First Cyclocondensations of 1,3-Bis(trimethylsilyloxy)buta-1,3-dienes with 1,1-Dimethoxy-4,4,4-trifluorobut-1-en-3-one

Mathias Lubbe,[a] Alina Bunescu,[a,b] Muhammad Sher,[a,b] Alexander Villinger,[a] Peter Langer*[a,b]

[a] Institut für Chemie, Universität Rostock, Albert Einstein Str. 3a, 18059 Rostock, Germany
E-mail: peter.langer@uni-rostock.de

[b] Leibniz-Institut für Katalyse, Universität Rostock e.V., Albert Einstein Str. 29a, 18059 Rostock, Germany

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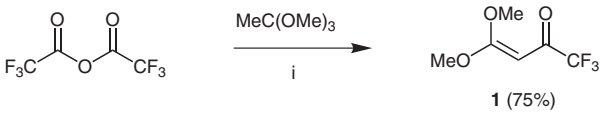
Abstract: The formal [3+3] cyclocondensation of 1,3-bis(trimethylsilyloxy)buta-1,3-dienes with 1,1-bis(methoxy)trifluoromethyl-1-en-3-ones afforded functionalized 3-methoxy-5-(trifluoromethyl)phenols with very good regioselectivity.

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

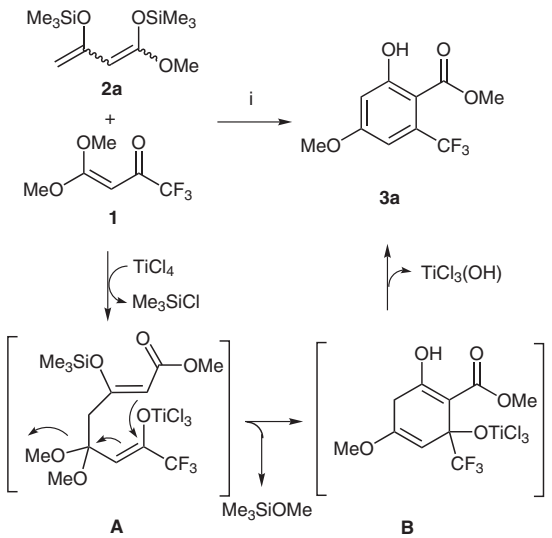
Trifluoromethyl-substituted arenes and hetarenes play an important role in drug discovery.[1] On the one hand, the size of the CF_3 group is similar to the methyl group. On the other hand, its high electronegativity results in a great change of the reactivity, which can play an important role in drug-receptor interactions. The increased lipophilicity of CF_3-substituted molecules often results in a better transport of the drug in vivo. Due to the high chemical and biological stability of the CF_3 group, undesirable metabolic transformations are often reduced. Besides, CF_3-substituted molecules play an important role as ligands[2] for catalytic reactions in fluorous biphasic systems,[3] as organocatalysts,[4] and as liquid crystals.[5]

Trifluoromethyl-substituted arenes and hetarenes have been prepared, for example, by reaction of aryl halides with trifluoromethylcopper.[6,7] Trifluoromethylcopper is rather unstable and rapidly undergoes decomposition in reactions with 'difficult' substrates. In addition, it has to be taken into consideration that the synthesis of complex aromatic starting materials is often a difficult task. Another approach relies on the transformation of carboxylic acids or CX_3 into CF_3 groups. However, these reactions are often applicable only to specific substrates. An alternative strategy is based on the use of CF_3-containing building blocks.[8] This includes cyclocondensation reactions,[9,10] reactions of metalated (trifluoromethyl)arenes,[11] Diels–Alder reactions,[12] and cyclizations of enamines with 1,1,1,5,5,5-hexafluoroacetylacetone.[13] Recently, we have reported[14] the synthesis of CF_3-substituted salicylates by formal [3+3] cyclizations[15,16] of 1,3-bis(silyl enol ethers)[17] with 4-ethoxy-1,1,1-trifluoroalk-3-en-2-ones. Despite its preparative utility, this method is limited by the fact that the products contain no functional group located at carbon atoms C-3 or C-5.[18] On the other hand, most biologically active salicylates and 2-acylphenols do contain a functional group at one of these positions, since they are derived from naturally occurring polyketides. Herein, we report a new and convenient method for the regioselective synthesis of 4-methoxy-6-(trifluoromethyl)salicylates and related compounds by what are, to the best of our knowledge, the first cyclocondensations of 1,3-bis(silyl enol ethers) with 1,1-bis(methoxy)-1-en-3-ones. The products are not readily available by other methods.

The reaction of trifluoroacetic anhydride with 1,1,1-trimethoxyethane afforded novel 1,1-dimethoxy-4,4,4-trifluorobut-1-en-3-one (**1**) in 75% yield (Scheme 1).[19] The $TiCl_4$-mediated reaction of **1** with 1,3-bis(silyloxy)buta-1,3-diene **2a**, readily available from methyl acetoacetate,[16] afforded methyl 4-methoxy-6-(trifluoromethyl)salicylate (**3a**) in 42% yield (Scheme 2).



Scheme 1 Synthesis of **1**. *Reagents and conditions*: (*i*) pyridine, $CHCl_3$, 20 °C, 12 h.



Scheme 2 Possible mechanism of the formation of **3a**. *Reagents and conditions*: (*i*) $TiCl_4$, CH_2Cl_2, –78 to 20 °C.

