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Synthesis of functionalized arylalkyl and diaryl ethers by [3+3] cyclization of 3-alkoxy- and 3-aryloxy-1-siloxy-1,3-butadienes with 3-(silyloxy)alk-2-en-1-ones

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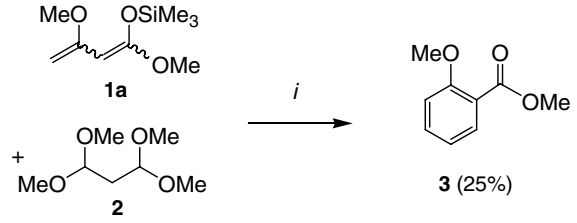
Abstract—Functionalized diaryl ethers were prepared by [3+3] cyclization of 3-aryloxy-1-siloxy-1,3-butadienes with 3-(silyloxy)alk-2-en-1-ones.

Diaryl ethers occur in a great variety of pharmacologically important natural products, such as the prominent antibiotic vancomycin.[1] Diaryl ethers containing an ester or carboxylic acid function next to the ether linkage constitute an important subgroup of naturally occurring diaryl ethers.[2] Classic syntheses of diaryl ethers rely on the Ullmann ether synthesis and related methods.[3] More recently, diaryl ethers have been prepared by various transition metal catalysed C–O coupling reactions.[4] Despite their great synthetic usefulness, the scope of these methods can be limited by the availability of the arene starting materials and by problems related to the synthesis of diaryl ethers containing a sterically encumbered ether linkage. Some years ago, Chan and co-workers reported[5] the synthesis of salicylates based on [3+3] cyclizations of 1,3-bis(silyl enol ethers) with 3-(siloxy)alk-2-en-1-ones.[6] We have recently reported the application of this methodology to the synthesis of a variety of functionalized arenes.[7] Chan and Prasad reported the synthesis of 2-(phenylthio)benzoates by [3+3] cyclization of 3-(silyloxy)alk-2-en-1-ones with 1-silyloxy-1-methoxy-3-phenylthio-1,3-butadiene.[8] Herein, we report [3+3] cyclizations of 3-alkoxy- and 3-aryloxy-1-siloxy-1,3-butadienes. These reactions provide a convenient approach to arylalkyl and diaryl ethers containing an ester function next to the ether linkage. In contrast to transition metal catalysed C–O coupling reactions, our method relies on the assembly of one of the two arene moieties.

3-Alkoxy-1-siloxy-1,3-butadienes **1a**–**c**[9] were prepared by phosphorus(V)chloride mediated chlorination of the respective β-ketoester, substitution of the chloride by an alkoxy group and subsequent silylation. The $TiCl_4$ mediated cyclization of 3-methoxy-1-methoxy-1-siloxy-1,3-butadiene (**1a**, Brassard's diene) with 1,1,3,3-tetramethoxypropane (**2**) afforded methyl 2-methoxybenzoate (**3**), albeit, in only low yield (Scheme 1).

The $TiCl_4$ mediated cyclization of **1a** with 3-(siloxy)alk-2-en-1-one **4a**, readily available from 3-methylacetylacetone, afforded methyl 2-methoxy-4,5,6-trimethylbenzoate (**5a**). The formation of **5a** can be explained, in analogy to the corresponding reaction of 1,3-bis(silyl enol ethers), by conjugate addition of the terminal carbon atom of **1a** onto **4a**, cyclization and aromatization



Scheme 1. Synthesis of **3**. Reagents and conditions: (i) $TiCl_4$, CH_2Cl_2, −78→20 °C.

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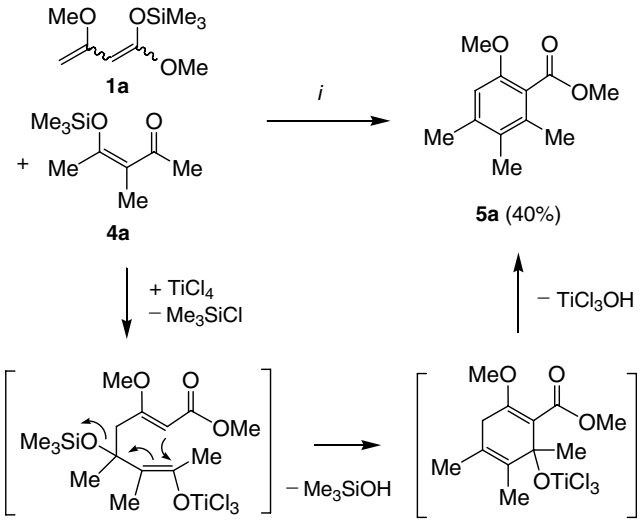
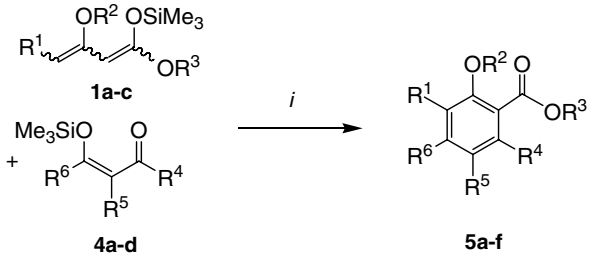


