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Chelation control in the [3+3] annulation reaction of alkoxy-substituted 1,1-diacylcyclopropanes with 1,3-bis(trimethylsilyloxy)-1,3-butadienes

Jennifer Hefner [a], Peter Langer [a,b,*]

[a] Institut für Chemie, Universität Rostock, Albert-Einstein-Strasse 3a, 18059 Rostock, Germany
[b] Leibniz-Institut für Katalyse e. V. an der Universität Rostock, Albert-Einstein-Strasse 29a, 18059 Rostock, Germany

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ABSTRACT

Functionalized arenes were prepared by chelation-controlled '[3+3] cyclization/homo-Michael' reactions of 1,3-bis(trimethylsilyloxy)-1,3-butadienes with benzyloxy- or methoxy-substituted 1,1-diacylcyclopropanes.

Highly substituted phenols are pharmacologically important molecules which occur in various natural products.[1] Recently, we have reported[2] the synthesis of functionalized phenols by $TiCl_4$-mediated [3+3] cyclization[3] of 1,3-bis(trimethylsilyloxy)-1,3-butadienes[4] with 1,1-diacylcyclopropanes. Although symmetrical cyclopropanes were employed in most cases, some unsymmetrical substrates have also been studied. The cyclization of 1,3-bis(silyloxy)-1,3-butadienes with 1-acetyl-1-formylcyclopropane and with 1-acetyl-1-benzoylcyclopropane proceeded by regioselective attack of the terminal carbon atom of the diene onto the more reactive carbonyl group (i.e., the formyl and the acetyl group, respectively). We were intrigued by the possibility of incorporating chelating[5,6] alkoxy substituents into the diacylcyclopropane, which could direct the regioselectivity of the cyclization. Herein, we report preliminary results of this study. Noteworthy, the annulation reactions reported provide a convenient and regioselective approach to a variety of sterically encumbered and highly functionalized phenols, which are not readily available by other methods.

The cyclopropanation of 1-methoxypentane-2,4-dione[7] afforded the novel cyclopropane **2a** in 40% yield.[8] The $TiCl_4$-mediated cyclization of **2a** with 1,3-bis(trimethylsilyloxy)-1,3-butadiene **1a**, readily available in two steps from methyl acetoacetate,[9] afforded the 5-chloroethyl-4-(methoxymethyl)salicylate **3a** (Scheme 1).[10]

The regioselective formation of **3a** can be explained by chelation of $TiCl_4$ by the methoxy and the neighboring carbonyl group (intermediate **A**). The $TiCl_4$-mediated attack of the terminal carbon atom of **1a** onto **2a** gives rise to the formation of intermediate **B**, which undergoes a cyclization via the central carbon atom of the 1,3-dicarbonyl unit (intermediate **C**). The product is subsequently formed by Lewis acid-assisted cleavage of the spirocyclopropane moiety and aromatization by attack of a chloride ion onto the cyclopropane (intermediate **D**) and hydrolysis upon aqueous work-up. The process can be regarded as a domino '[3+3] cyclization/homo-Michael' reaction.[11] The regioselectivity can be explained by the Lewis acid-directing effect of the methoxy group of the substrate. During the optimization of the reaction, the following parameters proved to be important. The best yields of **3a** were obtained when 1.0 equiv of **2a**, 1.5 equiv of **1a** and 2.0 equiv of $TiCl_4$ were employed. The low concentration (c(**2a**) = 0.01 M) and the presence of molecular sieves (4 Å) (for the removal of water) also played an important role.

The novel methoxy- and benzyloxy-substituted 1,1-diacylcyclopropanes **2b**, **2c**, and **2d** were prepared by cyclopropanation of 1-benzyloxypentane-2,4-dione,[12] 4-methoxy-1-phenylbutane-1,3-dione, and 4-methoxy-1-phenylbutane-1,3-dione in 42%, 40%, and 44% yield, respectively. The cyclization of **2a–d** with 1,3-bis(trimethylsilyloxy)-1,3-butadienes **1a–f**, in the presence of $TiCl_4$ or $TiBr_4$, afforded the functionalized phenols **3a–s** (Scheme 2, Table 1). All products were formed with very good regioselectivity by attack of the terminal carbon atom of the diene onto the carbonyl group located next to the alkoxy group. The structure of the products was confirmed by spectroscopic methods (2D NMR).

