NMR Studies and Crystal Structure Determinations of CF_3 Group-containing Bicyclic Phenolates

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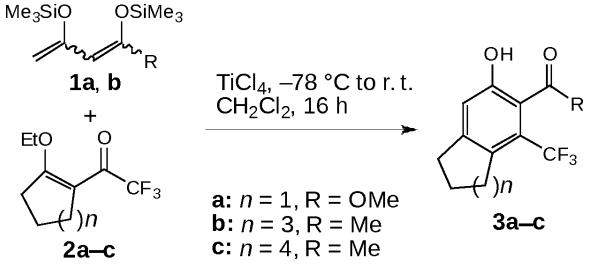
Three new CF_3-substituted bicyclic salicylate derivatives were synthesized by the $TiCl_4$-mediated cyclization of trifluoromethyl-containing ketones with 1,3-bis(silyl enol ethers) and characterized by NMR and IR, spectroscopy, mass spectrometry and elemental analysis. The crystal structures of the bicyclic derivatives have been determined by single crystal X-ray analysis. All structures exhibit hydrogen bonding.

Key words: ^{19}F NMR Spectroscopy, X-Ray Crystallography, CF_3 Salicylates, [3+3] Cyclization

Introduction

The salicylate scaffold is a basic element for a number of biologically active natural compounds and their analogs. One of the most famous and pharmaceutically relevant salicylate-based drugs is the acetylsalicylic acid [1]. In this context, phenols containing CF_3 groups are important precursors *e. g.* in drug design, agriculture [2] or material sience [3] due to the remarkable properties induced by fluorine and especially the CF_3 group in organic compounds. Synthetic pathways to these organics are limited. In 1980 Chan and coworkers reported an elegant Lewis acid-mediated cyclization reaction of bis(silyl enol ethers) with monosilylated diketones [4]. Based on this investigation we found a convenient synthetic approach to these CF_3-substituted arenes using the formal [3+3] cyclization of bis(silyl enol ethers) with CF_3-containing unsaturated ketones [5]. This method provides an access to a class of compounds with a wide variety of substitution patterns depending on the educts being used. It was possible to obtain single crystals of three bicyclic CF_3-substituted phenolates suitable for crystal structure determination. Herein, we report the corresponding results.



Scheme 1. Synthetic route to CF_3-containing phenols **3a** – **c**.

Results and Discussion

Synthesis and NMR studies

In an earlier research project of our laboratory, the syntheses and properties of trifluoromethylated phenols and salicylates were studied extensively [5b]. Beside a great number of monocyclic compounds, the respective bicyclic derivatives were the object of our studies. These compounds were obtained using the well investigated Lewis acid-mediated formal [3+3] cycloaddition [6] of silylated 1,3-diketones with α,β-unsaturated keto enol ethers. Scheme 1 indicates the synthetic pathway to the bicyclic CF_3-substituted phenols **3a** – **c**. The bis(silyl enol ethers) **1a**, **b** [7] and the fluorine-containing cyclic enol ethers **2a** – **c** [8] being used as starting material were prepared according to literature procedures. The desired salicylate derivatives **3a** – **c** were synthesized in good yields at −78 °C in dry dichloromethane with $TiCl_4$ as mediator. Pure products were obtained after column chromatography. All com-

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Table 1. ^{13}C and ^{19}F NMR data of the CF_3-containing phenol derivatives **3a – c**.

Compound	^1J(C,F) (Hz)	^2J(C,F) (Hz)	^3J(C,F) (Hz)	δ (^{13}C) CF_3 group (ppm)	δ (^{19}F) CF_3 group (ppm)
3a (R = OMe)	274.7	32.3	2.3	124.1	−56.1
3b (R = Me)	273.8	29.0	1.9	124.5	−51.1
3c (R = Me)	276.2	29.4	1.7	124.8	−51.6

pounds were identified by NMR and IR spectroscopy, mass spectrometry and elemental analysis. Crystals suitable for single crystal X-ray structure determination were obtained after dissolving the material in a mixture of cyclohexane and THF, followed by slow evaporation at r. t.

