Regioselective synthesis of 4-acyl-1-hydroxy-2,3-benzodioates by chelation-controlled [3+3] annulation of 3-acyl-4-ethoxy-2-oxo-3-enoates with 1,3-bis(trimethylsilyloxy)-1,3-butadienes†

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4-Acyl-1-hydroxy-2,3-benzodioates were regioselectively prepared by chelation-controlled [3+3] cyclization of 1,3-bis(trimethylsilyloxy)-1,3-butadienes with 3-acyl-4-ethoxy-2-oxo-3-enoates.

Introduction

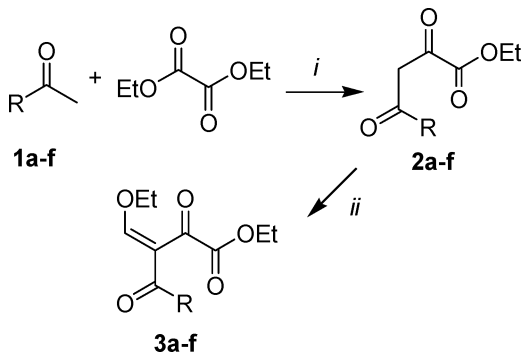
Highly functionalized benzene derivatives, such as hydroxylated benzoates and benzodioates, are of considerable interest as lead structures and synthetic building blocks in medicinal and agricultural chemistry.[1,2] Classical syntheses of such compounds are based on electrophilic substitution and oxidation reactions. Despite their great utility, electrophilic substitutions have several drawbacks (e.g., low regioselectivity and low reactivity of electron-poor substrates). Oxidations of toluene to benzoic acid derivatives often require drastic conditions. Transition metal-catalyzed functionalizations of functionalized benzene derivatives proceed under relatively mild conditions.[3] However, the synthesis of the required starting materials, highly functionalized or sterically encumbered benzene derivatives, can be a difficult task.

Functionalized benzene derivatives have also been prepared by application of a 'building block' strategy. Examples include base-mediated cyclizations of acetone-1,3-dicarboxylates,[4] condensations of 1,3-dicarbonyl dianions with carboxylic acid derivatives and subsequent intramolecular aldol reactions of the polyketides thus formed,[5] and [4+2] cycloadditions.[6] Chan and Brownbridge were the first to report[7] the synthesis of salicylates by formal [3+3] cyclizations of 1,3-bis(silyloxy)-1,3-butadienes[8] with 3-silyloxy-2-en-1-ones. This strategy has been widely applied in recent years.[9] However, its scope is mainly limited to 3-silyloxy-2-en-1-ones derived from symmetrical 1,3-diketones. Although a few exceptions have been reported,[7] cyclizations of 3-silyloxy-2-en-1-ones derived from unsymmetrical 1,3-diketones often proceed with low regioselectivity, due to $TiCl_4$-mediated isomerization of the 3-silyloxy-2-en-1-one.

In their early work, Chan and Brownbridge reported[7] an isolated example of a regioselective cyclocondensation of a 3-alkoxy- rather than a 3-silyloxy-2-en-1-one. Based on this observation, we recently started a program directed towards the development of new cyclizations of acceptor-substituted 3-alkoxy-2-en-1-ones. Herein, we report, for the first time, a convenient synthesis of 4-acyl-1-hydroxy-2,3-benzodioates by [3+3] cyclization of 1,3-(bis)trimethylsilyloxy-1,3-butadienes with 3-acyl-4-ethoxy-2-oxo-3-enoates. Although several electrophilic sites are present in the starting materials, the cyclizations proceed with excellent regioselectivity, which can be explained by the regiodirecting effect of the 2-oxoester moiety (chelation-control).[10,11] The products reported herein are not readily available by other methods.

Results and discussion

3-Acyl-4-ethoxy-2-oxo-3-enoates **3a–f** were prepared in good yield by reaction of the known 2,4-diketoesters **2a–f**, available from diethyl oxalate, with triethyl orthoformate and acetic anhydride (Scheme 1, Table 1).



