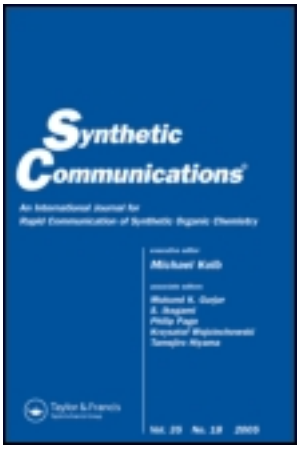

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Efficient Solvent-Free Knoevenagel Condensation Between β-Diketone and Aldehyde Catalyzed by Silica Sulfuric Acid

Fuyi Zhang [a], Yu-Xin Wang [a], Feng-Ling Yang [a], Hong-Yu Zhang [a] & Yu-Fen Zhao [a]

[a] Chemistry Department, Key Laboratory of Chemical Biology and Organic Chemistry of Henan Province, New Drug Research and Development Center, Zhengzhou University, Zhengzhou, China

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EFFICIENT SOLVENT-FREE KNOEVENAGEL CONDENSATION BETWEEN β-DIKETONE AND ALDEHYDE CATALYZED BY SILICA SULFURIC ACID

Fuyi Zhang, Yu-Xin Wang, Feng-Ling Yang, Hong-Yu Zhang, and Yu-Fen Zhao

Chemistry Department, Key Laboratory of Chemical Biology and Organic Chemistry of Henan Province, New Drug Research and Development Center, Zhengzhou University, Zhengzhou, China

Silica sulfuric acid has been utilized as an efficient heterogeneous recyclable catalyst for Knoevenagel condensation between poorly reactive β-diketones and aldehydes under solvent-free conditions. This protocol also works well with more reactive β-ketoesters. The condensation is efficient, clean, and mild. The scope and generality of the Knoevenagel condensation were investigated. The procedure led only to the Knoevenagel product, and no side product derived from a subsequent Michael addition of β-diketone to alkene was detected at rt. Increasing temperature led to a subsequent Michael addition, and it was applied to the efficient synthesis of 9-aryl-1,8-dioxo-octahydroxanthene derivatives.

Keywords: 9-Aryl-1,8-dioxo-octahydroxanthene derivatives; Knoevenagel condensation; silica sulfuric acid

INTRODUCTION

Knoevenagel condensation between an aldehyde and a methylene active compound is an important C=C bond-formation reaction and has been largely employed to synthesize Knoevenagel products, such as coumarin derivatives, cosmetics, perfumes, and pharmaceuticals.[1] In general, the condensations have been performed in the presence of a base.[2] Lewis acids such as $TiCl_4$,[3] $ZnCl_2$,[4] $CeCl_3 \cdot 7H_2O$,[5] $NbCl_5$,[6] $Mg(ClO_4)_2$,[7] and SmI_3[8] known to promote Knoevenagel condensations are employed as alternative catalysts. Various protocols performed in ionic liquids[9] or by microwave irradiation and fluorous biphasic system[10] have also been reported. To accomplish cleaner syntheses, different heterogeneous catalysts such as sepiolites,[11] zeolite,[12] faujasite,[13] layered silicate PLS-1,[14] clays,[15] layered double hydroxides (LDHs),[16] hydrotalcites,[17] and MgO/ZrO_2[18] have been employed to do Knoevenagel condensations. Most of these are solid base catalysts. Solid-supported acid as an alternative catalyst also has many advantages

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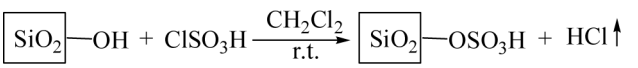
Address correspondence to Fuyi Zhang, Chemistry Department, Key Laboratory of Chemical Biology and Organic Chemistry of Henan Province, New Drug Research and Development Center, Zhengzhou University, Zhengzhou, China. E-mail: zhangfy@zzu.edu.cn



Scheme 1. Preparation of silica sulfuric acid by the reaction of silica gel with chlorosulfuric acid in CH_2Cl_2 at rt.

such as air and moisture tolerance, low toxicity, recovery and reuse, and low price. Because a reagent is dispersed on the surface of the support, the effective surface area of the reagent can be increased and the activity and selectivity of a reagent can be improved. The reaction is performed better than with the individual reagents.[19] However, very few examples of Knoevenagel condensation catalyzed by solid-supported acid have been reported.[20]