^{19}F NMR examination of the synthesized phenols showed that the signal of the CF_3 group is shifted downfield and appears at −56 ppm for the salicylate **3a** and at −51 ppm for the two acetophenone derivatives **3b**, **c**. For comparison, CF_3 groups attached to a simple benzene moiety usually give rise to a signal at δ = −64 ppm [9], and CF_3 groups located next to a carbonyl group resonate at about −70 ppm [8]. The CF_3 group located on the aromatic system is of advantage because of an easy assignment of carbon and hydrogen atoms due to the coupling with the fluorine nucleus. In the ^{13}C NMR spectra, the carbon atom of the CF_3 groups appears between 124.1 and 124.8 ppm. The signals appear as quartets with coupling constants around 274 Hz ($^1J_{C,F}$), 30 Hz ($^2J_{C,F}$), and 2 Hz ($^3J_{C,F}$) (Table 1). The ring size does not influence the chemical shift of the CF_3 group in the ^{19}F and ^{13}C NMR spectra.

*Crystal structures of **3a – c***

A view of the molecular structure of **3a** in the crystal is shown in Fig. 1. In the solid state hydrogen-bonded dimers are present which are arranged around a center of inversion with distances of 273.6 pm between the oxygen atoms O1 and O2*. In addition, there is a short contact of 253.4 pm between O1 and a proton at C6* of a neighboring molecule (symmetry code: x, y, $z+1$). Compound **3b** crystallizes in the noncentrosymmetric orthorhombic space group $P2_12_12_1$, but the absolute structure could not be determined. The molecular structure is presented in Fig. 2. Intermolecular hydrogen bonds link neighboring molecules *via* the O1 to O2* atoms with a distance of 273.0 pm (symmetry code: $-x+1$, $y+1/2$, $-z+3/2$). In addition, there is a short contact of 253.9 pm between F3 and a hydrogen of the C8-methyl group. Compound **3c** crystallizes in the monoclinic space group

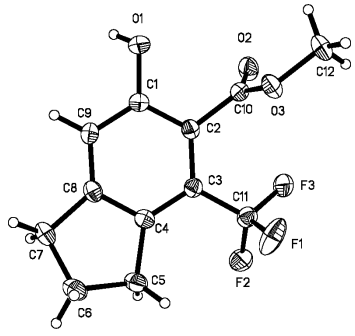

Fig. 1. Molecular structure of **3a** in the crystal (ORTEP, displacement ellipsoids at the 50 % probability level).

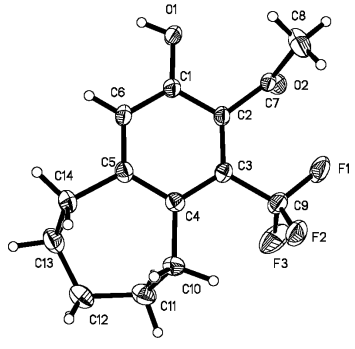

Fig. 2. Molecular structure of **3b** in the crystal (ORTEP, displacement ellipsoids at the 50 % probability level).

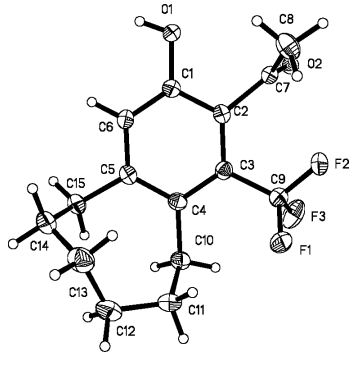

Fig. 3. Molecular structure of **3c** in the crystal (ORTEP, displacement ellipsoids at the 50 % probability level).

$P2_1/c$ (Fig. 3) with infinite chains of hydrogen-bonded molecules along the crystallographic c axis (symmetry code: x, $-y+3/2$, $z-1/2$).

Experimental Section

Reagents and techniques

All chemicals used for the cyclization reactions were of analytical grade and were used without purification.

Table 2. Crystal structure data for **3a – c**.