Scheme 1 Synthesis of **3a–f**; *i*: diethyl oxalate (1.0 equiv.), **1a–f** (1.0 equiv.), NaOEt (1.0 equiv.), *ii*: **2a–f** (1.0 equiv.), $HC(OEt)_3$ (1.2 equiv.), Ac_2O, reflux, 2–4 h, products exist as mixtures of *E*/*Z* isomers.

The $TiCl_4$-mediated cyclization of **3a** with **4a** afforded the 4-acetyl-1-hydroxy-2,4-benzodioate **5a** with excellent regioselectivity (Scheme 2). The best yield was obtained when the reaction was carried out in a highly concentrated solution. The formation of **5a** can be explained by reaction of **3a** with $TiCl_4$ to give oxocarbenium ion **A**. The attack of the terminal carbon atom of **4a** onto **A** resulted in the formation of intermediate **B**. The elimination of (ethoxy)trimethylsilane (intermediate **C**) and subsequent cyclization gave intermediate **D**. The elimination of titanium hydroxide and aromatization resulted in the formation of product **5a**.

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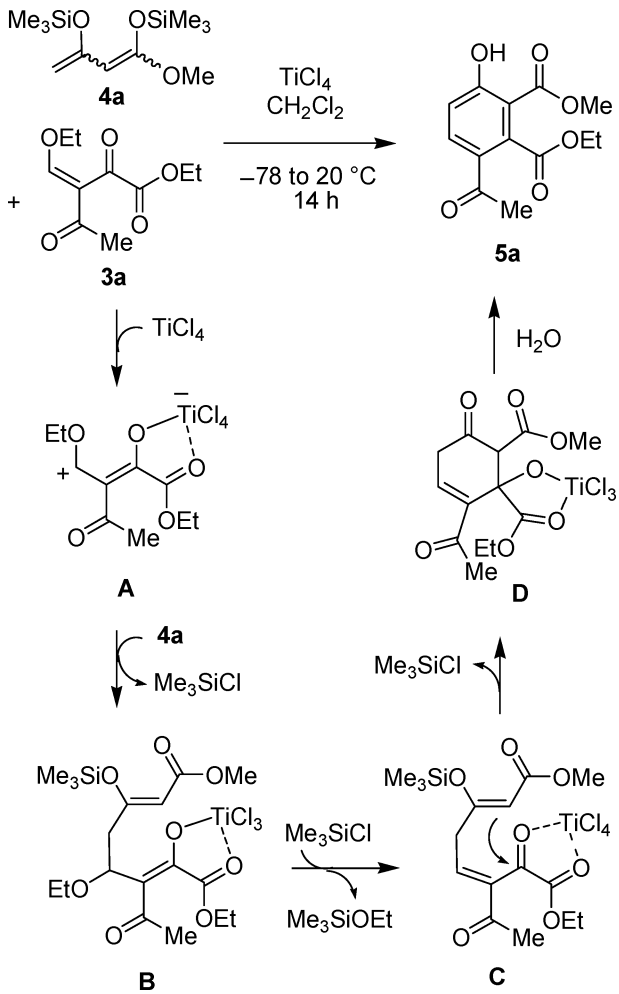
Table 1 Synthesis of **3a–f**

1,2,3	R	% (**2**)[a]	% (**3**)[a]
a	Me	76	97
b	Ph	79	96
c	4-MeC_6H_4	80	98
d	4-$MeOC_6H_4$	82	95
e	4-BrC_6H_4	75	92
f	OEt	74	99

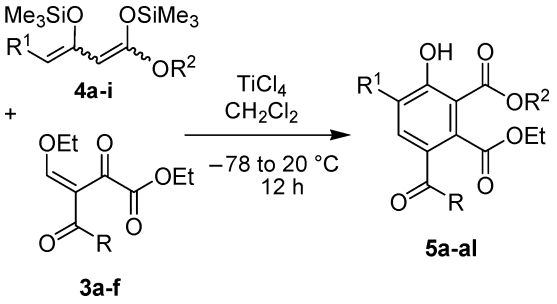
[a] Yields of isolated products.