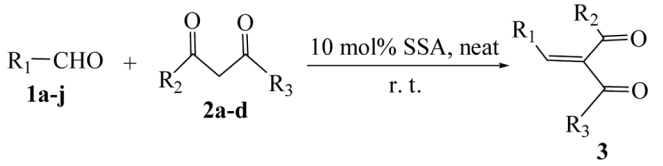
Silica sulfuric acid (SSA), a good solid acid introduced by M. A. Zolfigol in 2001,[21a] is easily and cleanly prepared by the reaction of silica gel with neat chlorosulfonic acid at rt. This method of preparation was slightly modified by performing the reaction in CH_2Cl_2 by Z. Li as shown in Scheme 1.[21b] SSA can make reaction processes convenient, more economical, and environmentally benign.[22] In recent years, SSA has been explored as a powerful catalyst for organic conversions under mild conditions.[21,23] Herein, we report an efficient solvent-free Knoevenagel condensation between β-diketone and aldehyde catalyzed by SSA.

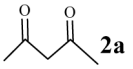
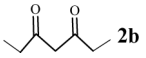
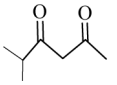
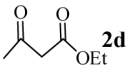
RESULTS AND DISCUSSION

The condensation of aldehydes with methylene active compounds such as malononitrile, cyanoacetates, malonates, and β-ketoesters have been extensively explored and largely used to prepare Knoevenagel products. Very few examples about β-diketones were reported, mainly because β-diketones easily form stable cyclic enols and thus have fewer activities.[20,24] The solvent-free reaction of benzaldehyde **1a** and acetoacetone **2a** (Table 1) was first investigated in the presence of various amounts of SSA at different temperatures. The best conditions for obtaining the desired αβ-unsaturated diketone **3aa** required the use of 10 mol% SSA with stirring for 10 h at rt. Increase of the temperature or the amount of catalyst (>10 mol%) led to the side product, which was formed by the subsequent Michael addition of acetoacetone **2a** to **3aa**. Addition of a solvent slows the reaction, which was the same as that of the $Mg(ClO_4)_2/MgSO_4$-promoted Knoevenagel condensation.[7]

The best reaction conditions were applied to the other substrates. The results are also shown in Table 1. The aromatic aldehydes **1b**–**1f** having electron-withdrawing groups showed more reactivity toward acetoacetone **2a** (entries 2–6) than benzaldehyde **1a**, and the Knoevenagel products **3ba**,[7,25] **3ca**,[7,26] **3da**,[7] **3ea**,[7,8] and **3fa**[8] were obtained in good to excellent yields. The presence of the electron-releasing group MeO on aromatic aldehyde **1g** retarded the reaction (entry 7).[12b] The αβ-unsaturated aldehydes did not give satisfactory condensation with β-diketones. For example, cinnamaldehyde **1h** was employed to react with acetoacetone **2a** at rt for 32 h, but only 25% yield of desired product **3ha** was obtained and the other unidentified side products were complicated (entry 8). Aliphatic aldehydes reacted smoothly with β-diketones (entries 9 and 10). The condensation of butyraldehyde and hexanal with acetoacetone **2a** produced only α,β-unsaturated

Table 1. Solvent-free Knoevenagel condensation between aldehydes **1** and β-diketones **2** catalyzed by SSA at rt



