hexahydroacridine-1,8-diones and 9,10-diaryl-3,3,6,6-tetramethyl-hexahydroacridine-1,8-diones could also be achieved using ammonium acetate and *p*-toluidine as the nitrogen source.

Keywords: Xanthenediones, acridinediones, solvent-free reaction, thermal heating condition

Introduction

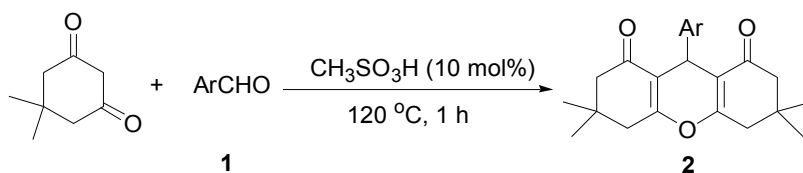
It is well documented that the title compounds xanthenediones and acridinediones are of great importance both in organic synthesis and in biological chemistry.¹ Synthetic methods for these compounds have been developed to a great extent, including conventional thermal reactions in the presence of organic solvents,^{1d,2} microwave irradiation-promoted reactions,^{1e,3} ionic liquid-mediated reactions,⁴ and others.⁵

On the other hand, the increasing environmental concerns and regulatory constraints faced in the chemical and pharmaceutical industries have been invoking more and more synthetic endeavors to develop more environmentally benign organic reactions. Fortunately, there have been extensive praiseworthy achievements in this field, especially those successful reactions achieved under solvent-free conditions, which demonstrate various obvious and significant advantages.⁶ However, most of the reported solvent-free accomplishments focus on reactions promoted by microwave irradiation, hand grinding and mechanical milling.⁶⁻⁸ In contrast, reports on direct heating of the reagents under melting conditions without any solvent are relatively less explored. All of the above points impel us to apply the direct thermal heating and melting

conditions to the synthesis of 9-aryl-3,3,6,6-tetramethyl-tetrahydroxanthene-1,8-diones, 9-aryl-3,3,6,6-tetramethyl-hexahydroacridine-1,8-diones and 9,10-diaryl-3,3,6,6-tetramethyl-hexahydroacridine-1,8-diones from aromatic aldehydes and 5,5-dimethyl-1,3-cyclohexanedione (dimedone).

Results and Discussion

We first investigated the synthesis of 9-aryl-3,3,6,6-tetramethyl-tetrahydroxanthene-1,8-diones **2a–h** by the solvent-free reactions of aromatic aldehydes **1a–h** with dimedone under thermal heating and melting conditions. After various attempts, we found that these reactions could proceed efficiently with 10 mol% of methanesulfonic acid as the catalyst. The substrates and the catalyst were simply mixed in a test tube and directly heated up to 120 °C, and the resulting molten mixture was stirred at this temperature for 1 h to afford essentially pure products **2a–h**. (Scheme 1). It should be noted that methanesulfonic acid has not been used for the synthesis of **2a–h** until now. The results are summarized in Table 1.



Scheme 1

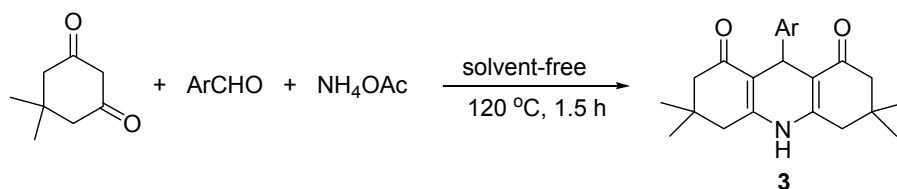
Table 1. Synthesis of products **2a–h** by the reactions of aromatic aldehydes with dimedone in the presence of methanesulfonic acid (10 mol %) under solvent-free and thermal heating conditions.

Entry	Ar	Product	Mp (°C)		Yield (%)
			Found	Reported	
1	C ₆ H ₅	2a	202–204	205 ^{2a}	94
2	4-CH ₃ C ₆ H ₄	2b	216–218	217–218 ^{5a}	94
3	4-CH ₃ OC ₆ H ₄	2c	240–242	241–243 ^{5a}	93
4	4-ClC ₆ H ₄	2d	226–228	228–230 ^{5a}	94
5	4-BrC ₆ H ₄	2e	230–232	234–236 ^{4a}	91
6	3-NO ₂ C ₆ H ₄	2f	166–168	171–172 ^{5a}	92
7	4-Me ₂ NC ₆ H ₄	2g	224–226	220–222 ^{2a}	90
8	3,4-Cl ₂ C ₆ H ₄	2h	250–252	/	95