Scheme 2 Possible mechanism of the formation of **5a**.

The regioselectivity of the first step (**A**→**B**) might be explained by the low steric hindrance and by the high positive charge density of the allylic carbon atom attached to the ethoxy group. The regioselectivity of the cyclization (**C**→**D**) might be explained by selective activation of the 2-oxoester moiety rather than the acetyl group, due to the formation of a chelate complex with $TiCl_4$ (intermediates **A**, **B** and **C**). An alternative explanation is just that the cyclization occurs onto the most electrophilic ketone carbonyl (which is the one adjacent to the ester group).

The $TiCl_4$-mediated cyclization of 3-acyl-4-ethoxy-2-oxo-3-enoates **3a–f** with 1,3-bis(trimethylsilyloxy)-1,3-butadienes **4a–i** afforded the 4-acyl-1-hydroxy-2,3-benzodioates **5a–al** in 48–70% yield (Scheme 3, Table 2). The best yields are obtained for aroyl derivatives **5g–ai** and for ester derivative **5l**.



Scheme 3 Synthesis of **5a–al**.

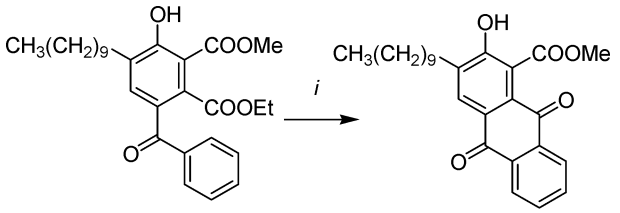
Treatment of **5n** with conc. sulfuric acid resulted in an intramolecular Friedel–Crafts acylation to give the anthraquinone **6** (Scheme 4).

In conclusion, we have reported the regioselective synthesis of 4-acyl-1-hydroxy-2,3-benzodioates by the first chelation-controlled [3+3] cyclizations of 1,3-bis(trimethylsilyloxy)-1,3-butadienes with 3-acyl-4-ethoxy-2-oxo-3-enoates.

Table 2 Synthesis of **5a–al**

4	3	5	R	R^1	R^2	% (**5**)[a]
a	**a**	**a**	Me	H	Me	48
b	**a**	**b**	Me	Me	Me	50
c	**a**	**c**	Me	Et	Et	50
d	**a**	**d**	Me	*n*Bu	Me	58
f	**a**	**e**	Me	*n*Hex	Me	59
g	**a**	**f**	Me	*n*Oct	Me	59
a	**b**	**g**	Ph	H	Me	65
b	**b**	**h**	Ph	Me	Me	67
c	**b**	**i**	Ph	Et	Et	62
d	**b**	**j**	Ph	*n*Bu	Me	65
f	**b**	**k**	Ph	*n*Hex	Me	65
g	**b**	**l**	Ph	*n*Oct	Me	66
h	**b**	**m**	Ph	*n*Non	Me	67
i	**b**	**n**	Ph	*n*Dec	Me	66
a	**c**	**o**	4-MeC_6H_4	H	Me	69
b	**c**	**p**	4-MeC_6H_4	Me	Me	70
d	**c**	**q**	4-MeC_6H_4	*n*Bu	Me	70
f	**c**	**r**	4-MeC_6H_4	*n*Hex	Me	65
g	**c**	**s**	4-MeC_6H_4	*n*Oct	Me	64
h	**c**	**t**	4-MeC_6H_4	*n*Non	Me	66
i	**c**	**u**	4-MeC_6H_4	*n*Dec	Me	65
a	**d**	**v**	4-$MeOC_6H_4$	H	Me	62
b	**d**	**w**	4-$MeOC_6H_4$	Me	Me	63
c	**d**	**x**	4-$MeOC_6H_4$	Et	Et	56
e	**d**	**y**	4-$MeOC_6H_4$	*n*Pen	Me	64
f	**d**	**z**	4-$MeOC_6H_4$	*n*Hex	Me	61
h	**d**	**aa**	4-$MeOC_6H_4$	*n*Non	Me	63
i	**d**	**ab**	4-$MeOC_6H_4$	*n*Dec	Me	64
a	**e**	**ac**	4-BrC_6H_4	H	Me	63
b	**e**	**ad**	4-BrC_6H_4	Me	Me	66
c	**e**	**ae**	4-BrC_6H_4	Et	Et	65
e	**e**	**af**	4-BrC_6H_4	*n*Pen	Me	66
f	**e**	**ag**	4-BrC_6H_4	*n*Hex	Me	70
h	**e**	**ah**	4-BrC_6H_4	*n*Non	Me	68
i	**e**	**ai**	4-BrC_6H_4	*n*Dec	Me	69
a	**f**	**aj**	OEt	H	Me	68
b	**f**	**ak**	OEt	Me	Me	69
e	**f**	**al**	OEt	*n*Pent	Me	69