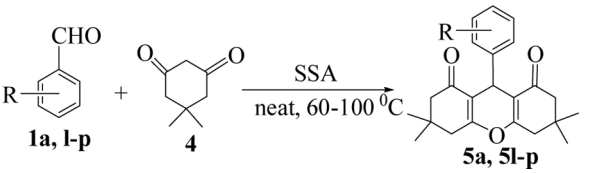
Entry	R_1	β-Diketone	Time (h)	Yield[a,b] (%) (Z:E ratio)	Product[lit]
1	C_6H_5	 **2a**	10	66	**3aa**[7,8,10b]
2	4-$NO_2C_6H_4$	**2a**	8	85	**3ba**[7,25]
3	2-$NO_2C_6H_4$	**2a**	8	83	**3ca**[7,26]
4	4-CNC_6H_4	**2a**	7	80	**3da**[7]
5	4-ClC_6H_4	**2a**	9	72	**3ea**[7,8]
6	4-BrC_6H_4	**2a**	9	70	**3fa**[8]
7	4-$MeOC_6H_4$	**2a**	12	61	**3ga**[12b]
8	*trans*-PhCH=CH	**2a**	32	25	**3ha**[7,8]
9	n-C_3H_7	**2a**	8	81	**3ia**[7,27]
10	n-C_6H_{13}	**2a**	8	68	**3ja**[7,28]
11	C_6H_5	 **2b**	12	60	**3ab**[30]
12	4-$NO_2C_6H_4$	**2b**	10	67	**3bb**[7]
13	4-CNC_6H_4	**2b**	12	73	**3db**[7]
14	4-$NO_2C_6H_4$	 **2c**	12	72 (5:1)	**3bc**[7]
15	C_6H_5	 **2d**	8	87 (2:1)	**3ad**[8,31]
16	4-$NO_2C_6H_4$	**2d**	6	88 (1.5:1)	**3bd**[31]
17	2-furyl	**2d**	7	85 (1:0)	**3jd**[9a,31]
18	4-$MeOC_6H_4$	**2d**	12	70 (2.5:1)	**3gd**[31]

[a]Isolated yield.
[b]The ratio found from ^{1}H NMR.

diketone **3ia**[7,27] and **3ja**[7,28] respectively in good yields, and no isomerization to β,γ-unsaturated ones was detected,[29] although there are two α-protons in the aldehydes.

We extended the procedure to the more bulkier β-diketones. The desired products were also obtained in good yields (entries 11–14). 3,5-Heptanedione **2b** exhibited a similar reactivity toward aldehydes, compared to the less bulky acetoacetone **2a**. The corresponding Knoevenagel products **3ab**,[30] **3bb**,[7] **3db**,[7] and **3bc**[7] were obtained in around 70% yields. Encouraged by this result, we extended the condensation reaction to asymmetric and bulkier 5-methylhexane-2,4-dione **2c** (entry 14). The corresponding desired product **3bc** was generated as a mixture of *Z*- and *E*-isomers in 72% with the *Z*-isomer as a major product. This protocol was then extended to the reaction of aromatic aldehydes with ethyl 3-oxobutanoate **2d**, the generally used reaction in the Knoevenagel condensation (entries 15–18). The substituted

Table 2. Solvent-free synthesis of 9-aryl-1,8-dioxo-octahydroxanthene derivatives **5** in the presence of 10 mol% SSA



Entry	R	Temperature (°C)	Time (h)	Yield (%)[a]	Product[lit]
1	H	80	1.5	82	**5a**[20,32]
2	2-Br	60	1	87	**5l**[32]
3	2-Cl	60	1	90	**5m**[20b,32]
4	3-Cl	60	1.5	85	**5n**[20,32]
5	4-Me	100	2	76	**5o**[20a,32]
6	4-MeO	100	2.5	73	**5p**[20a,32]

[a]Isolated yield.

alkenes **3ad**,[8,31] **3bd**,[31] **3jd**,[31] and **3gd**[31] were obtained in good or excellent yields, also with *Z*-isomers as major products.

As described previously, the solvent-free Knoevenagel condensation between aldehyde and β-diketone catalyzed by 10 mol% SSA at rt. gave α,β-unsaturated diketone. Increasing the temperature led to subsequent Michael addition of β-diketone to newly formed αβ-unsaturated diketone. Based on this experience, we extended this procedure to the Knoevenagel condensation between aromatic aldehydes and dimedone **4** (Table 2) and found an alternative method for the synthesis of 9-aryl-1,8-dioxo-octahydroxanthene derivatives **5**. These compounds were previously synthesized.[20,32] We investigated SSA-catalyzed reaction of aromatic aldehydes with dimedone **4** under solvent-free conditions. The reaction proceeded smoothly at 60–100 °C to give the corresponding products **5**, which were obviously formed by the Knoevenagel condensation, followed by Michael addition and cyclodehydration in one pot.[20a] The reaction of benzaldehyde **1a** with dimedone **4** was performed at 80 °C to generate 9-phenyl-1,8-dioxo-octahydroxanthene **5a** in 82%, and no other intermediate was isolated (Table 2, entry 1). The presence of an electron-withdrawing group on the aromatic aldehyde, such as Br and Cl, increases the reactivity and the desired products **5l**–**n** were obtained in excellent yields at 60 °C (entries 2–4). The aldehyde with strong electron-withdrawing groups, such as NO_2 and CN, has a high melting point and cannot perform a solvent-free reaction with dimedone **4**. The presence of an electron-releasing group on the aromatic aldehyde such as CH_3 and MeO decreases the reactivity, and the reaction worked at a slower rate to give less yield of **5o** and **5p** compared with the aldehyde having an electron-withdrawing group (entries 5 and 6).