During the optimization, it proved to be important to carry out the reaction in a highly concentrated solution.[20] The formation of **3a** can be explained by $TiCl_4$-mediated 1,4-addition of the terminal carbon atom of **2a** onto **1a** to give

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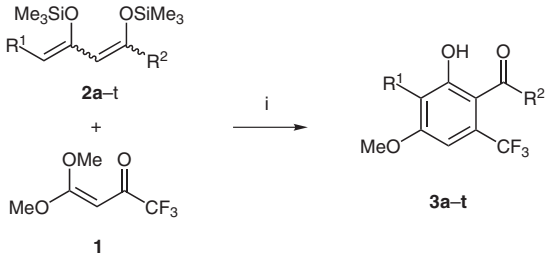
Table 1 Optimization of the Synthesis of **3a**

n (**1**) (mmol)	n (**2a**) (mmol)	V (CH_2Cl_2) (mL)	Yield of **3a** (%)[a]
1	1	1	34
1	1	2	38
1	1	5	26
1	1	10	19
1	1.5	2	40
1	2	2	47

[a] Yields of isolated products.

intermediate **A**. The latter underwent a cyclization by attack of the central carbon atom of **2a** onto the double bond to give intermediate **B**, which was finally transformed into the product by aromatization.

The $TiCl_4$-mediated reaction of **1** with 1,3-bis(silyloxy)buta-1,3-dienes **2a–v** afforded the 4-methoxy-6-(trifluoromethyl)salicylates **3a–f** and **3h–t** and the 3-methoxy-5-(trifluoromethyl)phenol **3g** in moderate yields (Scheme 3, Table 2). Noteworthy, the products are not readily available by other methods.



Scheme 3 Synthesis of **3a–t**. *Reagents and conditions*: (*i*) $TiCl_4$, CH_2Cl_2, –78 to 20 °C.

The structures of the products were confirmed by spectroscopic methods. The structure of **3l** was independently confirmed by X-ray crystal structure analysis.[21]

In conclusion, we reported a convenient and regioselective synthesis of functionalized 4-methoxy-6-(trifluoromethyl)salicylates by the first [3+3] cyclocondensations of 1,3-bis(trimethylsilyloxy)buta-1,3-dienes with 1,1-dimethoxy-4,4,4-trifluorobut-1-en-3-one. The preparative scope of our methodology and applications are currently being studied in our group.

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Table 2 Synthesis of **3a–t**

3	R^1	R^2	Yield (%) of **3**
a	H	OMe	42
b	H	OEt	34
c	H	OBn	32
d	H	O*i*-Pr	36
e	H	$O(CH_2)_2OMe$	35
f	Me	OMe	34
g	Me	Et	31
h	Et	OEt	44
i	Allyl	OMe	42
j	*n*-Pr	OMe	41
k	*n*-Bu	OMe	40
l	*n*-Hex	OMe	30
m	*n*-Oct	OMe	30
n	*n*-Undec	OMe	30
o	Bn	OMe	42
p	$(CH_2)_2Ph$	OMe	38
q	$(CH_2)_3Ph$	OMe	43
r	OMe	OMe	50
s	$(CH_2)_3Cl$	OMe	57
t	$(CH_2)_6Cl$	OMe	41

[a] Yields of isolated products.

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(20) **General Procedure for the Synthesis of 3a–t**
To a CH_2Cl_2 solution (2 mL/1 mmol of **1**) of **1** (1.0 mmol) was added **2** (2.0 mmol) and, subsequently, $TiCl_4$ (0.1 mL, 1.0 mmol) at –78 °C. The temperature of the solution was allowed to warm to 20 °C during 12–14 h with stirring. To the solution was added HCl (10%, 10 mL) and the organic and the aqueous layer were separated. The latter was extracted with CH_2Cl_2 (2 × 10 mL). The combined organic layers were dried (Na_2SO_4), filtered, and the filtrate was concentrated in vacuo. The residue was purified by chromatography.
Methyl 2-Hydroxy-3,4-dimethoxy-6-(trifluoromethyl)benzoate (3r)
Starting with **1** (0.184 g, 1.0 mmol), **2r** (0.581 g, 2.0 mmol) and $TiCl_4$ (0.1 mL, 1.0 mmol) in CH_2Cl_2 (2 mL), **3r** was isolated as a slightly yellow solid (0.140 g, 50%); mp 60–62 °C; R_f = 0.67 (*n*-heptane–EtOAc, 3:2). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.93, 3.95, 3.96 (s, 3 H, OCH_3), 6.90 (s, 1 H, H-5), 10.27 (s, 1 H, OH). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 52.7, 56.1, 60.7 (OCH_3), 103.6 (q, J_{C-F} = 6.7 Hz, C-5), 106.9 (C-1), 123.1 (q, J_{C-F} = 271.1 Hz, CF_3), 125.3 (q, J_{C-F} = 32.2 Hz, C-6), 138.8, 154.8, 155.0 (C), 168.8 (CO). ^{19}F NMR (282 MHz, $CDCl_3$): δ = –58.2 (CF_3). IR (ATR): ν = 2961 (w), 2855 (w), 1683 (m), 1602 (m), 1413 (m), 1256 (s), 1109 (s), 1023 (s), 963 (s), 922 (s), 840 (s), 709 (s) cm^{-1}. GC-MS (EI, 70 eV): *m/z* (%): 280 (54) [M$^+$], 249 (39), 248 (83), 247 (14), 220 (100), 219 (44), 205 (35), 189 (15), 188 (34), 93 (15). HRMS (EI, 70 eV): *m/z* calcd for $C_{11}H_{11}F_3O_5$ [M$^+$]: 280.05557; found: 280.05531. Anal. Calcd for $C_{11}H_{11}F_3O_5$ (280.20): C, 47.15; H, 3.96. Found: C, 47.11; H, 3.89.
(21) CCDC-686385 contains all crystallographic details for compound **3l** 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, Cambridge CB2 1EZ, UK; fax: +44(1223)336033 or deposit@ccdc.cam.ac.uk.