[a] Yields of isolated products.



5n **6** (85%)

Scheme 4 Synthesis of **6**; *i*: conc. sulfuric acid, 1 h.

Experimental section

General comments

All solvents were dried by standard methods and all reactions were carried out under an inert atmosphere. For ^{1}H and ^{13}C NMR spectra the deuterated solvents indicated were used. Mass spectrometric data (MS) were obtained by electron ionization (EI, 70 eV), chemical ionization (CI, isobutane) or electrospray ionization (ESI). For preparative scale chromatography silica gel 60 (0.063–0.200 mm, 70–230 mesh) was used.

General procedure for the synthesis of 2a–f. To a suspension of sodium ethoxide (1.0 equiv.) in benzene (0.5 mL/1.0 mmol EtONa), was dropwise added diethyl oxalate (1.0 equiv.) at 0 °C followed by dropwise addition (during 30 min) of **1a–f** (1.0 equiv.). The temperature of the solution was allowed to warm to 20 °C during 14 h with stirring. To the solution was added hydrochloric acid (10%, 20 mL) and the organic and the aqueous layers were separated. The latter was extracted with ether (3 × 20 mL) and washed with brine. The combined organic layers were dried (Na_2SO_4), filtered and the filtrate was concentrated *in vacuo* to give products **2**. The synthesis of **2a–f** has been previously reported.

General procedure for the synthesis of 3a–f. To a solution of **2a–f** (1.0 equiv.) in acetic anhydride (2.0 equiv.) was added triethylorthoformate (1.2 equiv.). The mixture was heated under reflux for 2 h at 120 °C and for further 4 h at 140 °C. The mixture was concentrated *in vacuo* to give **3** (92–99%).

Ethyl 3-(ethoxymethylene)-2,4-dioxopentanoate (3a). Starting with **2a** (4.30 g, 27.2 mmol), triethyl orthoformate (5.16 g, 32.6 mmol), and acetic anhydride (8.60 g, 54.4 mmol), **3a** was isolated as a red oil (5.64 g, 97%). ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 1.28$ (t, $^{3}J = 7.2$ Hz, 3 H, OCH_2CH_3), 1.40 (t, $^{3}J = 7.1$ Hz, 3 H, OCH_2CH_3), 2.36 (s, 3 H, CH_3), 4.24 (q, $^{3}J = 7.2$ Hz, 2 H, OCH_2CH_3), 4.35 (q, $^{3}J = 7.1$ Hz, 2 H, OCH_2CH_3), 7.85 (s, 1 H, CH_{Olf}). ^{13}C NMR ($CDCl_3$, 75 MHz): $\delta = 13.7$, 15.0, 30.4 (CH_3), 61.8, 74.4 (OCH_2), 117.4 (COCCO), 164.5 (CO), 169.4 (CH_{Olf}), 186.8, 195.8 (CO). IR (neat, cm^{-1}): $\tilde{\nu} = 2984$ (w), 2940 (w), 2255 (w), 1780 (w), 1732 (m), 1661 (m), 1577 (m), 1473 (w), 1389 (w), 1367 (w), 1312 (m), 1255 (m), 1224 (m), 1172 (m), 1097 (m), 1022 (m), 907 (s), 862 (w), 725 (s), 684 (w), 648 (m), 601 (w). GC-MS (EI, 70 eV): m/z (%) = 214 ($[M]^+$, 1.4), 141 (100), 113 (55), 99 (23), 71 (82), 43 (48), 29 (20). HRMS (EI): Calcd. for $C_{10}H_{14}O_5$ ($[M]^+$): 214.08358; found: 214.083886.