CONCLUSION

In conclusion, we have used an inexpensive, easily prepared heterogenous catalyst (SSA) to carry out a Knoevenagel condensation between various aldehydes

and poorly active diketones to produce trisubstituted functionalized alkenes under solvent-free conditions. The procedure led only to the Knoevenagel product, and no side product derived from a subsequent Michael addition of β-diketone to alkene was detected at rt. Increasing the temperature led to a subsequent Michael addition. The aliphatic aldehyde gave the only product, and no isomerization of a newly formed double bond was detected. SSA-promoted condensation was applied to the solvent-free synthesis of 9-aryl-1,8-dioxo-octahydroxanthene derivatives in one pot. The reaction of aromatic aldehydes with dimedone at 60–100 °C gave good to excellent yields of the desired products. The aromatic aldehyde having an electron-withdrawing group works better than that with an electron-releasing group.

EXPERIMENTAL

SSA was prepared according to the reported modified protocol.[21b] All of the products are known compounds and were characterized by comparision of their spectroscopic data with those reported in the literature. NMR spectra were recorded on a Bruker DXP-400 spectrometer in pure deuterated solvents. Chemical shifts (δ) are reported in parts per million (ppm), and coupling constants (*J*) are given in hertz (Hz). The multiplicities of the signals are abbreviated by s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), and br (broad). Electrospray ionization (ESI)–high resolution (HR) mass spectra were determined on a Waters Micromass Q-Tof Micro instrument. Thin-layer chromatography (TLC) was performed on precoated plates of silica gel 60 F_{254}.

General Procedure for the Synthesis of α,β-Unsaturated Diketones and α,β-Unsaturated Ketoesters

A mixture of aldehyde **1** (1 mmol) and β-diketone or ethyl 3-oxobutanoate **2** (1 mmol) was stirred at rt. If the aldehyde was solid, the stirring continued until the solution became clear. SSA (10 mol%) was added. The mixture was stirred at rt and monitored by TLC. After completion, the reaction mixture was filtered, washed with CH_2Cl_2, and evaporated. The crude product **3** was purified by flash chromatography on silica gel, eluting with an appropriate mixture of petroleum ether/EtOAc. The products were characterized, and the spectroscopic data were identical with the reported ones.

Selected Spectroscopic Data

3-Benzylidene-pentane-2,4-dione (Table 1, Entry 1). Mp 184–187 °C (lit. 185–188 °C);[10b] ^{1}H NMR (400 MHz, $CDCl_3$): 7.47 (s, 1H, CH), 7.39 (s, 5H, Ph), 2.42 (s, 3H, CH_3), 2.30 (s, 3H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): 205.3 (C=O), 196.2 (C=O), 142.6 (C), 139.7 (CH), 132.8 (CH), 130.7 (CH), 129.5 (C), 128.9 (CH), 31.5 (CH_3), 26.6 (CH_3). HRMS (ESI) (m/z): 211.0735 ($[M + Na]^+$).

3-Butylidenepentane-2,4-dione (Table 1, Entry 9). Oil (lit. liquid);[27] ^{1}H NMR (400 MHz, $CDCl_3$): 6.62 (t, $J = 7.7$ Hz, 1H, CH), 2.24 (s, 3H, CH_3), 2.27 (s, 3H, CH_3), 2.12–2.19 (m, 2H, CH_2), 1.41–1.52 (m, 2H, CH_2), 0.91 (t, $J = 7.5$ Hz,

3H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): 203.6 (C=O), 197.2 (C=O), 146.7 (C), 145.1 (CH), 31.7 (CH_3), 31.3 (CH_2), 26.0 (CH_3), 21.7 (CH_2), 13.8 (CH_3). HRMS (ESI) (m/z): 177.0891 ($[M + Na]^+$).

