

NMR Studies and Crystal Structure Determinations of CF₃ Group-containing Bicyclic Phenolates

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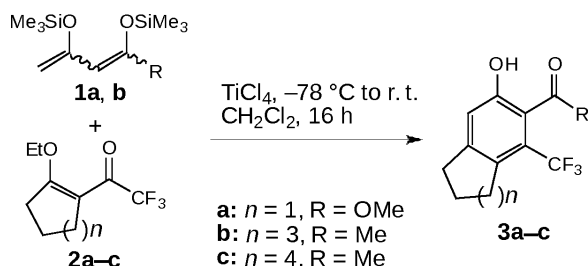
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Three new CF₃-substituted bicyclic salicylate derivatives were synthesized by the TiCl₄-mediated cyclization of trifluoromethyl-containing ketones with 1,3-bis(silyl enol ethers) and characterized by NMR and IR, spectroscopy, mass spectrometry and 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: ¹⁹F NMR Spectroscopy, X-Ray Crystallography, CF₃ 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 CF₃ groups are important precursors *e. g.* in drug design, agriculture [2] or material science [3] due to the remarkable properties induced by fluorine and especially the CF₃ 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 CF₃-substituted arenes using the formal [3+3] cyclization of bis(silyl enol ethers) with CF₃-containing unsaturated ketones [5].



Scheme 1. Synthetic route to CF₃-containing phenols **3a–c**.

rated 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 CF₃-substituted phenolates suitable for crystal structure determination. Herein, we report the corresponding results.

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 CF₃-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 TiCl₄ as mediator. Pure products were obtained after column chromatography. All com-

Table 1. ¹³C and ¹⁹F NMR data of the CF₃-containing phenol derivatives **3a–c**.

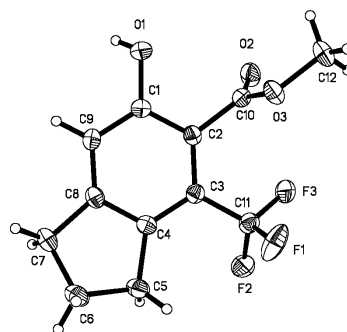
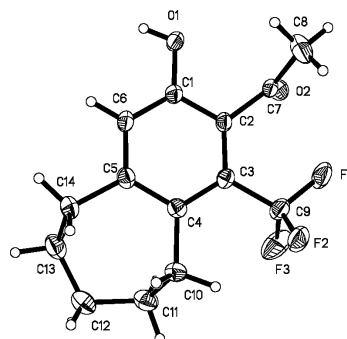
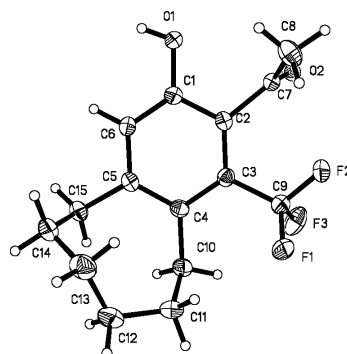
Compound	¹ J(C,F) (Hz)	² J(C,F) (Hz)	³ J(C,F) (Hz)	δ (¹³ C) CF ₃ group (ppm)	δ (¹⁹ F) CF ₃ group (ppm)
3a (R = OMe)	274.7	32.3	2.3	124.1	−56.1
3b (R = Me)	273.8	29.0	1.9	124.5	−51.1
3c (R = Me)	276.2	29.4	1.7	124.8	−51.6

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.

¹⁹F NMR examination of the synthesized phenols showed that the signal of the CF₃ 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, CF₃ groups attached to a simple benzene moiety usually give rise to a signal at δ = −64 ppm [9], and CF₃ groups located next to a carbonyl group resonate at about −70 ppm [8]. The CF₃ 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 ¹³C NMR spectra, the carbon atom of the CF₃ 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 CF₃ group in the ¹⁹F and ¹³C 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 non-centrosymmetric orthorhombic space group *P*2₁2₁, 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).

*P*2₁/*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.

