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ORIGINAL PAPER

Synthesis of 9-substituted 1,8-dioxooctahydroxanthenes by using diethyl ethoxymethylenemalonate as a double Michael acceptor synthon

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Abstract Tandem Michael addition/elimination/Michael addition/cyclization reactions of diethyl ethoxymethylenemalonate as a double Michael acceptor with cyclic β-diketones furnished novel 9-substituted 1,8-dioxooctahydroxanthenes.

Keywords Diethyl ethoxymethylenemalonate · Double Michael acceptor · 9-Substituted-1 · 8-Dioxooctahydroxanthenes

Introduction

Diethyl ethoxymethylenemalonate (DEEM) (also abbreviated as EMME, DEMM) and similar "alkoxyacrylic" derivatives are Michael acceptors, utilized extensively in organic synthesis, particularly in preparation of pharmacologically active substances. "Oxacine" type anti-bacterials having quinoline and naphthyridine structures are good examples [1–5]. This group of Michael acceptors usually forms Michael monoadducts with retention of the double bond. They react with a variety of nucleophiles; in addition, a broad range of their applications in the synthesis of chain, cyclic, heterocyclic, and fused heterocyclic structures has been reported and reviewed [6–8]. In these reviews, the reactions of nucleophilic nitrogen atoms with "alkoxyacrylic" compounds prevail, but there are also a few reports about reactions of nucleophilic carbons, especially with DEEM.

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Xanthenes constitute a structural unit in a number of ring systems of natural products [9–14] and because of having inherent reactivity of the inbuilt pyran ring are versatile synthons [15, 16]. Some of these derivatives have received considerable attention in bioorganic and medicinal areas, as they exhibited antitumoral [17–19], antiviral [20], anti-inflammatory [21–24], fungicidal, and bactericidal properties [25–27]. They are also being developed to act as new clinical agents in cancer therapy [28]. Furthermore, xanthene derivatives are very useful and important organic compounds widely used as dye [29], in laser technologies [30], and fluorescent materials for visualization of biomolecules [31]. Thus, the synthesis of these heterocyclic compounds is interesting for both organic synthesis and medicinal chemistry.

Their conventional synthesis involves acid as well as base catalyzed condensation of active methylene groups of dimedone or 1, 3-cyclohexanediones with aldehydes [32–38]. Such 1,8-dioxooctahydroxanthenes have only an aryl group on the 9-position of the molecule.

Few successful attempts for the synthesis of non-hydrocarbon group 9-position functionalized xanthenediones have been reported. Luna et al. [39, 40] have synthesized 9-carbomethoxymethyl derivatives, through a two-step process. In the first step L-proline catalyzed double Michael reaction of 1,3-cyclohexanedione or dimedone with methyl propiolate in DMSO at room temperature within 3 days to obtain a number of tetraketones followed by I_2 cyclization to xanthene structures. However, Singh et al. [41] have reported functionalization of the methylene bridge by acid catalyzed condensation of dimedone and cyclohexanedione with a 1,3-oxazinane (masked aldehyde). Rohr et al. [28] prepared 9-carboxaldehyde and 9-carboxylate derivatives, using glyoxal dimethyl acetal and methyl glyoxylate, respectively. In another report one

mole of dimedone is converted to 2-{bis(benzylthio) methylene}-5,5-dimethylcyclohexane-1,3-dione, using carbon disulfide and benzyl chloride [42]. The bis(benzylthio) derivative is then reacted with a second mole of dimedone to produce tetraketone, which is then cyclized to 9-benzylthio-1,8-dioxo-octahydroxanthene.