4-Benzylidene-heptane-3,5-dione (Table 1, Entry 11). Oil (lit. clear oil);[30b] ^1H NMR (400 MHz, $CDCl_3$): 7.54 (s, 1H, CH), 7.23–7.40 (m, 5H, Ph), 2.8 (q, $J = 7.2$ Hz, 2H, CH_2), 2.48 (q, $J = 7.2$ Hz, 2H, CH_2), 1.14 (t, $J = 7.2$ Hz, 3H, CH_3), 1.05 (t, $J = 7.2$ Hz, 3H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): 208.7 (C=O), 199.1 (C=O), 142.5 (C), 138.7 (CH), 133.6 (CH), 130.5 (CH), 129.6 (C), 129.0 (CH), 37.2 (CH_2), 31.7 (CH_2), 7.8 (CH_3), 7.3 (CH_3). HRMS (ESI) (m/z): 239.1048 ($[M + Na]^+$).

(Z)-Ethyl 2-benzylidene-3-oxobutanoate (Table 1, Entry 15). Mp 79–81 °C (lit. 78–80 °C);[31c] ^1H NMR (400 MHz, $CDCl_3$): 7.58 (s, 1H, CH), 7.41–7.49 (m, 5H, Ph), 4.36 (q, $J = 7.0$ Hz, 2H, CH_2), 2.45 (s, 3H, CH_3), 1.30 (t, $J = 7.0$ Hz, 3H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): 194.7 (C=O), 167.9 (COO), 141.3 (CH), 134.7 (C), 133.0 (C), 130.8 (CH), 129.6 (CH), 128.9 (CH), 61.6 (CH_2), 26.4 (CH_3), 13.7 (CH_3). HRMS (ESI) (m/z): 241.0841 ($[M + Na]^+$).

(E)-Ethyl 2-benzylidene-3-oxobutanoate (Table 1, Entry 15). Mp 43–44 °C (lit. 44–45 °C);[10b] ^1H NMR (400 MHz, $CDCl_3$): 7.68 (s, 1H, CH), 7.36–7.39 (m, 5H, Ph), 4.28 (q, $J = 7.0$ Hz, 2H, CH_2), 2.35 (s, 3H, CH_3), 1.33 (t, $J = 7.0$ Hz, 3H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): 203.4 (C=O), 164.2 (COO), 140.5 (CH), 133.8 (C), 132.9 (C), 130.4 (CH), 129.4 (CH), 128.7 (CH), 61.4 (CH_2), 31.2 (CH_3), 14.1 (CH_3). HRMS (ESI) (m/z): 241.0841 ($[M + Na]^+$).

(Z)-Ethyl 2-(4-nitrobenzylidene)-3-oxobutanoate (Table 1, Entry 16). Mp 159–161 °C (lit. 160–161 °C);[31b] ^1H NMR (400 MHz, $CDCl_3$): 8.25 (d, $J = 8.8$ Hz, 2H, ArH), 7.60 (s, 1H, CH), 7.61 (d, $J = 8.8$ Hz, 2H, ArH), 4.33 (q, $J = 7.2$ Hz, 2H, CH_2), 2.46 (s, 3H, CH_3), 1.27 (t, $J = 7.2$ Hz, 3H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): 193.8 (C=O), 166.7 (COO), 148.5 (C), 139.5 (C), 138.0 (CH), 137.3 (C), 129.8 (CH), 123.9 (CH), 62.3 (CH_2), 26.7 (CH_3), 13.7 (CH_3). HRMS (ESI) (m/z): 302.0425 ($[M + K]^+$).

(E)-Ethyl 2-(4-nitrobenzylidene)-3-oxobutanoate (Table 1, Entry 16). Mp 60–62 °C; ^1H NMR (400 MHz, $CDCl_3$): 8.21 (d, $J = 8.8$ Hz, 2H, ArH), 7.67 (s, 1H, CH), 7.55 (d, $J = 8.8$ Hz, 2H, ArH), 4.32 (q, $J = 6.8$ Hz, 2H, CH_2), 2.35 (s, 3H, CH_3), 1.36 (t, $J = 6.8$ Hz, 3H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): 202.3 (C=O), 163.5 (COO), 148.0 (C), 139.2 (C), 137.7 (CH), 137.5 (C), 130.0 (CH), 124.0 (CH), 62.1 (CH_2), 31.2 (CH_3), 14.1 (CH_3). HRMS (ESI) (m/z): 302.0425 ($[M + K]^+$), 286.0691 ($[M + Na]^+$).

