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Regioselective synthesis of 2-acetyl- and 2-alkoxycarbonyl-3-(trifluoromethyl)phenols by [3+3] cyclization of 1,3-bis-silyl enol ethers with 4-ethoxy- and 4-silyloxy-1,1,1-trifluoroalk-3-en-2-ones

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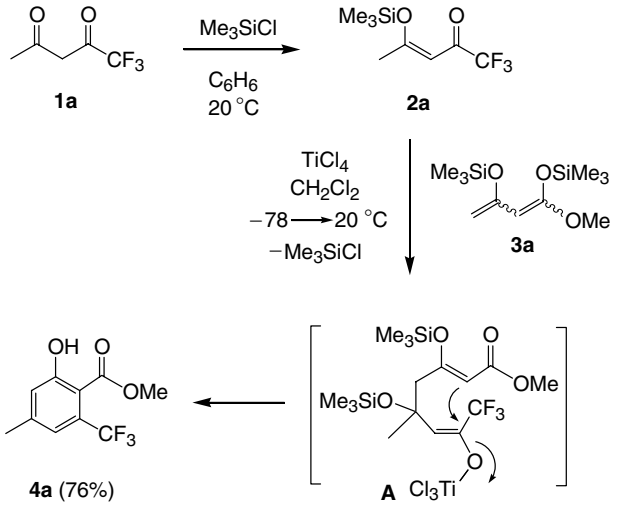
Dedicated to Professor Ralf Miethchen on the occasion of his 65th birthday

Abstract—2-Acetyl- and 2-alkoxycarbonyl-3-(trifluoromethyl)phenols were prepared by [3+3] cyclization of 1,3-bis-silyl enol ethers with 4-ethoxy- and 4-silyloxy-1,1,1-trifluoroalk-3-en-2-ones.

(Trifluoromethyl)benzenes are present in a great variety of pharmaceuticals,[1,2] pesticides and ligands.[3] The trifluoromethyl group strongly increases the lipophilicity of arenes and heterocycles.[1] In fact, functionalized (trifluoromethyl)benzenes represent important building blocks for the development of novel lead structures in medicinal chemistry. They have been prepared mainly by trifluoromethylation of aromatic compounds[4] or by reactions of appropriate fluorine-containing building blocks.[5] However, these reactions often suffer from low regioselectivities. Therefore, the development of new strategies for the synthesis of functionalized benzenes with a trifluoromethyl group located at a specific position is of considerable current interest. Some years ago, Chan and co-workers reported[6] an elegant approach to salicylates based on cyclization of 1,3-bis-silyl enol ethers (d^4-synthons)[7] with 3-(silyloxy)alk-2-en-1-ones.[8] Very recently, Kostyuk and co-workers reported the synthesis of 3,5-bis(trifluoromethyl)anilines by cyclization of enamines with 1,1,1,5,5,5-hexafluoroacetylacetone.[9]

Herein, we report a new synthesis of 2-acetyl- and 2-alkoxycarbonyl-3-(trifluoromethyl)phenols based on [3+3] cyclizations of 1,3-bis-silyl enol ethers with 4-ethoxy- and 4-silyloxy-1,1,1-trifluoroalk-3-en-2-ones. From a preparative viewpoint, these transformations offer a



Scheme 1. Possible mechanism of the formation of **4a**.

Keywords: Arenes; Cyclizations; Organic fluorine compounds; Silyl enol ethers.
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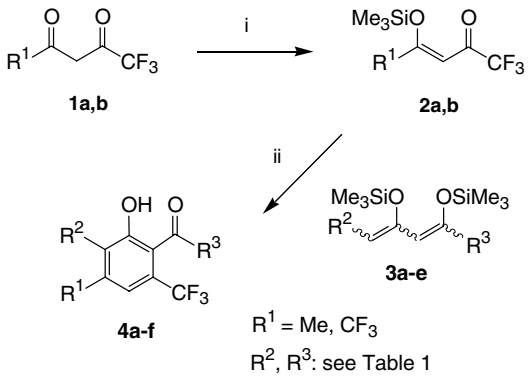
convenient and regioselective approach to functionalized (trifluoromethyl)phenols, which are not readily available by other methods. The starting materials—3-alkoxyalk-2-en-1-ones—are readily available by acylation of enol ethers.

1,1,1-Trifluoro-4-silyloxypent-3-en-2-one (**2a**) and 1,1,1,5,5,5-hexafluoro-4-silyloxypent-3-en-2-one (**2b**) were prepared by silylation of the corresponding 1,3-diketones according to a literature procedure.[9] The $TiCl_4$ mediated cyclization of **2a** with 1,3-bis-silyl enol ethers **3a**—prepared from methyl acetoacetate—afforded the desired 2-ethoxycarbonyl-3-(trifluoromethyl)phenol **4a** (Scheme 1).[†] The regioselective formation of the product can be explained—following general observations by Chan et al.[6]—by conjugate addition of the terminal carbon atom of **3a** onto **2a** and subsequent cyclization by attack of the central carbon atom of the bis-silyl enol ether onto the carbonyl group (Mukaiyama aldol reaction).