	3a	**3b**	**3c**
Formula	$C_{12}H_{11}F_3O_3$	$C_{14}H_{15}F_3O_2$	$C_{15}H_{17}F_3O_2$
M_r	260.21	272.26	286.29
Crystal size, mm^3	$0.30 \times 0.23 \times 0.13$	$0.32 \times 0.26 \times 0.06$	$0.43 \times 0.17 \times 0.08$
Crystal system	triclinic	orthorhombic	monoclinic
Space group	$P\bar{1}$	$P2_12_12_1$	$P2_1/c$
a, Å	8.4361(2)	8.0419(2)	10.2763(4)
b, Å	8.6202(2)	9.3209(2)	14.6427(6)
c, Å	8.8239(2)	17.1699(4)	9.9607(4)
α, deg	73.970(2)	90	90
β, deg	81.625(2)	90	112.627(2)
γ, deg	63.780(1)	90	90
V, $Å^3$	553.06(2)	1287.02(5)	1383.45(10)
Z	2	4	4
D_{calcd}, $g\,cm^{-3}$	1.563	1.405	1.375
$\mu(MoK_\alpha)$, cm^{-1}	0.144	0.121	0.116
$F(000)$, e	268	568	600
hkl range	$-10 \le h \le +10$	$-8 \le h \le +10$	$-12 \le h \le +13$
	$-11 \le k \le +11$	$-12 \le k \le +11$	$-19 \le k \le +19$
	$-11 \le l \le +11$	$-12 \le l \le +23$	$-12 \le l \le +12$
$((\sin\theta)/\lambda)_{max}$, $Å^{-1}$	0.6497	0.6802	0.6497
Refl. measured/unique	14631/2531	8156/1953	14309/3167
R_{int}	0.0232	0.0237	0.0257
Param. refined	168	174	183
$R1/wR2\ [I \ge 2\sigma(I)]$	0.0326/0.0874	0.0313/0.0819	0.0366/0.0908
$R1(F)/wR2(F^2)$[a] (all refl.)	0.0380/0.0924	0.0351/0.0841	0.0477/0.0985
x/y (weighting scheme)[a]	0.0504/0.1458	0.0527/0.1379	0.0460/0.4891
GoF (F^2)[a]	1.046	1.036	1.035
$\Delta\rho_{fin}$ (max/min), e $Å^{-3}$	0.28/−0.35	0.27/−0.21	0.29/−0.29

[a] $R1 = \|\|F_o| - |F_c\|/\Sigma|F_o|$, $wR2 = [\Sigma w(F_o^2 - F_c^2)^2/\Sigma w(F_o^2)^2]^{1/2}$, $w = [\sigma^2(F_o^2) + (xP)^2 + yP]^{-1}$, where $P = (\mathrm{Max}(F_o^2, 0) + 2F_c^2)/3$, $\mathrm{GoF} = [\Sigma w(F_o^2 - F_c^2)^2/(n_{obs} - n_{param})]^{1/2}$.

Dichloromethane (anhydrous, 99.8 %) was purchased from Acros and was used as received. $TiCl_4$ was freshly distilled under an argon atmosphere prior to use. Melting points are uncorrected. NMR spectra were recorded on a Bruker AC 250 instrument; chemical shifts are reported in ppm using the solvent shift ($CDCl_3$: δ = 7.26 ppm) as standard for protons and $CFCl_3$ as internal standard for ^{19}F nuclei.

General synthetic procedure

Under an argon atmosphere the 1,3-bis(silyl enol ether) **1a**, **b** (2 mmol) and the CF_3 enol ether **2a – c** (1 eq.) were dissolved in dry CH_2Cl_2 (4 mL). The solution was cooled to −78 °C, and $TiCl_4$ (2 eq.) was added. The temperature of the solution was allowed to rise to 20 °C during 20 h. Afterwards the solution was poured into an aqueous solution of HCl (10 %). The organic and the aqueous layer were separated, and the latter was extracted three times with CH_2Cl_2, the combined organic layers dried with Na_2SO_4, filtered and the filtrate concentrated *in vacuo*. Purification was done *via* column chromatography (silica gel, *n*-heptane/EtOAc = 10 : 1).