Scheme 2. Synthesis of **5a**. Reagents and conditions: (i) $TiCl_4$, CH_2Cl_2, −78→20 °C.

(Scheme 2). During the optimization, the amount of the Lewis acid, the concentration, the temperature and the work-up procedure proved to be important parameters. As a side-product, methyl 2-hydroxy-4,5,6-trimethylbenzoate was formed by partial hydrolytic cleavage of the methoxy group. The byproduct could be removed by washing the reaction mixture with an aqueous solution of sodium hydroxide.

The preparative scope was next studied. The cyclization of 1-alkoxy-3-siloxy-1,3-butadienes **1a**–**c** with 3-(siloxy)alk-2-en-1-ones **4a**–**d** afforded the 2-alkoxybenzoates **5a**–**f** (Scheme 3).[10] The formation of **5e** and **5f** proceeded with very good regioselectivity, which can be explained as previously reported for the reactions of 1,3-bis(silyl enol ethers) (Table 1).[5,7]

The preparation of 1-aryloxy-3-alkoxy-3-siloxy-1,3-butadienes has, to the best of our knowledge, not yet been



Scheme 3. Synthesis of **5a**–**f**. Reagents and conditions: (i) $TiCl_4$, CH_2Cl_2, −78→20 °C.

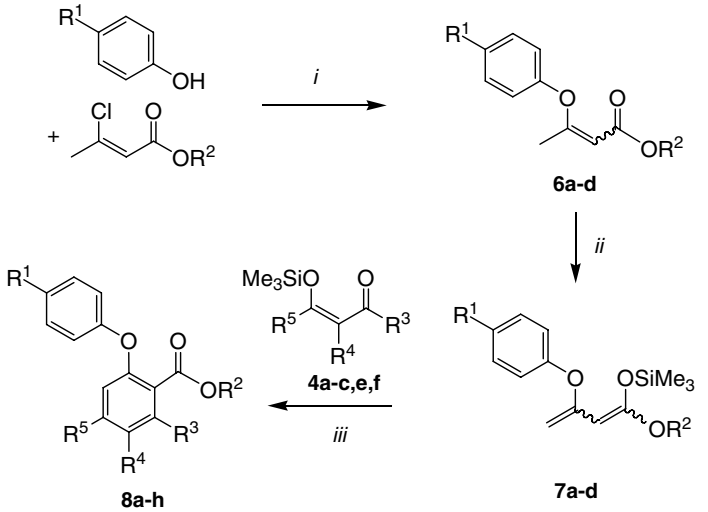
Table 1. Products and yields

1	4	5	R^1	R^2	R^3	R^4	R^5	R^6	% (5)[a]
a	**a**	**a**	H	Me	Me	Me	Me	Me	40
b	**b**	**b**	H	Et	Et	Me	H	Me	48
b	**a**	**c**	H	Et	Et	Me	Me	Me	34
c	**a**	**d**	Et	Et	Et	Me	Me	Me	36[b]
a	**c**	**e**	H	Me	Me	Ph	H	Me	43
a	**d**	**f**	H	Me	Me	–$(CH_2)_4$–		Me	28

[a] Yields of isolated products.
[b] A small amount of ethyl 3-ethyl-4,5,6-trimethylsalicylate could not be separated.

reported. 1-Aryloxy-3-siloxy-1,3-butadienes **7a**–**d** were prepared by reaction of the corresponding 3-chlorocrotonates and phenols to give the 3-(aryloxy)crotonates **6a**–**d** and subsequent deprotonation (LDA) and silylation of the latter. The cyclization of **7a**–**d** with 3-(siloxy)alk-2-en-1-ones **4a**–**c**,**e**,**f** afforded diaryl ethers **8a**–**h** (Scheme 4). The best yields were obtained in the reactions of the alkyl-substituted 3-(siloxy)alk-2-en-1-ones **4a** and **4b** (Table 2).