Recently, we have reported use of "DEEM" synthon as a double Michael acceptor for the synthesis of novel bridge functionalized bisindoles. We decided to use DEEM for the synthesis of 9-substituted 1,8-dioxooctahydroxanthenes in order to examine both new applications for push–pull olefins (β-ethoxyacrylic synthons) such as DEEM with carbon nucleophiles, and find a simple method to functionalize 1, 8-dioxooctahydroxanthenes. The present paper reports for the first time, a simple process for the synthesis of novel 9-bis(carboethoxy)methyl-1,8-dioxo-3,3,6,6-tetramethyl-tetrahydroxanthenes, having a malonate group on the methylene bridge, using DABCO-catalyzed double Michael addition of dimedone or 1,3-cyclohexanedione to DEEM. It is noteworthy that both the reagent and catalyst are easily available and of low cost. Extensive survey of literature showed no report, neither for the synthesis of compounds presented in this report, nor for the use of DEEM for a tandem Michael addition–elimination–Michael addition–cyclization reaction sequence.

Experimental

Chemicals and apparatus

All chemicals were purchased from Merck & Co. Inc. Melting points were measured using Barnstead-Electrothermal 9200 melting point apparatus. GC/Mass analyses were performed using Agilent 6890 GC system Hp-5 capillary 30 m × 530 μm × 1.5 μm nominal. IR spectra were recorded as KBr disc on the FT-IR Bruker Tensor 27 spectrometer. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker DRX-500-AVANCE spectrometer at 500 (^{1}H) and 125 MHz (^{13}C).

Procedure for the synthesis of 9-(carboethoxy) methyl-3, 3, 6, 6-tetramethyl-tetrahydroxanthene-1,8-diones

A 50 mL round bottom flask was charged with cyclohexane-1, 3-dione or dimedone (20 mmol), and DEEM (20 mmol, 4.4 g). DABCO (2 mmol, 0.2 g) was added to the stirring solution. The mixture was magnetically stirred at 60 °C. The progress of the reaction was monitored by TLC using petroleum ether: EtOAc (4:1) as eluent. When all the starting materials (cyclohexane-1,3-dione or dimedone) were consumed (Table 1), the reaction mixture was cooled to room temperature and diluted with 50 mL of EtOAc. 1 N hydrochloric acid (40 mL) was then added to the mixture and stirred for 20 min. The organic phase was separated, washed with water (1 × 50), dried over anhydrous sodium sulfate, and concentrated by evaporation. Resulting residue dissolved in EtOAc (10 mL) and petroleum ether (30 mL) was added to precipitate the product. The produced solid was filtered, and dried under reduced pressure to afforded target xanthene-1,8-diones (**3a** or **3b**). Further purification of the product was not normally needed. The filtrate was evaporated and the residue then purified by preparative thin layer chromatography on silica gel (petroleum ether/ethyl acetate ratio was 5:1) to afford **2a** or **4b**.

Table 1 Study on the preparation of 1, 8-dioxooctahydroxanthenes

Entry	Starting material	Reaction conditions[a]	Time	Product (yield%)[b]
1	**1a**	$Si(CH_3)_3Cl$, C_2H_5OH, 35 °C	3d	**2a** (85)[b]
2	**1a**	$Si(CH_3)_3Cl$, C_2H_5OH, reflux	2d	**3a** (60)[b], **2a** (15)[b]
3	**1a**	PTSA, C_2H_5OH, 35 °C	5d	**2a** (30), **3a** (15)[c]
4	**1a**	PTSA, C_2H_5OH, reflux	3d	**2a** (10), **3a** (47)[c]
5	**1a**	CH_3COOH, reflux	5d	**3a** (18)[c]
6	**1a**	PPA/SiO_2, CH_3OH	3d	No reaction
7	**1a**	$H_{14}[NaP_5W_{30}O_{110}]$, C_2H_5OH, reflux	4d	No reaction
8	**1a**	CH_3ONa, C_2H_5OH, reflux	5d	**3a** (27)[b]
9	**1a**	t-BuONa, toluene, reflux	2d	**3a** (20)[b]
10	**1a**	DABCO, DMF, room temp	1d	**3a** (15)[b]
11	**1a**	DABCO, CH_3CN, reflux	14 h	**3a** (40)[b]
12	**1a**	DABCO, neat, 90 °C	45 min	**3a** (60)[b]
13	**1a**	DABCO, neat, 60 °C	3 h	**3a** (83), **2a** (10)[b]
14	**1b**	DABCO, DMF, room temp	1d	**3b** (8), **4b** (71)[b]
15	**1b**	DABCO, neat, 60 °C	3 h	**3b** (80), **4b**(10)[b]

