Regioselective Synthesis of Polyketide-Type Phenols by Formal [3+3]-Cyclocondensations of 1,3-Bis(silyloxy)-1,3-butadienes with 3-Oxoorthoesters

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Abstract: A variety of 4-methoxysalicylates and related polyketide-type phenols are regioselectively prepared by the first formal [3+3]-cyclocondensations of 1,3-bis(trimethylsilyloxy)-1,3-butadienes with 3-oxoorthoesters.

Key words: arenes, cyclizations, regioselectivity, silyl enol ethers

Many pharmacologically important, naturally occurring phenols are biosynthetically derived from poly(β-oxo)carboxylic acids (polyketides).[1] Harris and co-workers reported the biomimetic synthesis of various 1,3,5,7-tetracarbonyl compounds and their higher homologues based on condensations of 1,3-dicarbonyl dianions or 1,3,5-tricarbonyl trianions with carboxylic acid derivatives.[2] These products are unstable and rapidly undergo an intramolecular aldol condensation to give polyhydroxylated arenes.

Chan and Brownbridge developed[3] a convenient synthesis of salicylates by cyclocondensation of 1,3-bis(silyloxy)-1,3-butadienes, masked 1,3-dicarbonyl dianions,[4] with 3-silyloxy-2-en-1-ones. In recent years, we have extended the scope of this chemistry and studied its application to the synthesis of a variety of functionalized arenes.[5] In most reactions developed so far, the products, functionalized salicylates, contain no functional group located at carbon atoms C4 and C6. This is a severe limitation, since naturally occurring, polyketide-derived phenols contain a free or masked hydroxyl group at one of these positions.

Chan and Stössel were the first to report[6] an elegant approach to 4-hydroxysalicylates by Lewis acid mediated formal [5+1]-cyclization of 1-methoxy-1,3,5-tris(trimethylsilyloxy)-1,3,5-hexatriene with acid chlorides or imidazolides. However, the preparative scope of this method is limited by the availability of the 1,3,5-tris(silyl enol ether). In fact, trienes derived from substituted 3,5-dioxoalkanoates and from 1,3,5-triketones, proved to be unstable and could not be successfully employed. Therefore, only methyl salicylates containing a hydrogen atom located at carbon atoms C3 and C5 can be prepared by this method.

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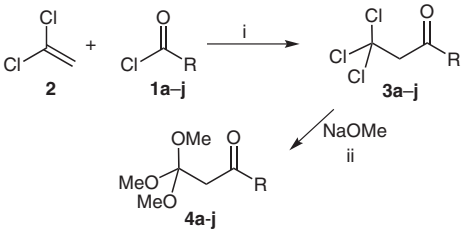
Recently, we reported[7] a regioselective synthesis of 4-hydroxy- and 6-hydroxysalicylates by cyclization of 1,3-bis(silyloxy)-1,3-butadienes with 3,3-dimethoxypentanoyl chloride. However, this method is limited so far to the synthesis of ethyl-substituted derivatives. Herein, we report a new and convenient synthesis of 4-methoxysalicylates and related polyketide-type phenols by what are, to the best of our knowledge, the first formal [3+3]-cyclocondensations of 1,3-bis(silyloxy)-1,3-butadienes with 3-oxoorthoesters.[8] This method provides a rather general and regioselective approach to a wide range of substituted salicylates which are not readily available by other methods.

The 3-oxoorthoesters **4a–j** were prepared following a known procedure in two steps (Scheme 1, Table 1). The $AlCl_3$-mediated reaction[9a–9c] of 1,1-dichloroethene (**2**) with acid chlorides **1a–j** afforded the 3,3,3-trichloroketones **3a–j**. The reaction[9d] of the latter with methanol afforded the 3-oxoorthoesters **4a–j** in good overall yields (except for **4f**). The synthesis of **4a**[9d,e] and **4c**[9d] has been previously reported. 1,3-Bis(trimethylsilyloxy)-1,3-butadienes **5a–c**,**e**,**h–j** were prepared from the corresponding β-ketoesters in two steps.[3] Dienes **5d**,**f**,**g** were prepared from the corresponding 1,3-diketones in one step.[10]



Scheme 1 Synthesis of **4a–j**. *Reagents and conditions*: (i) $AlCl_3$, CH_2Cl_2, 20 °C, 2–14 h; (ii) MeOH, 20 °C, 2–14 h.