General procedure for the synthesis of 5a–al. To a CH_2Cl_2 solution (2 mL/1 mmol of **3a–f**) of **3a–f** was added **4a–i** (1.1 mmol) and, subsequently, $TiCl_4$ (1.1 mmol) at −78 °C. The temperature of the solution was allowed to warm to 20 °C during 14 h with stirring. To the solution was added hydrochloric acid (10%, 20 mL) and the organic and the aqueous layers were separated. The latter was extracted with CH_2Cl_2 (3 × 20 mL). The combined organic layers were dried (Na_2SO_4), filtered and the filtrate was concentrated in vacuo. The residue was purified by chromatography (silica gel, heptanes/EtOAc) to give **5a–al**.

2-Ethyl 1-methyl 3-acetyl-6-hydroxyphthalate (5a). Starting with **3a** (0.321 g, 1.5 mmol) and **4a** (0.429 g, 1.65 mmol), **5a** was isolated after chromatography (silica gel, *n*-heptane/EtOAc) as a yellowish solid (0.191 g, 48%), mp. 95–97 °C. ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 1.17$ (t, $^{3}J = 7.2$ Hz, 3 H, OCH_2CH_3), 2.32 (s, 3 H, CH_3), 3.72 (s, 3 H, OCH_3), 4.20 (q, $^{3}J = 7.7$ Hz, 2 H, OCH_2CH_3), 6.87 (d, $^{3}J = 9.0$ Hz, 1 H, CH_{Ar}), 7.73 (d, $^{3}J = 9.0$ Hz, 1 H, CH_{Ar}), 11.37 (s, 1 H, OH). ^{13}C NMR ($CDCl_3$, 75 MHz): $\delta = 14.0$, 27.5 (CH_3), 53.2 (OCH_3), 61.8 (OCH_2), 110.5 ($CCOOCH_3$), 118.5 (CH_{Ar}), 126.9 ($CCOCH_3$), 136.2 (CH_{Ar}), 137.4 ($CCOOC_2H_5$), 164.9 (COH), 168.3, 169.4, 195.7 (CO). IR (neat, cm^{-1}): $\tilde{\nu} = 3119$ (w), 3076 (w), 2981 (w), 2919 (w), 2850 (w), 1729 (m), 1674 (s), 1580 (m), 1470 (w), 1443 (m), 1389 (w), 1362 (m), 1328 (m), 1304 (m), 1248 (s), 1207 (s), 1155 (m), 1137 (s), 1100 (m), 1026 (m), 965 (m), 937 (m), 872 (m), 847 (m), 811 (m), 757 (m), 733 (m), 706 (m), 688 (m), 647 (m), 598 (m), 580 (m), 540 (m). GC-MS (EI, 70 eV): m/z (%) = 266 ($[M]^+$, 24), 251 (11), 221 (27), 220 (33), 192 (10), 191 (100), 190 (18), 189 (42), 188 (15), 162 (39), 120 (12), 119 (29), 43 (10). HRMS (EI): Calcd. for $C_{13}H_{14}O_6$ ($[M]^+$): 266.07849; found: 266.079233.

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