[a] Entries 5, 9, molar ratio of DEEM/dimedone 1:2; Entry 6, molar ratio of DEEM/dimedone 2:1; other entries molar ratio of DEEM/dimedone 1:1

[b] Yields refer to isolated products

[c] Yields refer to GC analysis

Compound **2a**: White solid; mp: 106–108 °C; yield: 0.43 g (10%)

IR (KBr): 2,961, 1,737 (C=O), 1,664 (α, β unsaturated C=O), 1,607, 1,466, 1,422, 1,379, 1,202, 1,160, 1,041, 870, 742, 572 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): $\delta = 1.11$ (12H, s, $C(CH_3)_2$), 1.27 (6H, t, $J = 7.1$ Hz, $OCH_2\underline{CH_3}$), 2.26–2.35 (4H, AB q, $J = 16.3$ Hz, $2CH_2$), 2.41–2.50 (4H, AB q, $J = 16$ Hz, $2CH_2$), 3.92 (1H, d, $J = 3.6$ Hz,–$\underline{CH}$–$CH(CO_2Et)_2$), 4.13 (2H, q, $J = 7.1$ Hz, $O\underline{CH_2}CH_3$), 4.38 (1H, d, $J = 3.1$ Hz,–CH–$\underline{CH}(CO_2Et)_2$); ^{13}C NMR (125.7 MHz, $CDCl_3$): $\delta = 14.4$, 26.9, 27.0, 30.1, 32.2, 41.4, 51.1, 53.3, 61.6, 112.0, 166.3, 168.3, 197.01; MS: *m/z* (%) = 432 [M^+] (5), 340 (34), 286 (17), 273 (100), 257 (38), 217 (13), 201 (12), 161 (8), 77 (3).

Compound **3a**: White solid; mp: 125.2–127 °C; yield: 3 g (83%)

IR (KBr): 2,963, 2,877, 1,720 (C=O), 1,678, 1,655 (α, β unsaturated C=O), 1,623 (C=C), 1,466, 1,422, 1,380, 1,201, 1,164, 1,137, 1,033, 742, 573 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): $\delta = 1.11$ (12H, s, $C(CH_3)_2$), 1.16 (3H, t, $J = 7.1$ Hz, $OCH_2\underline{CH_3}$), 2.29 (4H, s, $–CH_2C–O$), 2.39 (4H, s, $–CH_2C(O)$), 2.72 (2H, d, $J = 4.1$ Hz, CH_2 α-ester), 3.8 (1H, t, $J = 7.1$ Hz, $\underline{CH}–CH_2$), 3.98 (2H, q, $J = 7.1$ Hz, $O\underline{CH_2}CH_3$); ^{13}C NMR (125.7 MHz, $CDCl_3$): $\delta = 14.6$, 24.1, 27.4, 29.8, 32.4, 36.8, 41.2, 51.2, 60.3, 113.5, 164.9, 172.5, 197.4. MS: *m/z* (%) = 360 [M^+] (3), 286 (26), 273 (100), 257 (5), 217 (12), 161 (7), 55 (5).

Compound **3b**: White solid; mp: 102–104 °C; yield: 2.43 g (80%)