(Z)-Ethyl 2-((furan-2-yl)methylene)-3-oxobutanoate (Table 1, Entry 17). Oil (lit. yellowish liquid);[9a] ^1H NMR (400 MHz, $CDCl_3$): 7.55 (d, $J = 1.8$ Hz, 1H), 7.31 (s, 1H), 6.80 (d, $J = 3.6$ Hz, 1H), 6.50 (dd, $J_1 = 3.6$ Hz, $J_2 = 1.8$ Hz, 1H), 4.41 (q, $J = 6.8$ Hz, 2H), 2.35 (s, 3H), 1.37 (t, $J = 6.8$ Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): 193.8 (C), 167.3 (C), 148.7 (C), 146.4 (CH), 129.7 (C), 126.4 (CH), 118.8 (CH), 112.8 (CH), 61.7 (CH_2), 26.4 (CH_3), 14.1 (CH_3). HRMS (ESI) (m/z): 231.0630 ($[M + Na]^+$), 247.0361 ($[M + K]^+$).

(Z)-Ethyl 2-(4-methoxybenzylidene)-3-oxobutanoate (Table 1, Entry 18). Mp 91–92 °C (lit. 90–92 °C);[31a] ^{1}H NMR (400 MHz, $CDCl_3$): 7.51 (s, 1H), 7.43 (d, $J = 8.7$ Hz, 2H), 6.90 (d, $J = 8.7$ Hz, 2H), 4.37 (q, $J = 7.4$ Hz, 2H), 3.86 (s, 3H), 2.41 (s, 3H), 1.33 (t, $J = 7.4$ Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): 194.6 (C), 168.4 (C), 161.6 (C), 141.1 (CH), 132.3 (C), 131.6 (CH), 125.1 (C), 114.3 (CH), 61.4 (CH_2), 55.2 (CH_3), 26.5 (CH_3), 14.1 (CH_3). HRMS (ESI) (m/z): 271.0941 ($[M + Na]^+$).

(E)-Ethyl 2-(4-methoxybenzylidene)-3-oxobutanoate (Table 1, Entry 18). Mp 65–68 °C; ^{1}H NMR (400 MHz, $CDCl_3$): 7.60 (s, 1H), 7.35 (d, $J = 8.8$ Hz, 2H), 6.87 (d, $J = 8.8$ Hz, 2H), 4.28 (q, $J = 7.2$ Hz, 2H), 3.84 (s, 3H), 2.39 (s, 3H), 1.34 (t, $J = 7.2$ Hz, 3H); NMR (100 MHz, $CDCl_3$): 204.1 (C), 164.6 (C), 161.5 (C), 140.2 (CH), 131.8 (CH), 131.5 (C), 125.4 (C), 114.2 (CH), 61.2 (CH_2), 55.3 (CH_3), 31.2 (CH_3), 14.1 (CH_3). HRMS (ESI) (m/z): 271.0941 ($[M + Na]^+$), 287.0681 ($[M + K]^+$).

General Procedure for the Synthesis of 9-Aryl-1,8-dioxo-octahydroxanthene Derivatives

A mixture of aldehyde **1** (1 mmol) and dimedone **4** (2 mmol) was heated to 60–100 °C, to which SSA (10 mol%) was added. The reaction was monitored by TLC. After completion, the mixture was cooled to rt and diluted with EtOAc. The catalyst was filtered off, washed with EtOAc, and evaporated. The residue was crystallized from ethanol to give pure 9-aryl-1,8-dioxooctahydroxanthene **5** as a crystal.

Selected Data

3,3,6,6-Tetramethyl-9-phenyl-1,8-dioxo-octahydroxanthene (Table 2, Entry 1). Mp 203–205 °C (lit. 204–206 °C);[20b] ^{1}H NMR (400 MHz, DMSO-d_6): 7.20 (m, 5H, Ph), 4.67 (s, 1H, H-9), 2.46 (s, 4H, $2 \times CH_2$, H-2, H-7), 2.21 (dd, $J_1 = 1.8$ Hz, $J_2 = 2.4$ Hz, 4H, $2 \times CH_2$, H-4, H-5), 1.13 (s, 6H, $2 \times CH_3$), 0.97 (s, 6H, $2 \times CH_3$). HRMS (ESI) (m/z): 373.1773 ($[M + Na]^+$).