From Table 1 it can be seen that the reactions generally gave products **2a–h** with almost quantitative yields regardless of the structural variations of the aromatic aldehydes. Compared with existing methods, the main advantages of the present protocol are obvious: simple energy-

providing mode, high yield, short reaction time, no usage of any organic solvent together with straightforward and easy work-up procedure. The reasons for the efficiency of the current melting procedure may be due to an enhanced second-order reaction rate resulting from ultimately high concentrations of reactants in the absence of solvent. Herein, the reaction temperature was crucial in terms of the reaction rate and product yield. Taking the synthesis of product **2f** as an example, the reaction of 3-nitrobenzaldehyde with dimedone, which was carried out at 80 °C, 100 °C and 120 °C, gave **2f** in 60%, 85% and 92% yield, respectively. Further increase of the temperature higher than 120 °C could not improve the yields visibly and was thus not necessary.

In order to study the generality of our methodology towards polycyclic compounds, the solvent-free synthesis of 9-aryl-3,3,6,6-tetramethyl-hexahydroacridine-1,8-diones **3a–h** was also explored. Ammonium acetate was employed as the nitrogen source, and the reactions were performed under the above melting conditions to afford a series of products **3a–h** (Scheme 2). Ammonium acetate was used with a little excess (1.2 equiv.) due to volatilization of ammonia generated during the reaction process. The results summarized in Table 2 showed the high efficiency for the one-pot multi-component reaction.

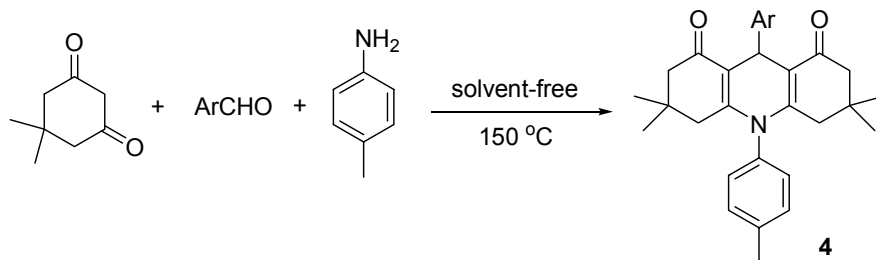


Scheme 2

Table 2. Synthesis of products **3a–h** by the reactions of aromatic aldehydes with dimedone and ammonium acetate under solvent-free and thermal heating conditions.

Entry	Ar	Product	Mp (°C)		Yield (%)
			Found	Reported	
1	C ₆ H ₅	3a	277–278	279–280 ^{3c}	92
2	4-CH ₃ C ₆ H ₄	3b	>300	>300 ^{5d}	92
3	4-CH ₃ OC ₆ H ₄	3c	272–273	269–270 ^{2d}	88
4	4-ClC ₆ H ₄	3d	294–296	296–298 ^{3c}	92
5	4-HOC ₆ H ₄	3e	>300	>300 ^{5d}	88
6	3-NO ₂ C ₆ H ₄	3f	287–289	285–286 ^{3c}	92
7	4-Me ₂ NC ₆ H ₄	3g	265–267	263–265 ^{2d}	90
8	3,4-Cl ₂ C ₆ H ₄	3h	>300	>300 ^{5d}	96

The excellent results obtained for the reaction shown in Scheme 2 impelled us to extend this protocol to the synthesis of 9,10-diaryl-3,3,6,6-tetramethyl-hexahydroacridine-1,8-diones **4a-h** by using *p*-toluidine as the nitrogen source (Scheme 3).



Scheme 3

Here the loading of *p*-toluidine was not excessive because of its low volatility, but its reaction was relatively slow, as demonstrated from the illustrative reaction of 4-methylbenzaldehyde with dimedone (2.0 equiv.) and *p*-toluidine (1.0 equiv.), which afforded only 56% yield of product **4b** at 120 °C for 3 h. To improve this poor conversion, we elevated the temperature up to 150 °C, and the reaction was carried out for 1.5 h, giving **4b** in 88 % yield. The reaction times and product yields for various substrates are summarized in Table 3. The product yields were also very high in general. So we can assert that the present protocol provides a practical and environmental synthesis of these heterocyclic compounds with a good applicability to various substrates. It should be noted that we have reported the synthesis of unsymmetrical acridinediones by the reaction of preformed cyclic enaminones with aldehydes and 1,3-cyclohexanedione under solvent-free conditions.⁹ However, the preparation of symmetrical acridinediones by the solvent-free reaction directly from dimedone, aldehydes and amines is unknown until now.

Table 3. Synthesis of products **4a-h** by the reactions of aromatic aldehydes with dimedone and *p*-toluidine under solvent-free and thermal heating conditions.