IR (KBr): 2,949, 2,899, 1,737 (C=O), 1,654 (α, β unsaturated C=O), 1,615 (C=C), 1,382, 1,278, 1,176, 1,132, 1,043, 1,011, 959, 847, 566 cm^{-1}; ^1H NMR (500 MHz, DMSO-d_6): $\delta = 1.11$ (3H, t, $J = 7.1$ Hz, $OCH_2\underline{CH_3}$), 1.83 (2H, m, CH_2), 1.94 (2H, m, CH_2), 2.32 (6H, t, $J = 7.7$ Hz, $3CH_2$), 2.47 (4H, m, $2CH_2$), 3.69 (1H, t, $J = 4.5$ Hz,CH), 3.89 (2H, q, $J = 7.1$, $O\underline{CH_2}CH_3$); ^{13}C NMR (125.7 MHz, DMSO-d_6): $\delta = 14.8$, 20.8, 24.1, 27.3, 37.2, 38.6, 60.4, 114.1, 166.8, 171.3, 197.5; MS: *m/z* (%) = 304 [M^+] (3), 231 (21), 217 (100), 175(7), 55(5).

Compound **4b**: White solid; mp: 155–157 °C; yield: 0.23 g (10%)

IR (Nujol): 3,200, 1,670, 1,630, 1,610, 1,530, 1,460, 1,390, 1,200 cm^{-1}. ^1H NMR (500 MHz, DMSO-d_6): $\delta = 1.89$ (4H, s, $2CH_2$), 2.36 (6H, s, $3CH_2$), 2.49 (2H, s, CH_2), 7.25 (1H, s, CH), 7.44 (1H, s, OH).^{13}C NMR (125.7 MHz, DMSO-d_6): $\delta = 19.37$, 37.3, 38.6, 123.8, 196.4. MS: *m/z* (%) = 234 [M^+] (69), 216 (85), 187 (76), 150 (100), 136 (60), 77 (90), 55 (54), 41(80).

Results and discussion

In our initial studies, we isolated 9-substituted 1,8-dioxooctahydroxanthene **2a** (Table 1, entry1) as sole product, from Si $(CH_3)_3Cl$ catalyzed reaction of DEEM with dimedone in C_2H_5OH in quantitative yield (based on consumed starting materials) after 3 days at 35 °C. Other experiments were conducted under different conditions. Results of all experiments are summarized in Table 1.

Refluxing C_2H_5OH shortened the reaction time, but led to partial hydrolysis of product **2a** to **3a**, Scheme 1 (Table 1, entry 2). When *p*-TsOH is used as catalyst, both **2a** and **3a** are produced in varying temperature dependent proportions (Table 1, entries 3, 4). The reaction did not occur when heterogeneous catalysts such as PPA/SiO_2 or HPA were used (Table 1, entries 6, 7). Unexpectedly, in the case of cyclohexane-1,3-dione, the reactions did not occur under acidic conditions even after prolonged reaction times. When alkoxides were used in catalytic amounts at ambient temperature, only starting materials were recovered. By raising the temperature to reflux in ethanol or toluene, **3a** was produced in very low yields as sole product, and mostly starting materials were again recovered (Table 1, entries 8, 9). Increasing the alkoxides type catalysts to equimolar ratios, give rise to the production of **4b** in excellent yield.

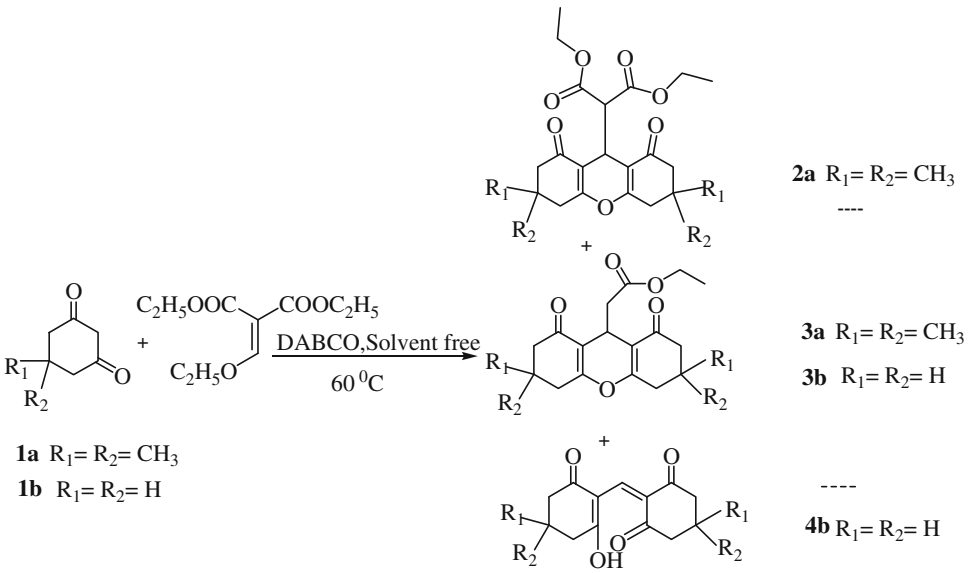
After many trials, we finally discovered that 1,4-diazabicyclo [2.2.2] octane "DABCO" is the most efficient catalyst for this reaction with molar ratios of: dimedone/DEEM/DABCO = 1:1.5:0.01, in a solvent-free reaction at 60 °C (Table 1, entries 13, 15).