	3a	3b	3c
Formula	C ₁₂ H ₁₁ F ₃ O ₃	C ₁₄ H ₁₅ F ₃ O ₂	C ₁₅ H ₁₇ F ₃ O ₂
<i>M_r</i>	260.21	272.26	286.29
Crystal size, mm ³	0.30 × 0.23 × 0.13	0.32 × 0.26 × 0.06	0.43 × 0.17 × 0.08
Crystal system	triclinic	orthorhombic	monoclinic
Space group	<i>P</i> 1	<i>P</i> 2 ₁ 2 ₁ 2 ₁	<i>P</i> 2 ₁ / <i>c</i>
<i>a</i> , Å	8.4361(2)	8.0419(2)	10.2763(4)
<i>b</i> , Å	8.6202(2)	9.3209(2)	14.6427(6)
<i>c</i> , 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
<i>V</i> , Å ³	553.06(2)	1287.02(5)	1383.45(10)
<i>Z</i>	2	4	4
<i>D</i> _{calcd} , g cm ^{−3}	1.563	1.405	1.375
μ(MoKα), cm ^{−1}	0.144	0.121	0.116
<i>F</i> (000), e	268	568	600
<i>hkl</i> range	−10 ≤ <i>h</i> ≤ +10 −11 ≤ <i>k</i> ≤ +11 −11 ≤ <i>l</i> ≤ +11	−8 ≤ <i>h</i> ≤ +10 −12 ≤ <i>k</i> ≤ +11 −12 ≤ <i>l</i> ≤ +23	−12 ≤ <i>h</i> ≤ +13 −19 ≤ <i>k</i> ≤ +19 −12 ≤ <i>l</i> ≤ +12
((sin θ)/λ) _{max} , Å ^{−1}	0.6497	0.6802	0.6497
Refl. measured/unique	14631/2531	8156/1953	14309/3167
<i>R</i> _{int}	0.0232	0.0237	0.0257
Param. refined	168	174	183
<i>R</i> 1/ <i>wR</i> 2 [<i>I</i> ≥ 2σ(<i>I</i>)]	0.0326/0.0874	0.0313/0.0819	0.0366/0.0908
<i>R</i> 1(<i>F</i>)/ <i>wR</i> 2(<i>F</i> ²) ^a (all refl.)	0.0380/0.0924	0.0351/0.0841	0.0477/0.0985
<i>x</i> / <i>y</i> (weighting scheme) ^a	0.0504/0.1458	0.0527/0.1379	0.0460/0.4891
GoF (<i>F</i> ²) ^a	1.046	1.036	1.035
Δρ _{fin} (max/min), e Å ^{−3}	0.28/−0.35	0.27/−0.21	0.29/−0.29

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

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

Dichloromethane (anhydrous, 99.8 %) was purchased from Acros and was used as received. TiCl₄ 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 (CDCl₃: δ = 7.26 ppm) as standard for protons and CFCl₃ as internal standard for ¹⁹F nuclei.

General synthetic procedure

Under an argon atmosphere the 1,3-bis(silyl enol ether) **1a, b** (2 mmol) and the CF₃ enol ether **2a–c** (1 eq.) were dissolved in dry CH₂Cl₂ (4 mL). The solution was cooled to −78 °C, and TiCl₄ (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 CH₂Cl₂, the combined organic layers dried with Na₂SO₄, 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 TiCl₄ (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, CDCl₃): δ = 9.33 (s, 1 H, OH), 7.03 (s, 1 H, 7-H), 3.93 (s, 3 H, OCH₃), 2.98–3.09 (m, 2 H, 3-H), 2.89 (t, ³*J* = 7.6 Hz, 2 H, 1-H), 2.04 (quint, ³*J* = 7.6 Hz, 2 H, 2-H). – ¹⁹F NMR (235 MHz, CDCl₃): 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 TiCl₄ (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, CDCl₃): 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, COCH₃), 1.57–1.85 (m, 6 H, 6-H, 7-H, 8-H). – ¹⁹F NMR (235 MHz, CDCl₃): 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 TiCl₄ (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, CDCl₃): 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, COCH₃), 1.62–1.74 (m, 4 H, 6-H, 9-H), 1.32–1.39 (m, 4 H, 7-H, 8-H). – ¹⁹F NMR (235 MHz, CDCl₃): δ = –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 compound **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 CCDC 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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