Synthesis of Functionalized Diaryl Ethers by [3+3] Cyclization of 1,3-Bis(Silyl Enol Ethers) with 2-Aryloxy-3-(silyloxy)alk-2-en-1-ones

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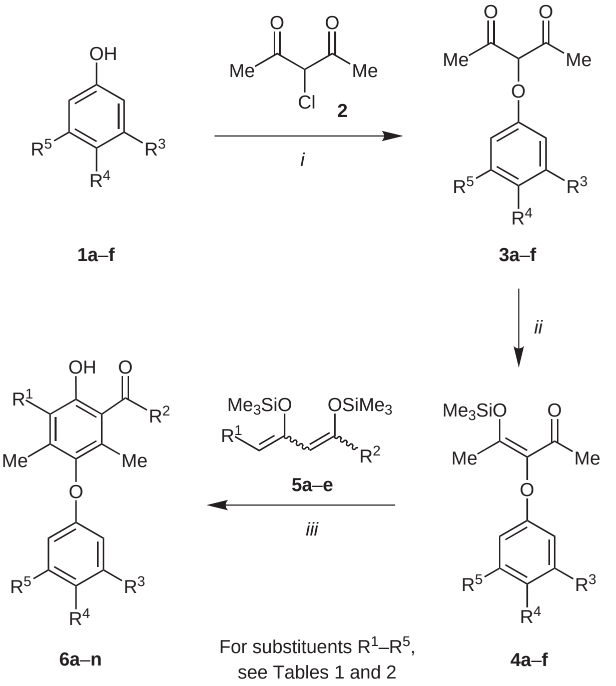
Abstract: Functionalized and sterically encumbered diaryl ethers were prepared by [3+3] cyclization of 1,3-bis(silyl enol ethers) with 2-aryloxy-3-(silyloxy)alk-2-en-1-ones.

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

Diaryl ethers are of considerable pharmacological relevance and occur in various natural products.[1] Functionalized diaryl ethers containing an ester or carboxylic acid function are present, for example, in geodinhydrate methylester and methyl chloroasterrate,[2a,b] 1-desgalloylsanguiin,[2c] dehydrotrigallic acid,[2d] epiphorellic acid,[2e] jolkianin,[2f] remurin A,[2g] or micareic acid.[2h] Diaryl ethers have been prepared, for example, based on the Ullmann ether synthesis and related methods[3] and by various transition-metal-catalyzed C–O coupling reactions.[4] Despite their synthetic usefulness, the scope of these methods is limited in many cases by the fact that the starting materials are not readily available. In addition, the formation of diaryl ethers containing a sterically encumbered ether linkage often proceeds in low yield or not at all. Some years ago, Chan and coworkers reported[5] an elegant approach to salicylates by [3+3] cyclization of 1,3-bis(silyl enol ethers)[6] with 3-(siloxy)alk-2-en-1-ones. In recent years, we have reported the application of this method to the synthesis of a variety of functionalized arenes.[7] Herein, we report what are, to the best of our knowledge, the first [3+3] cyclizations of 1,3-bis(silyl enol ethers) with 2-aryloxy-3-(silyloxy)alk-2-en-1-ones. These reactions provide a convenient approach to sterically encumbered and functionalized diaryl ethers which are not readily available by other methods. In contrast to transition-metal-catalyzed C–O coupling reactions, our method relies on the assembly of one of the two arene moieties.

The potassium carbonate mediated reaction of phenols **1a**–**f** with 3-(chloro)pentane-2,4-dione (**2**) afforded, following a known procedure,[8] the 3-(aryloxy)pentane-2,4-diones **3a**–**f** which were transformed into the 2-aryloxy-3-(silyloxy)alk-2-en-1-ones **4a**–**f** (Scheme 1, Table 1). The $TiCl_4$-mediated cyclization of **4a**–**f** with 1,3-bis(silyl enol ethers) **5a**–**e** afforded the sterically encumbered diaryl ethers **6a**–**n** (Scheme 1, Table 2).[9] During the optimization, the amount of the Lewis acid, the concentration, the temperature and the work-up procedure proved to be important parameters. All products were isolated in moderate to good yields.