The substituted arenes prepared represent useful synthetic building blocks. For example, salicylate **3g** was transformed into

* Corresponding author. Tel.: +49 381 4986410; fax: +49 381 4986412.
E-mail address: peter.langer@uni-rostock.de (P. Langer).

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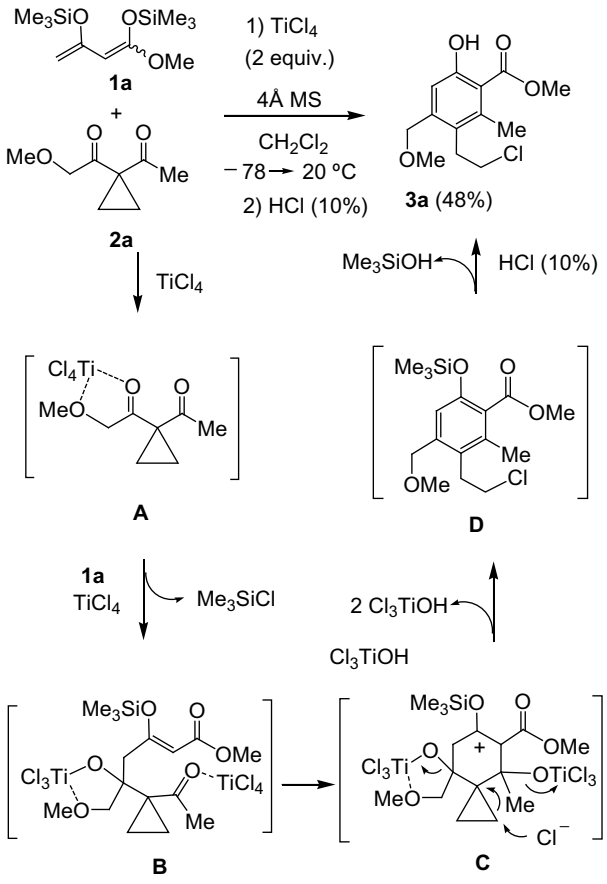
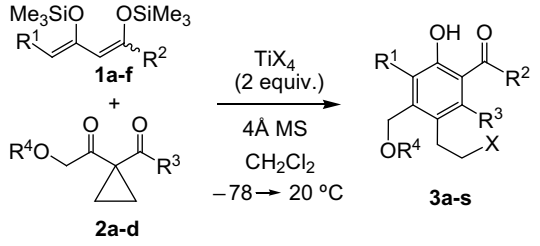


Scheme 1. Possible mechanism of the formation of **3a**.

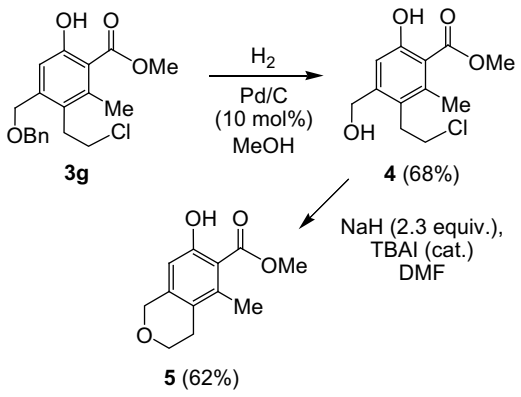


Scheme 2. Synthesis of **3a–s**.

Table 1
Products and yields

1	2	3	R^1	R^2	R^3	R^4	X	Yield[a] (%)
a	**a**	**a**	H	OMe	Me	Me	Cl	44
b	**a**	**b**	H	OEt	Me	Me	Cl	38
c	**a**	**c**	Me	OMe	Me	Me	Cl	30
d	**a**	**d**	Me	Et	Me	Me	Cl	30
a	**a**	**f**	H	OMe	Me	Me	Br	46
a	**b**	**g**	H	OMe	Me	Bn	Cl	40
c	**b**	**h**	Me	OMe	Me	Bn	Cl	44
e	**b**	**i**	Et	OMe	Me	Bn	Cl	41
a	**b**	**j**	H	OMe	Me	Bn	Br	79
a	**c**	**k**	H	OMe	Ph	Me	Cl	63
c	**c**	**l**	Me	OMe	Ph	Me	Cl	48
f	**c**	**m**	H	Me	Ph	Me	Cl	33
d	**c**	**n**	Me	Et	Ph	Me	Cl	36
a	**c**	**o**	H	OMe	Ph	Me	Br	49
a	**d**	**p**	H	OMe	Ph	Bn	Cl	40
e	**d**	**q**	Et	OMe	Ph	Bn	Cl	64
d	**d**	**r**	Me	Et	Ph	Bn	Cl	33
a	**d**	**s**	H	OMe	Ph	Bn	Br	52

[a] Yields of isolated products.