The $TiCl_4$ mediated cyclization of **2a** with 1,3-bis-silyl enol ethers **3b–e**—prepared from ethyl acetoacetate, acetylacetone, ethyl 3-oxopentanoate and ethyl 3-oxohexanoate—afforded the desired 2-alkoxycarbonyl-3-(trifluoromethyl)phenols **4b**,**d**,**e** and the 2-acetyl-3-(trifluoromethyl)phenol **4c** (Scheme 2, Table 1). The cyclization of 1,3-bis-silyl enol ether **3c** with **2b** afforded 2-acetyl-3,5-bis(trifluoromethyl)phenol (**4f**). The formation of regioisomeric products was not observed. However, the concentration of the starting materials proved to be an important parameter during the optimization.

The 4-ethoxy-1,1,1-trifluorobut-3-en-2-ones **6a–c** were prepared by reaction of enol ethers with trifluoroacetic anhydride according to a literature procedure.[10] The $TiCl_4$ mediated cyclization of **6a–c** with 1,3-bis-silyl enol ethers **3a–e** afforded the 3-(trifluoromethyl)phenols **7a–g**



Scheme 2. Synthesis of **4a–f**. Reagents and conditions: (i) Me_3SiCl, NEt_3, C_6H_6, 20 °C, 3 d; (ii) $TiCl_4$, CH_2Cl_2, −78→20 °C, 20 h.

Table 1. Products and yields

2	3	4	R^1	R^2	R^3	Yield (%)[a]
a	**a**	**a**	Me	H	OMe	76
a	**b**	**b**	Me	H	OEt	40
a	**c**	**c**	Me	H	Me	61
a	**d**	**d**	Me	Me	OEt	75
a	**e**	**e**	Me	Et	OEt	72
b	**c**	**f**	CF_3	H	Me	35

[a] Isolated yields.

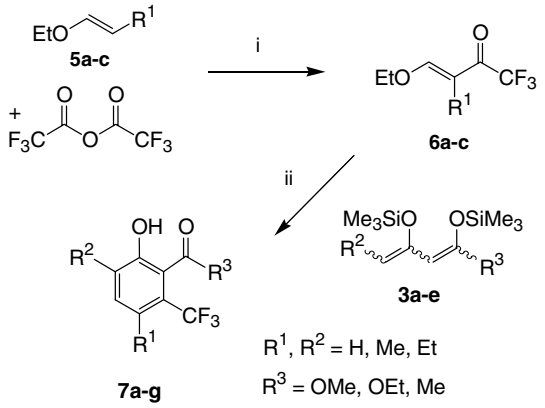
(Scheme 3, Table 2).[‡] All products were formed with very good regioselectivity. The reactions proceeded by regioselective attack of the terminal carbon atom of the 1,3-bis-silyl enol ether onto the carbon atom attached to the ethoxy group of the enone and subsequent cyclization by attack of the central carbon atom of **3** onto the carbonyl group.[11] During the optimization of the cyclization reaction, the concentration of the starting materials and the use of an excess of **3** (2.0 equiv) played an important role. Only moderate yields were obtained in some cases, since non-dehydrated cyclic products

[†] General procedure for the synthesis of **4a–f**: To a CH_2Cl_2 solution (5 mL) of 1,3-bis-silyl enol ether **3** (2.4 mmol) and 4-(silyloxy)alk-3-en-2-one **2a**,**b** (2.2 mmol) was added $TiCl_4$ (2.4 mmol) at −78 °C under argon atmosphere. The temperature of the reaction mixture was allowed to rise to 20 °C during 14 h and, subsequently, a saturated aqueous solution of $NaHCO_3$ (20 mL) was added. The organic layer was separated and extracted with diethyl ether (3 × 20 mL). The combined organic layers were dried (Na_2SO_4), filtered and the filtrate was concentrated in vacuo. The residue was purified by column chromatography (silica gel, *n*-heptane/EtOAc = 20:1).