A plausible explanation of "DABCO" being a better catalyst than alkoxides may be due to the solubility of the transient intermediate enolate in comparison with alkali metal enolate salts produced when using alkoxides. In addition, protonated "DABCO" may act as an activator of DEEM, being a proton donor (Scheme 2).

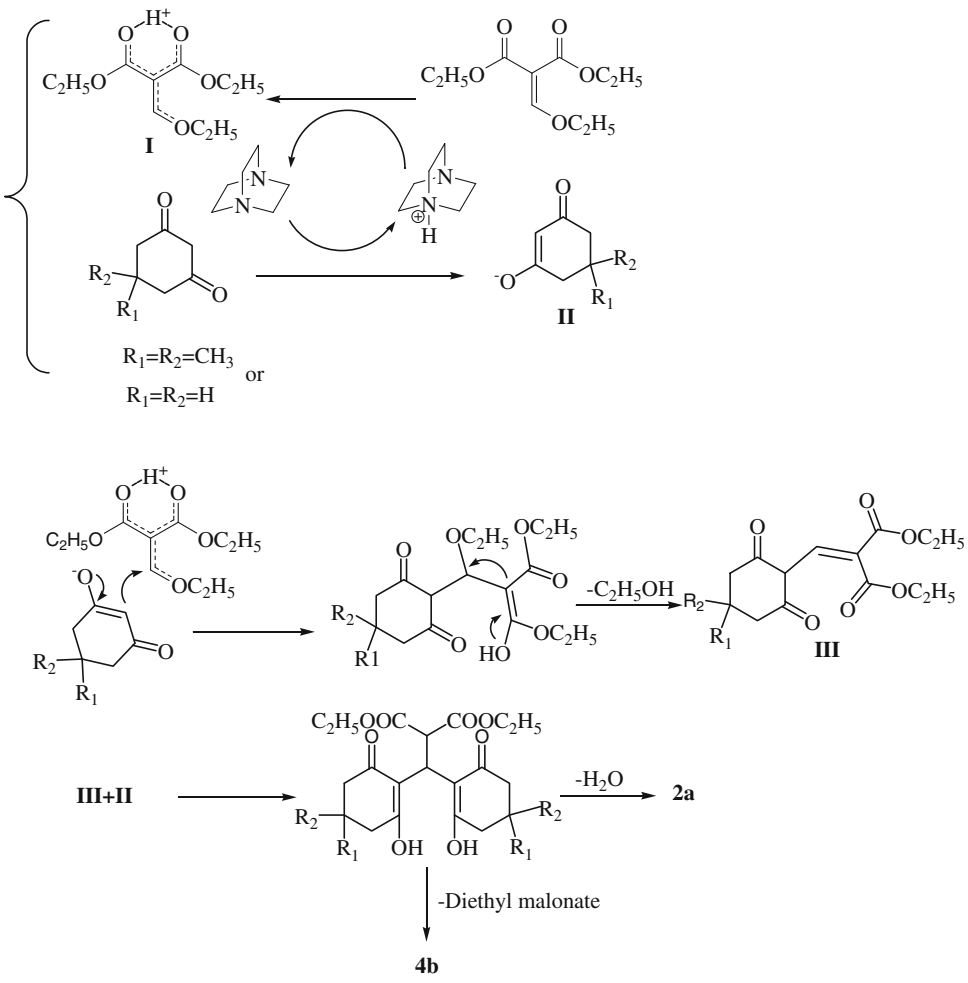
The reaction seems to occur via a reaction sequence of addition–elimination, Michael addition, cyclization via condensation the two adjacent carbonyl groups (Schemes 2, 3).