Entry	Ar	Product	Time (h)	Mp (°C)		Yield (%)
				Found	Reported	
1	C ₆ H ₅	4a	5	264–266	262–263 ^{3d}	75
2	4-CH ₃ C ₆ H ₄	4b	4	294–295	285–287 ^{5b}	88
3	4-CH ₃ OC ₆ H ₄	4c	4	285–287	282–283 ^{3d}	89
4	4-ClC ₆ H ₄	4d	2.5	271–272	273–274 ^{3d}	87
5	4-HOC ₆ H ₄	4e	3	>300	>300 ^{5b}	90
6	3-NO ₂ C ₆ H ₄	4f	2	285–287	285–287 ^{5b}	92
7	4-CNC ₆ H ₄	4g	3	273–275	/	89
8	3,4-Cl ₂ C ₆ H ₄	4h	2	>300	/	91

Conclusions

The current work presents a powerful method for the preparation of 9-aryl-3,3,6,6-tetramethyl-tetrahydroanthene-1,8-diones, 9-aryl-3,3,6,6-tetramethylhexahydroacridine-1,8-diones, and 9,10-diaryl-3,3,6,6-tetramethyl-hexahydroacridine-1,8-diones. This general and efficient procedure offers several advantages including no usage of any solvent, wide scope of substrates, usage of very cheap and readily available methanesulfonic acid as the catalyst, high yield and the facile separation of the products by simple Büchner filtration after washing with water. All of these points make this process as a very useful and practical alternative in the synthesis of these compounds, even in large-scale preparation.

Experimental Section

General Procedures. Reagents and solvents were obtained from commercial sources and were not further purified before use. All melting points were uncorrected. Infrared spectra were recorded in KBr pellet and reported in cm^{-1} . ^1H NMR spectra were recorded at 300 MHz and are reported in parts per million (ppm) relative to tetramethylsilane (δ 0.00). ^{13}C NMR spectra were recorded at 75 MHz and are reported in parts per million (ppm) relative to CDCl_3 (δ 77.0). High-resolution mass spectra (HRMS) were recorded with EI mode.

General procedure for the preparation of 9-aryl-3,3,6,6-tetramethyl-tetrahydroanthene-1,8-diones **2a–h**

A mixture containing benzaldehyde **1a** (**1b–h**, 1.0 mmol), dimedone (280 mg, 2.0 mmol) and methanesulfonic acid (9.6 mg, 0.1 mmol) was introduced into a test tube. After heated up to 120 C, the melt mixture was kept stirring at this temperature for 1 h. When the reaction was completed, water (5 mL) was added and the resulting reaction mixture was stirred for several minutes. The desired product was collected by Büchner filtration, washed with additional water and air-dried to afford **2a** (**2b–h**) as white powder, which could be directly used as NMR analysis sample. The melting point data was obtained from the sample by recrystallization from EtOH-H₂O (9:1).

General procedure for the preparation of 9-aryl-3,3,6,6-tetramethyl- hexahydroacridine-1,8-diones **3a–h**

A mixture containing aryl aldehyde (1.0 mmol), dimedone (280 mg, 2.0 mmol) and ammonium acetate (92.4 mg, 1.2 mmol) was introduced into a test tube. After heated up to 120 °C, the melt mixture was kept stirring at this temperature for 1.5 h. The same work-up procedure as **2a–h** afforded **3a–h** as pale yellow powder.

General procedure for the preparation of 9,10-diaryl-3,3,6,6-tetramethyl-hexahydroacridine-1,8-diones 4a–h

A mixture containing aryl aldehyde (1.0 mmol), dimedone (280 mg, 2.0 mmol) and *p*-toluidine (107 mg, 1.0 mmol) was introduced into a test tube. After heated up to 150 °C, the melt mixture was kept stirring at this temperature for a desired time. The same work-up procedure as **2a–h** gave **4a–h** as pale yellow powder.

Compounds **2a**,^{2a} **2b–d**,^{5a} **2e**,^{4a} **2f**,^{5a} **2g**,^{2a} **3a**,^{3c} **3b**,^{5d} **3c**,^{2d} **3d**,^{3c} **3e**,^{5d} **3f**,^{3c} **3g**,^{2d} **3h**,^{5d} **4a**,^{3d} **4b**,^{5b} **4c**,^{3d} **4d**,^{3d} **4e**,^{5b} and **4f**,^{5b} were previously reported and were confirmed by comparison of their melting points and spectral data with the reported data. Characterization data for new compounds **2h**, **4g**, and **4h** are shown below:

9-(3,4-Dichlorophenyl)-3,3,6,6-tetramethyl-tetrahydroanthene-1,8-dione (2h): White solid; Mp 250–252 °C; IR (KBr): ν_{\max} = 3062, 2964, 2872, 1660, 1620, 1466, 1361, 1198, 1166, 1136, 1025, 1000, 981, 884 cm^{-1} ; ¹H NMR (300 MHz, CDCl₃): δ 0.98 (s, 6H), 1.11 (s, 6H), 2.16 (d, *J* = 16.3 Hz, 2H), 2.25 (d, *J* = 16.3 Hz, 2H), 2.48 (s, 4H), 4.80 (s, 1H), 7.42 (d, *J* = 8.1 Hz, 1H), 7.67 (d, *J* = 8.1 Hz, 1H), 7.40 (s, 1H); ¹³C NMR (75 MHz, CDCl₃, all 1C unless indicated): δ 27.5, 29.3, 31.6, 32.3, 41.0 (2 C), 50.8 (2 C), 114.9 (2 C), 128.3, 130.1, 130.36, 130.44, 144.6, 162.8 (2 C), 196.4 (2 C); HR-MS (EI-TOF): *m/z* = 418.1099 [*M*⁺], calcd. for C₂₃H₂₄O₃³⁵Cl₂: 418.1103. tetramethylhexahydroanthracene-1,8-dione

9-(4-Cyanophenyl)-3,3,6,6-tetramethyl-10-*p*-tolyl-hexahydroacridine-1,8-dione (4g): Pale yellow solid; Mp 273–275 °C; IR (KBr): ν_{\max} = 3035, 2957, 2872, 2360, 2224, 1633, 1605, 1574, 1513, 1471, 1361, 1300, 1277, 1224, 1176, 1144, 1123, 1019, 1002, 853, 568, 527 cm^{-1} ; ¹H NMR (300 MHz, CDCl₃): δ 0.78 (s, 6H), 0.95 (s, 6H), 1.84 (d, *J* = 17.4 Hz, 2H), 2.08 (d, *J* = 17.4 Hz, 2H), 2.08 (d, *J* = 17.4, 2H), 2.15 (d, *J* = 17.4, 2H), 2.49 (s, 3H), 5.30 (s, 1H), 7.08 (d, *J* = 7.8 Hz, 2H), 7.15 (d, *J* = 7.8 Hz, 2H), 7.54 (s, 4H); ¹³C NMR (75 MHz, CDCl₃, all 1C unless indicated): δ 21.4, 26.8 (2 C), 29.7 (2C), 32.5 (2 C), 33.8, 41.9 (2C), 50.2 (2C), 109.7, 113.6 (2C), 119.4, 128.8, 128.9 (2C), 129.5, 130.9 (2C), 132.0, 132.1 (2C), 136.1, 139.9, 150.7, 151.7, 195.8 (2C); HR-MS (EI-TOF): *m/z* = 464.2460 [*M*⁺], calcd. for C₃₁H₃₂N₂O₂: 464.2464.

9-(3,4-Dichlorophenyl)-3,3,6,6-tetramethyl-10-*p*-tolyl-hexahydroacridine-1,8-dione (4h): Pale yellow solid; Mp >300 °C; IR (KBr): ν_{\max} = 3035, 2958, 2871, 1639, 1574, 1512, 1468, 1424, 1360, 1301, 1262, 1219, 1177, 1144, 1025, 881, 833, 753, 673, 571, 527 cm^{-1} ; ¹H NMR (300 MHz, CDCl₃): δ 0.82 (s, 6H), 0.95 (s, 6H), 1.84 (d, *J* = 17.3 Hz, 2H), 2.07 (d, *J* = 17.3 Hz, 2H), 2.13 (d, *J* = 16.4 Hz, 2H), 2.21 (d, *J* = 16.4 Hz, 2H), 2.48 (s, 3H), 5.22 (s, 1H), 7.07 (d, *J* = 8.4 Hz, 2H), 7.32-7.36 (m, 4H), 7.46 (s, 1H); ¹³C NMR (75 MHz, CDCl₃, all 1C unless indicated): δ 21.4, 26.8 (2C), 29.7 (2C), 32.45 (2C), 32.51, 41.8 (2C), 50.2 (2C), 113.8 (2C), 127.7, 128.7, 129.6 (br), 129.7 (br), 130.0 (2 C), 131.0 (br), 131.7 (br), 131.9, 136.1, 139.8, 146.7, 150.6 (2C), 195.8 (2C); HR-MS (EI-TOF): *m/z* = 507.1723 [*M*⁺], calcd. for C₃₀H₃₁NO₂³⁵Cl₂: 507.1732.

Acknowledgements

The authors are grateful for the financial support from National Natural Science Foundation of China (Nos. 20621061 and 20772117).

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