2-(Ethoxycarbonyl)-5-methyl-3-(trifluoromethyl)phenol (**4b**). Starting with **2a** and **3b**, **4b** was isolated as a yellow solid (220 mg, 40%), mp = 28 °C; $R_f = 0.48$ (*n*-heptane/EtOAc = 2:1). ^{1}H NMR (250 MHz, $CDCl_3$): $\delta = 10.90$ (s, 1H, OH), 7.13 (s, 1H, H-4), 7.01 (s, 1H, H-6), 4.43 (q, 2H, $^3J = 7.2$ Hz, OCH_2CH_3), 2.38 (s, 3H, CH_3), 1.41 (t, 3H, $^3J = 7.2$ Hz, OCH_2CH_3). ^{13}C NMR (63 MHz, $CDCl_3$): $\delta = 169.3$ (C=O), 162.1 (C-1), 145.0 (C-5), 130.1 (q, $J_{C,F} = 34$ Hz, C-3), 123.2 (q, $J_{C,F} = 275$ Hz, CF_3), 122.0 (C-6), 120.4 (q, $J_{C,F} = 7$ Hz, C-4), 108.6 (C-2), 62.3 (CH_2), 21.5 (CH_3), 13.4 (CH_2CH_3). ^{19}F NMR (235 MHz, $CDCl_3$): $\delta = -58.0$ (s, CF_3). Anal. Calcd for $C_{11}H_{11}F_3O_3$: C, 53.23; H, 4.47. Found: C, 52.85; H, 4.69. All new compounds gave correct spectroscopic and analytical and/or high resolution mass data.

[‡] General procedure for the synthesis of **7a–g**: To a CH_2Cl_2 solution (10 mL) of 1,3-bis-silyl enol ether **3** (7.7 mmol) and **6** (3.8 mmol) was added $TiCl_4$ (3.8 mmol) at −78 °C under argon atmosphere. The temperature of the reaction mixture was allowed to rise to 20 °C during 14 h and, subsequently, an aqueous solution of HCl (20 mL, 10%) was added. The organic layer was separated and extracted with CH_2Cl_2 (3 × 20 mL). The combined organic layers were dried (Na_2SO_4), filtered and the filtrate was concentrated in vacuo. The residue was purified by column chromatography (silica gel, *n*-heptane/EtOAc = 10:1).

Methyl 5-ethyl-6-(trifluoromethyl)salicylate (**7f**). Starting with **6c** (750 mg, 3.8 mmol), **3b** (2.00 g, 7.7 mmol) and $TiCl_4$ (1.2 mL, 3.8 mmol), **7f** was isolated as a colourless solid (670 mg, 71%), mp = 84 °C; $R_f = 0.46$ (*n*-heptane/EtOAc = 2:3). IR (Nujol): $\tilde{\nu} = 3663$ (w), 1710 (s) cm^{-1}. ^{1}H NMR (250 MHz, $CDCl_3$): $\delta = 8.14$ (br, 1H, OH), 7.32 (d, 1H, $^3J = 8.5$ Hz, H-6), 7.09 (d, 1H, $^3J = 8.5$ Hz, H-5), 3.93 (s, 3H, OMe), 2.75 (m, 2H, $^3J = 7.3$ Hz, CH_2CH_3), 1.23 (t, 3H, $^3J = 7.3$ Hz, CH_2CH_3). ^{13}C NMR (62 MHz, $CDCl_3$): $\delta = 169.6$ (C=O), 155.2 (C-1), 136.5 (C-4), 135.4 (C-5), 127.2 (q, $J_{C,F} = 31$ Hz, C-3), 124.1 (q, $J_{C,F} = 276$ Hz, CF_3), 120.8 (C-6), 115.2 (C-2), 53.1 (OMe), 26.6 (CH_2CH_3), 16.1 (CH_2CH_3). ^{19}F NMR (235 MHz, $CDCl_3$): $\delta = -54.4$ (CF_3). MS (EI, 70 eV): m/z (%) = 248 (27) [M^+], 217 (29) [M^+−OMe], 216 (100) [M^+−HOMe]. HRMS (EI): calcd for $C_{11}H_{11}F_3O_3$: 248.0655; found: 248.0651.



Scheme 3. Synthesis of **7a**–**g**. Reagents and conditions: (i) CH_2Cl_2, pyridine, 0 °C; (ii) $TiCl_4$, CH_2Cl_2, −78→20 °C, 20 h.

Table 2. Products and yields

3	6	7	R^1	R^2	R^3	Yield (**7**) (%)[a]
b	**a**	**a**	H	H	OEt	30
d	**a**	**b**	H	Me	OEt	20
e	**a**	**c**	H	Et	OEt	26
a	**b**	**d**	Me	H	OMe	45
c	**b**	**e**	Me	H	Me	60
a	**c**	**f**	Et	H	OMe	71
c	**c**	**g**	Et	H	Me	40

[a] Isolated yields.

were formed as side products. The latter could not be transformed into the desired phenols by treatment with acid.

In conclusion, we have reported a new approach to 2-acetyl- and 2-alkoxycarbonyl-3-(trifluoromethyl)-phenols based on [3+3] cyclizations of 1,3-bis-silyl enol ethers with 4-ethoxy- and 4-silyloxy-1,1,1-trifluoro-alk-3-en-2-ones.

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