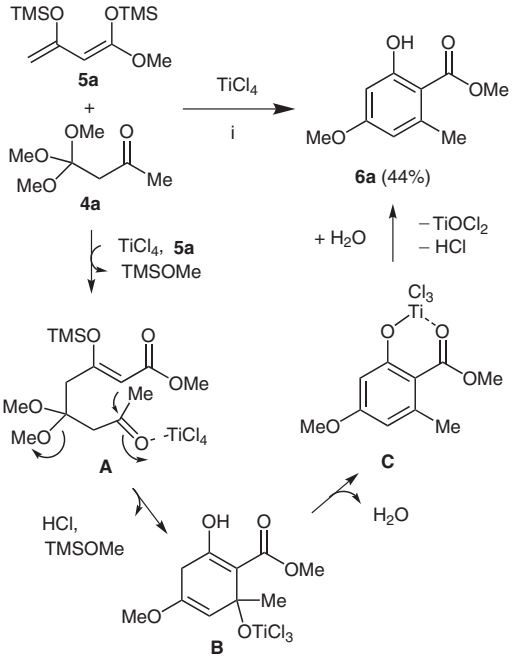
The $TiCl_4$-mediated cyclization of **4a** with 1,3-bis(trimethylsilyloxy)-1,3-butadiene **5a** regioselectively afforded 4-methoxysalicylate **6a** (Scheme 2). The formation of the isomeric 6-methoxysalicylate was not observed. The best yields were obtained when **5a**, **4a** and $TiCl_4$ were employed in a stoichiometric ratio of 2:1:1 and when the reaction was carried out in a relatively concentrated solution [c(**4a**) = 0.5 M].

The formation of **6a** can be explained by $TiCl_4$-mediated attack of the terminal carbon atom of **5a** onto the ortho-

Table 1 Synthesis of **4a–j**

1,3,4	R	Yield (%) of **3**[a]	Yield (%) of **4**[a]
a	Me	75	88
b	Et	86	94
c	*n*-Pr	77	62
d	Ph	97	66
e	4-ClC_6H_4	92	53
f	*c*-Pr	82	30
g	*c*-Bu	95	93
h	*c*-Pent	94	86
i	*c*-Hex	92	79
j	$(CH_2)_2$(*c*-Pent)	96	92

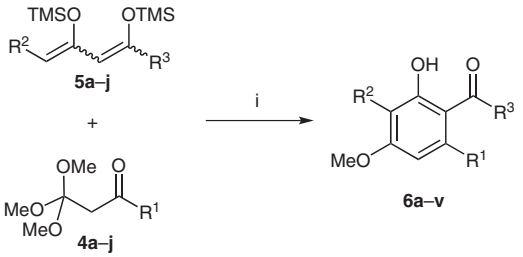
[a] Yields of isolated products.



Scheme 2 Possible mechanism of the formation of **6a**. *Reagents and conditions*: (i) 1. $TiCl_4$ (1.0 equiv), CH_2Cl_2, –78 °C → 20 °C, 14 h; 2. HCl (10%).

ester to give intermediate **A**, subsequent cyclization by attack of the central carbon atom of the dicarbonyl moiety onto the double bond (intermediate **B**), aromatization (intermediate **C**) and hydrolysis upon aqueous workup. The $TiCl_4$-mediated reaction of **5a** with trimethyl orthoacetate has been previously reported.[8] Alternatively, the cyclocondensation may proceed by $TiCl_4$-mediated transformation of **4a** into 4,4-dimethoxy-3-buten-2-one, conjugate addition of the terminal carbon atom of **5a** onto the latter and subsequent cyclization. The conjugate addition follows the mechanism earlier suggested for the cyclization of 1,3-bis(trimethylsilyloxy)-1,3-butadienes with 3-alkoxy- and 3-silyloxy-2-en-1-ones.[3,5]

The $TiCl_4$-mediated cyclization of 3-oxoorthoesters **4a–j** with 1,3-bis(trimethylsilyloxy)-1,3-butadienes **5a–j** afforded the 4-methoxysalicylates **6a–v** in moderate to good yields with very good regioselectivity (Scheme 3, Table 2).[11] A wide range of products could be successfully prepared. This includes salicylic acid esters **6a–c**,**e**,**g**,**j**,**k**,**m–t**,**v** and 6-acyl-3-methoxyphenols **6d**,**f**,**h**,**i**,**l**,**u**. The substituents R^2 attached to carbon atom C3 of the



Scheme 3 Synthesis of **6a–v**. *Reagents and conditions*: (i) 1. $TiCl_4$ (1.0 equiv), CH_2Cl_2, –78 to 20 °C, 14 h; 2. HCl (10%).

Table 2 Synthesis of **6a–v**

4	5	6	R^1	R^2	R^3	Yield (%) of **6**[a]
a	**a**	**a**	Me	H	OMe	44
a	**b**	**b**	Me	Et	OMe	47
b	**c**	**c**	Et	Me	OMe	56
b	**d**	**d**	Et	H	Me	30
c	**a**	**e**	*n*-Pr	H	OMe	42
c	**d**	**f**	*n*-Pr	H	Me	40
c	**e**	**g**	*n*-Pr	OMe	OMe	53
c	**f**	**h**	*n*-Pr	H	Ph	48
c	**g**	**i**	*n*-Pr	Me	Et	35
d	**a**	**j**	Ph	H	OMe	31
d	**e**	**k**	Ph	OMe	OMe	33
d	**d**	**l**	Ph	H	Me	58
e	**a**	**m**	4-ClC_6H_4	H	OMe	34
f	**h**	**n**	*c*-Pr	H	O*i*-Pr	48
f	**i**	**o**	*c*-Pr	*n*-Pr	OMe	52
g	**j**	**p**	*c*-Bu	H	O*i*-Bu	50
h	**h**	**q**	*c*-Pent	H	O*i*-Pr	67
h	**i**	**r**	*c*-Pent	*n*-Pr	OMe	71
i	**h**	**s**	*c*-Hex	H	O*i*-Pr	67
i	**i**	**t**	*c*-Hex	*n*-Pr	OMe	88
i	**d**	**u**	*c*-Hex	H	Me	63
j	**h**	**v**	$(CH_2)_2$(*c*-Pent)	H	O*i*-Pr	67