*Methyl 6-hydroxy-4-(trifluoromethyl)indane-5-carboxylate (**3a**)*

Following the general procedure, **1a** (1.80 g, 7.4 mmol), **2a** (770 mg, 3.7 mmol) and $TiCl_4$ (0.26 mL, 2.4 mmol) yielded **3a** as a colorless solid (423 mg, 68 %). M. p. 76 °C. – R_f = 0.47 (*n*-heptane/EtOAc 1 : 1). – ^1H NMR (250 MHz, $CDCl_3$): δ = 9.33 (s, 1 H, OH), 7.03 (s, 1 H, 7-H), 3.93 (s, 3 H, OCH_3), 2.98 – 3.09 (m, 2 H, 3-H), 2.89 (t, ^3J = 7.6 Hz, 2 H, 1-H), 2.04 (quint, ^3J = 7.6 Hz, 2 H, 2-H). – ^{19}F NMR (235 MHz, $CDCl_3$): δ = −56.1.

*2-Acetyl-3-hydroxy-1-(trifluoromethyl)-6,7,8,9-tetrahydro-5H-benzocyclohept-2-ene (**3b**)*

Following the general procedure, **1b** (1.03 g, 4.24 mmol), **2b** (500 mg, 2.12 mmol) and $TiCl_4$ (0.23 mL, 2.12 mmol) yielded **3b** as a colorless solid (231 mg, 40 %). M. p. 152 °C. – R_f = 0.42 (*n*-heptane/EtOAc 1 : 1). – ^1H NMR (250 MHz, $CDCl_3$): δ = 8.16 (s, 1 H, OH), 6.88 (s, 1 H, 4-H), 2.50 – 2.90 (m, 4 H, H5, 9-H), 2.48 (s, 3 H, $COCH_3$), 1.57 – 1.85 (m, 6 H, 6-H, 7-H, 8-H). – ^{19}F NMR (235 MHz, $CDCl_3$): δ = −51.1.

*2-Acetyl-3-hydroxy-1-(trifluoromethyl)-5,6,7,8,9,10-hexahydrobenzocyclooctene (**3c**)*

Following the general procedure, **1b** (782 mg, 3.2 mmol), **2c** (400 mg, 1.6 mmol) and $TiCl_4$ (0.18 mL, 1.6 mmol) yielded **3c** as a colorless solid (138 mg, 40 %). M. p. 105 °C. – R_f = 0.38 (*n*-heptane/EtOAc 1 : 1). – ^1H NMR (250 MHz, $CDCl_3$): δ = 7.50 (br. s, 1 H, OH), 6.85 (s, 1 H,

4-H), 2.82 – 2.90 (m, 2 H, 10-H), 2.68 – 2.75 (m, 2 H, 5-H), 2.49 (s, 3 H, $COCH_3$), 1.62 – 1.74 (m, 4 H, 6-H, 9-H), 1.32 – 1.39 (m, 4 H, 7-H, 8-H). – ^{19}F NMR (235 MHz, $CDCl_3$): $\delta = -51.6$.

X-Ray crystal structure determination

Crystallographic data of **3a** – **c** were collected on a Bruker X8Apex CCD diffractometer system with MoK_α radiation (λ = 0.71073 Å) and graphite monochromator. The structures were solved by Direct Methods using SHELXS-97 [10] and refined against F^2 on all data by full-matrix least-squares procedures (SHELXL-97 [10]). All non-hydrogen atoms were refined anisotropically; all hydrogen atoms were placed into theoretical positions which were refined by using a riding model. Because the absolute structure of compund **3b** could not be determined reliably by refinement of the Flack parameter, all equivalents including the Friedel pairs were merged in the final refinement cycles (Table 2).

CCDC 644285 (**3a**), CCDC 644287 (**3b**) and CDCC 644288 (**3c**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre *via* www.ccdc.cam.ac.uk/data_request/cif.

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