The ^1HNMR spectra of the xanthenediones in general show the characteristic signals. The methyl groups present in the 3 and 6 positions due to 12 protons appear as a singlet around a 1.0–1.1 ppm. The protons at the 2 and 7 positions and at the 4 and 5 positions appear around 2.3–2.5 ppm as singlets in general. Compound **2a** shows

Scheme 1 Double Michael addition of dimedone or 1,3-cyclohexanedione to DEEM

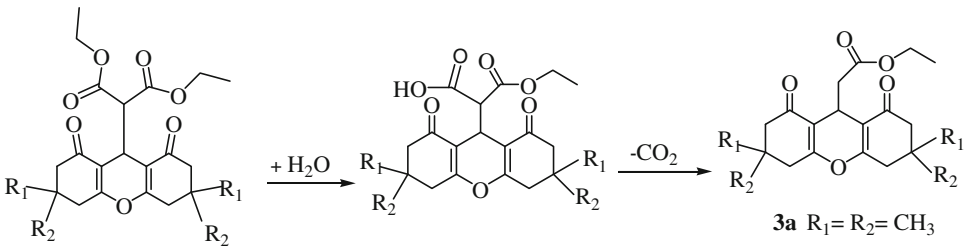


Scheme 2 Plausible mechanism for the formation of **2a** and **4b**



the C_2 and C_7 methylene protons as an AB quartet at 2.2–2.7 ppm. This splitting may be due to the effect of the diethylmalonate substituent at the 9 position, which makes the C_2 (and C_7) methylene protons exhibit geminal coupling. In case **3a**, protons at the 2 and 7 positions and at the 4 and 5 positions appear as singlets.

Scheme 3 Formation of **3a** and **3b**



2a $R_1 = R_2 = CH_3$

2b $R_1 = R_2 = H$

3a $R_1 = R_2 = CH_3$

3b $R_1 = R_2 = H$

Conclusion

The present paper reports for the first time a simple synthesis of 9-(carboethoxy)methyl-1,8-dioxo-3,3,6,6-tetramethyl-tetrahydroxanthenes, having a malonate or carboethoxy methylene group on the methylene bridge, using DABCO-catalyzed double Michael addition of dimedone or 1,3-cyclohexanedione to DEEM. This protocol entails four novel aspects of the known organic transformations:

1. Previously unreported nucleophilic reaction(s) of dimedone or 1,3-cyclohexane dione with the so-called push–pull olefins (β-ethoxyacrylic synthons) to produce bridge "malonate" substituted 1,8-dioxohydroxanthenes.
2. Simple and straightforward method for the synthesis of 9-substituted 1,8-dioxo hydroxanthenes using low cost and commercially available reagents and catalyst.
3. New application of these synthons as double Michael acceptors, via a tandem sequence of Michael addition/elimination/Michael addition reactions.
4. There are few reports on C-nucleophile Michael additions to DEEM and other push–pull olefins. Our report furnishes new examples for this type of reactions.

These novel compounds reported here, may be useful directly for screening as potential drugs or can also be further built up and used as scaffold for the synthesis of more complex molecules. Novel compound **2a**, having a good leaving group in form of a malonate moiety and they are potential precursors of 3,3,6,6-tetramethyl-1,2,3,4,5,6,7,8-octahydroacridine-1,8-dione. Development of this reaction for preparation of analogs is being investigated.

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