Scheme 1 Synthesis of **6a**–**n**. *Reagents and conditions*: *i*: K_2CO_3, acetone, 2 h, reflux; *ii*: Me_3SiCl, Et_3N, C_6H_6, 20 °C, 72 h; *iii*: $TiCl_4$, CH_2Cl_2, –78 °C to 20 °C, 20 h.

Table 1 Synthesis of **3a**–**f** and **4a**–**f**

Compd **3** and **4**	R^3	R^4	R^5	Yield of **3** (%)[a]	Yield of **4** (%)[a]
a	H	H	H	–[b]	79
b	Me	H	Me	20	94
c	H	Et	H	35	80
d	H	Cl	H	–[b]	96
e	H	OMe	H	24	95
f	OMe	OMe	H	40	97

[a] Yields of isolated products.
[b] Commercially available.

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Table 2 Synthesis of **6a**–**n**

Compd **4**	Compd **5**	Compd **6**	R^1	R^2	R^3	R^4	R^5	Yield of **6** (%)[a]
a	**a**	**a**	H	OEt	H	H	H	35
a	**b**	**b**	Me	OEt	H	H	H	30
a	**c**	**c**	Et	OEt	H	H	H	32
b	**a**	**d**	H	OEt	Me	H	Me	58
b	**b**	**e**	Me	OEt	Me	H	Me	39
c	**a**	**f**	H	OEt	H	Et	H	60
c	**b**	**g**	Me	OEt	H	Et	H	36
d	**d**	**h**	H	OMe	H	Cl	H	54
d	**b**	**i**	Me	OEt	H	Cl	H	49
d	**c**	**j**	Et	OEt	H	Cl	H	43
d	**e**	**k**	H	Me	H	Cl	H	35
e	**b**	**l**	Me	OEt	H	OMe	H	30
f	**a**	**m**	H	OEt	OMe	OMe	H	58
f	**b**	**n**	Me	OEt	OMe	OMe	H	35

[a] Yields of isolated products.

In conclusion, a variety of functionalized and sterically encumbered diaryl ethers were prepared by [3+3] cyclizations of 1,3-bis(silyl enol ethers) with 2-aryloxy-3-(silyloxy)alk-2-en-1-ones.

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(9) **General Procedure for the Synthesis of Diaryl Ethers 6a–n.**
To a CH_2Cl_2 solution (2 mL/mmol) of **4** (1.0 mmol) and **5** (1.0 mmol) was added $TiCl_4$ (1.0 mmol) at –78 °C. The solution was allowed to warm to ambient temperature within 20 h. To the solution was added a sat. solution of $NaHCO_3$ (10 mL). The organic and the aqueous layer were separated and the latter was extracted with Et_2O (3 × 30 mL). The filtrate was concentrated in vacuo and the residue was purified by chromatography (silica gel, EtOAc–*n*-heptane, 1:4).
Synthesis of Methyl 4,6-Dimethyl-5-(4-chlorophenoxy)salicylate (6h).
Starting with 1,3-bis(silyl enol ether) **5d** (500 mg, 1.9 mmol), 3-(siloxy)alk-2-en-1-one **4d** (574 mg, 1.9 mmol) and

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$TiCl_4$ (0.21 mL, 1.9 mmol), **6h** was isolated as a colorless solid (315 mg, 54%); mp 83 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.09 (s, 3 H, CH_3), 2.30 (s, 3 H, CH_3), 3.95 (s, 3 H, OCH_3), 6.67 (d, 2 H, J = 9.0 Hz, ArH), 6.76 (s, 1 H, ArH), 7.20 (d, 2 H, J = 9.0 Hz, ArH), 11.10 (s, 1 H, OH). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 15.2, 17.1, 52.2 (CH_3), 111.1 (C), 115.7 (2 C), 117.6 (CH), 126.3 (C), 129.6 (2 C, CH), 133.5, 139.7, 143.6, 156.5, 159.7, 171.7 (C). IR (KBr): 3431 (m), 2959 (w), 1661 (s), 1486 (s), 1442 (m), 1361 (m), 1326 (s), 1318 (s), 1074 (m), 825 (m), 803 (m) cm^{-1}. GC-MS (EI, 70 eV): *m/z* (%) = 306 (33) [M$^+$], 274 (100), 246 (10), 163.1 (8). Anal. Calcd (%) for $C_{16}H_{15}ClO_4$ (306.74): C, 62.65; H, 4.93. Found: C, 62.42; H, 4.68.

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