In conclusion, functionalized arylalkyl and diaryl ethers were prepared by [3+3] cyclizations of 3-alkoxy- and 3-aryloxy-1-siloxy-1,3-butadienes with 3-(silyloxy)alk-2-en-1-ones.



Scheme 4. Synthesis of **8a**–**h**. Reagents and conditions: (i) K_2CO_3, acetone, reflux, 8 h; (ii) (1) LDA, THF, −78 °C, 30 min, (2) Me_3SiCl, −78→20 °C; (iii) $TiCl_4$, CH_2Cl_2, −78→20 °C.

Table 2. Products and yields

4	7	8	R^1	R^2	R^3	R^4	R^5	% (**8**)[a]
b	**a**	**a**	H	Et	Me	H	Me	45
a	**a**	**b**	H	Et	Me	Me	Me	44
c	**a**	**c**	H	Et	Ph	H	Me	37[b]
a	**b**	**d**	Me	Me	Me	Me	Me	56
c	**b**	**e**	Me	Me	Ph	H	Me	22
a	**c**	**f**	Cl	Me	Me	Me	Me	47
e	**d**	**g**	OMe	Me	Me	OAr[c]	Me	18
f	**d**	**h**	OMe	Me	Et	H	Et	15

[a] Yields of isolated products.

[b] A small amount of ethyl 4-methyl-6-phenylsalicylate could not be separated.

[c] Ar = 4-EtC_6H_4.

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10. *Typical procedure for the synthesis of arylalkyl and diaryl ethers*: To a dichloromethane solution (9 mL) of **2** (2.0 mmol) and of **7** (2.0 mmol) was added a dichloromethane solution (1 mL) of $TiCl_4$ (0.23 mL, 2.0 mmol) at −78 °C. The solution was allowed to warm to ambient temperature within 14 h. To the solution was added 25 mL of dichlormethane and 30 mL of hydrochloric acid (10%). The organic and the aqueous layer were separated and the latter was extracted with dichloromethane (3 × 15 mL). The combined organic layers were washed four times with an aqueous solution of sodium hydroxide (2 M), dried (Na_2SO_4), and filtered. The filtrate was concentrated in vacuo and the residue was purified by chromatography (silica gel, EtOAc/*n*-heptane = 1:20, column length = 30 cm, diameter = 4 cm).
Synthesis of ethyl 4,6-trimethyl-2-phenoxysalicylate (**8a**): Starting with 4-(trimethylsiloxy)pent-3-en-2-on (**4a**) (0.372 g, 2.0 mmol), 1-ethoxy-3-phenoxy-1-(trimethylsiloxy)buta-1,3-diene (**7a**) (1.0 mmol), $TiCl_4$ (0.23 mL, 2.0 mmol, dissolved in 1 mL of CH_2Cl_2), and CH_2Cl_2 (9 mL), **8a** was isolated as a slightly yellow oil (0.121 g, 45%). Dienes **7** could not be isolated in pure form. They were used as a defined mixture (by ^1H NMR) of **7** and **6** containing 1.0 mmol of **7**. Dienes **1a–c** were obtained and used in pure form. ^1H NMR (250 MHz, $CDCl_3$): $\delta = 1.19$ (t, $^3J = 7.2$ Hz, 3H, OCH_2CH_3), 2.24 (s, 3H, CH_3), 2.34 (s, 3H, CH_3), 4.25 (q, $^3J = 7.2$ Hz, 2H, OCH_2CH_3), 6.57 (q, $^4J = 0.6$ Hz, 1H, Ar), 6.79 (m, $^4J = 0.6$ Hz, 1H, Ar), 6.95–7.09 (m, 3H, Ph), 7.25–7.32 (m, 2H, Ph). ^{13}C NMR (75.5 MHz, $CDCl_3$): $\delta = 14.1$ (CH_3), 19.4, 21.3 (CH_3), 61.0 (CH_2), 118.4, 118.8, 122.9 (CH_{Ar}), 126.3 (C_{Ar}), 129.5, 129.7 (CH_{Ar}), 137.2, 140.9, 153.9, 157.7 (C_{Ar}), 167.6 (CO). IR (neat, cm^{-1}): $\tilde{\nu} = 2981$ (w), 2926 (w), 1728 (s), 1616 (m), 1591 (m), 1489 (s), 1455 (m), 1303 (s), 1270 (s), 1216 (s), 1160 (m), 1087 (s), 1021 (m). MS (EI, 70 eV): *m/z* (%) = 270 (M^+, 88), 225 (100), 223 (73), 170 (99). Anal. Calcd for $C_{17}H_{18}O_3$ (270.33): C, 75.53; H, 6.77. Found: C, 75.58; H, 6.58.