Scheme 3. Synthesis of tetrahydrobenzopyran **5**.

tetrahydrobenzopyran **5** by debenzylation and subsequent Williamson reaction (Scheme 3). A number of related products were successfully prepared.

In conclusion, we have reported the first substrate-directed domino '[3+3] cyclization/homo-Michael' reaction of 1,3-bis(trimethylsilyloxy)-1,3-butadienes with 1,1-diacylcyclopropanes. These reactions provide a convenient approach to highly functionalized phenols, which are not readily available by other methods. The regioselectivity can be explained by the Lewis acid-directing effect of the alkoxy groups of the substrates. We believe that the strategy outlined herein can be applied also to other annulation reactions of 1,3-bis(silyl enol ethers).

Acknowledgment

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8. *Typical procedure for the synthesis of diacylcyclopropanes* **2a–d**: To a DMSO solution (100 mL) of methoxyacetylacetone (5.00 g, 38.5 mmol) and potassium carbonate (15.90 g, 115.5 mmol) was added 1,2-dibromoethane (9.40 g, 50.0 mmol) dropwise. The mixture was stirred at 20 °C for 24 h. The mixture was poured into water (400 mL), and the mixture was extracted with diethyl ether (3 × 100 mL). The combined organic layers were washed with water and with brine, dried (Na_2SO_4), filtered, and concentrated in vacuo. Vacuum destillation (bp = 46 °C, 0.15 mbar) afforded **2a** (2.41 g, 40%) as a yellowish oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.44 (m, 2H, CH_2), 1.51 (m, 2H, CH_2), 2.10 (s, 3H, CH_3), 3.38 (s, 3H, OCH_3), 4.31 (s, 2H, CH_2). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 17.4 (CH_2), 26.3 (CH_3), 41.0 (C), 59.1 (OCH_3), 77.1 (CH_2OCH_3), 202.9, 203.6 (CO).
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10. *Typical procedure for the synthesis of phenols* **3a–s**. To a CH_2Cl_2 solution (100 mL) of **2a** (156 mg, 1.0 mmol) and **1a** (391 mg, 1.5 mmol) in the presence of molecular sieves (4 Å, 1.00 g) was added $TiCl_4$ (0.22 mL, 2.0 mmol) dropwise at −78 °C under an argon atmosphere. The solution was allowed to warm to 20 °C over 18 h with stirring and subsequently filtered. The filtrate was poured into hydrochloric acid (10%, 100 mL) and the mixture was extracted with CH_2Cl_2

(3 × 100 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 = 10:1→7:1) to give **3a** as a slightly yellow solid (120 mg, 44%), mp = 77–78 °C. R_f = 0.38 (heptanes/EtOAc = 3:1). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.50 (s, 3H, CH_3), 3.09 (m, 2H, CH_2), 3.42 (s, 3H, OCH_3), 3.54 (m, 2H, CH_2Cl), 3.97 (s, 3H, OCH_3), 4.43 (s, 2H, CH_2OCH_3), 6.90 (s, 1H, Ar), 10.61 (s, 1H, OH). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 14.5 (CH_3), 32.9, 43.3 (CH_2), 52.7, 59.9 (OCH_3), 73.8 (CH_2OCH_3), 113.9 (C_{Ar}), 116.8 (CH_{Ar}), 127.3, 140.0, 143.8 (C_{Ar}), 160.7 ($C_{Ar}OH$), 172.0 ($COOCH_3$). IR (KBr, cm^{-1}): 3025 (m), 2966 (w), 2929 (w), 2892 (w), 1660 (s). MS (EI, 70 eV): *m/z* (%) = 274 (M^+, ^{37}Cl, 16), 272 (M^+, ^{35}Cl, 46), 240 (100), 133 (96). HRMS (EI): Calcd for $C_{13}H_{17}ClO_4$ ($[M]^+$, ^{35}Cl): 272.08099, found 272.08061. Anal. Calcd for $C_{13}H_{17}ClO_4$ (272.72): C, 57.25; H, 6.28. Found: C, 57.24; H, 6.39. All new products gave correct spectroscopic data and elemental analyses and/or high resolution mass data.

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