[a] Yields of isolated products.

benzene system include, besides hydrogen, alkyl groups and the methoxy group. Various substituents can be introduced at carbon atom C6 (substituent R^1). This includes alkyl, aryl and various cycloalkyl groups. It is noteworthy that the cyclopropyl, cyclobutyl, cyclopentyl and cyclohexyl group proved to be compatible with the reaction conditions. No decrease of the yield was observed despite the steric hindrance of these groups. The cyclopropyl group was not cleaved during the reaction. The synthesis of cycloalkyl-substituted arenes by formal [3+3]-cyclizations has, to the best of our knowledge, not been reported to date.

The configuration of all products was established by spectroscopic methods (2D NMR). The structure of **6j** was independently confirmed by X-ray crystal structure analysis (Figure 1).[12]

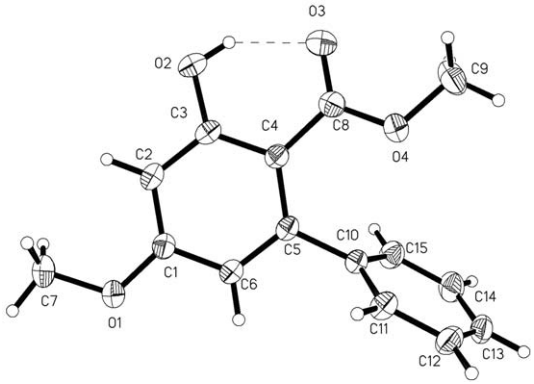


Figure 1 ORTEP plot of **6j**

In conclusion, a variety of 4-methoxysalicylates and related polyketide-type phenols were prepared by what are, to the best of our knowledge, the first [3+3]-cyclizations of 1,3-bis(trimethylsilyloxy)-1,3-butadienes with 3-oxoorthoesters. The scope and application of this methodology are currently being studied.

Acknowledgment

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(11) **Typical Procedure for the Synthesis of Methyl 2-hydroxy-4-methoxy-6-(*n*-propyl)benzoate (6e)**: To a CH_2Cl_2 solution (2 mL) of **4c** (0.191 g, 1.0 mmol) and **5a** (0.521 g, 2.0 mmol) was added $TiCl_4$ (0.11 mL, 1.0 mmol) at –78 °C under an argon atmosphere. The temperature of the reaction mixture was allowed to rise to 20 °C during 14 h with stirring. To the mixture was added hydrochloric acid (10%, 10 mL). The organic and the aqueous layer were separated and the latter was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic layers were dried (Na_2SO_4), filtered and the filtrate was concentrated in vacuo. After column chromatography (silica gel; heptanes–EtOAc, 1:1), **6e** was obtained as a colorless oil (92 mg, 42%); R_f 0.88 (heptanes–EtOAc, 1:1). ^{1}H NMR (250 MHz, $CDCl_3$): δ = 11.73 (s, 1 H, OH), 6.33 (s, 1 H, ArH), 6.30 (s, 1 H, ArH), 3.93 (s, 3 H, OMe), 3.38 (s, 3 H, OMe), 2.83 (t, ^3J = 7.7 Hz, 2 H, $ArCH_2$), 1.49–1.63 (m, 2 H, CH_2CH_3), 0.95 (t, ^3J = 7.4 Hz, 3 H, Me). ^{13}C NMR (63 MHz, $CDCl_3$): δ = 172.0 (C=O), 165.5, 163.9 (CO), 147.7 (C), 110.7 (CH), 104.6 (C), 98.7 (CH), 55.3, 51.8 (OMe), 38.9 ($ArCH_2$), 24.9 (CH_2CH_3), 14.2 (Me). IR (ATR): 2956 (br m), 2871 (w), 2846 (w), 1649 (s), 1611 (s), 1575 (s) cm^{-1}. MS (EI, 70 eV): *m/z* (%) = 224 (33) [M$^+$], 192 (100), 164 (34), 135 (45). Anal. Calcd for $C_{12}H_{16}O_4$ (224.26): C, 64.27; H, 7.19. Found: C, 64.27; H, 7.39.

(12) CCDC 690564 contains all crystallographic details of this publication and is available free of charge at www.ccdc.cam.ac.uk/conts/retrieving.html or can be ordered from the following address: Cambridge Crystallographic Data Centre, 12 Union Road, GB-Cambridge CB21EZ; Fax: +44 (1223)336033; or deposit@ccdc.cam.ac.uk.