3,3,6,6-Tetramethyl-9-(2-bromophenyl)-1,8-dioxo-octahydroxanthene (Table 2, Entry 2). Mp 227–229 °C (lit. 226–229 °C);[32a] ^{1}H NMR (400 MHz, DMSO-d_6): 7.22–7.31 (m, 4H, ArH), 4.62 (s, 1H, H-9), 2.48 (s, 4H, $2 \times CH_2$, H-2, H-7), 2.31 (dd, 4H, $J_1 = 1.8$ Hz, $J_2 = 3.2$ Hz, $2 \times CH_2$, H-4, H-5), 1.03 (s, 6H, $2 \times CH_3$), 1.01 (s, 6H, $2 \times CH_3$). HRMS (ESI) (m/z): 451.0880 ($[M + Na]^+$), 429.1061 ($[M + 1]^+$).

3,3,6,6-Tetramethyl-9-(2-chlorophenyl)-1,8-dioxo-octahydroxanthene (Table 2, Entry 3). Mp 225–226 °C (lit. 225–227 °C);[20b] ^{1}H NMR (400 MHz, DMSO-d_6): 7.25–7.36 (m, 4H, ArH), 4.65 (s, 1H, H-9), 2.50 (s, 4H, $2 \times CH_2$, H-2, H-7), 2.07 (dd, $J_1 = 1.8$ Hz, $J_2 = 3.2$ Hz, 4H, $2 \times CH_2$, H-4, H-5), 1.11 (s, 6H, $2 \times CH_3$), 0.98 (s, 6H, $2 \times CH_3$). HRMS (ESI) (m/z): 407.1383 ($[M + Na]^+$).

3,3,6,6-Tetramethyl-9-(3-chlorophenyl)-1,8-dioxo-octahydroxanthene (Table 2, Entry 4). Mp 183–185 °C (lit. 182–184 °C);[20b] ^{1}H NMR (400 MHz, DMSO-d_6): 7.10–7.24 (m, 4H, ArH), 4.73 (s, 1H, H-9), 2.48 (s, 4H, $2 \times CH_2$, H-2, H-7), 2.31 (dd, 4H, $J_1 = 1.8$ Hz, $J_2 = 3.8$ Hz, $2 \times CH_2$, H-4, H-5), 1.13 (s, 6H,

$2 \times CH_3$), 1.01 (s, 6H, $2 \times CH_3$). HRMS (ESI) (m/z): 407.1380 ($[M + Na]^+$), 423.1121 ($[M + K]^+$).

3,3,6,6-Tetramethyl-9-(4-methylphenyl)-1,8-dioxo-octahydroxanthene (Table 2, Entry 5). Mp 216–217 °C (lit. 217–218 °C);[20b] ^{1}H NMR (400 MHz, $CDCl_3$): 7.12 (d, $J = 8.7$ Hz, 2H, ArH), 6.68 (d, $J = 8.7$ Hz, 2H, ArH), 4.61 (s, 1H, CH, H-9), 2.45 (s, 3H, $ArCH_3$), 2.43 (s, 4H, $2 \times CH_2$, $2 \times CH_2$, H-2, H-7), 2.17 (dd, $J_1 = 1.6$ Hz, $J_2 = 2.4$ Hz, 4H, $2 \times CH_2$, H-4, H-5), 1.12 (s, 6H, $2 \times CH_3$), 1.02 (s, 6H, $2 \times CH_3$). HRMS (ESI) (m/z): 387.1931 ($[M + Na]^+$).

3,3,6,6-Tetramethyl-9-(4-methoxyphenyl)-1,8-dioxo-octahydroxanthene (Table 2, Entry 6). Mp 242–243 °C (lit. 240–242 °C);[20b] ^{1}H NMR (400 MHz, DMSO-d_6): 6.66–7.27 (m, 4H, ArH), 4.71 (s, 1H, H-9), 3.74 (s, 3H, CH_3O), 2.47 (s, 4H, $2 \times CH_2$, H-2, H-7), 2.21 (dd, $J_1 = 1.8$ Hz, $J_2 = 2.2$ Hz, 6H, $2 \times CH_2$, H-4, H-5), 1.10 (s, 6H, $2 \times CH_3$), 1.02 (s, 6H, $2 \times CH_3$). HRMS (ESI) (m/z): 403.1885 ($[M + Na]^+$), 365.2110 ($[M + H]^+$).

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