One-Pot Synthesis of a New Series of 3-Alkoxy-5-hydroxy-5-trifluoromethyl-pyrrolidin-2-ones from 1,1,1-Trifluoro-4-alkoxyalk-3-en-2-ones

Nilo Zanatta,* Luciana S. Rosa, Maria F. M. Cortelini, Simone Beux, Ana P. D. Santos, Helio G. Bonacorso, Marcos A. P. Martins

Núcleo de Química de Heterociclos (NUQUIMHE), Departamento de Química, Universidade Federal de Santa Maria, 97. 105-900, Santa Maria, RS, Brazil
Fax +55(55)2208031; E-mail: zanatta@base.ufsm.br
Received 28 September 2001; revised 27 August 2002

Abstract: The synthesis of a new series of 3-alkoxy-5-hydroxy-5-trifluoromethyl pyrrolidin-2-ones **2a**–**h** from the reaction of 1,1,1-trifluoro-4-alkoxyalk-3-en-2-ones **1a**–**h** of the general formula $F_3CC(O)C(R^2)=C(R^1)OR$, where: R = Me, Et, $-(CH_2)_2-$, $-(CH_2)_3-$; R^1 = H, Me, Ph, *p*-Me-Ph, *p*-F-Ph; and R^2 = H, Me, $-(CH_2)_2-$, $-(CH_2)_3-$ with sodium cyanide in hydro-alcoholic medium is reported.

Key words: ketones, pyrrolidin-2-ones, lactams, heterocycles, fluorine

The presence of trifluorinated groups in organic molecules was shown to induce special chemical, physical and biological properties to these molecules largely due to the elevated electronegative and lipophilic character of fluorine atoms. As a consequence, in recent years much attention has been devoted to the synthesis of trifluorinated compounds[1–11] and many have proven to be of important therapeutic value.[12,13]

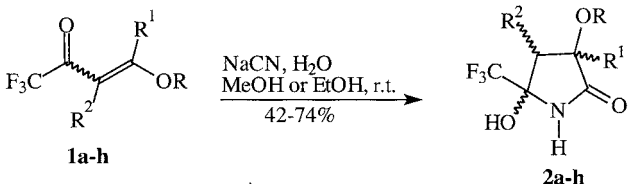
In a recent publication, the synthesis of 3-ethoxy-5-hydroxy-5-trifluoromethylpyrrolidin-2-one from the reaction of 1,1,1-trifluoro-4,4-diethoxy-2,2-diol and sodium cyanide in ethanol, was reported.[14] Lately we discover that ketones **1a**–**h** also react with sodium cyanide in hydro-alcoholic medium furnishing 3-alkoxy-5-hydroxy-5-trifluoromethylpyrrolidin-2-ones **2a**–**h**, in a one pot reaction. However, the reaction of related 4-alkoxyvinyl ketones with trimethylsilyl cyanide has been shown by Gerus et al.[4] to undergo 1,2- and 1,4-addition of the trimethylsilyl cyanide to the 4-alkoxyvinyl ketones giving the corresponding open chain 1,2- and 1,4-trimethylsilyloxy nitrile adducts instead of pyrrolidinones.

Pyrrolidin-2-ones have been the subject of very few studies, if compared to pyrroles, largely due to a lack of a simple general method of synthesis.[15–19] The synthesis of pyrrolidin-2-ones closely related to the method presented in this work was reported by Stevens et al. in 1971.[20] This method relies on the reaction of 4-methylpent-3-en-2-one with potassium cyanide in methanol to obtain a mixture of 5-hydroxy-3,3,5-trimethylpyrrolidin-2-one and 5-cyano-3,3,5-trimethylpyrrolidin-2-one which were used a building blocks for the synthesis of corrins and related ligands.[20] Corrins are molecules capable of complexing metals such as cobalt to form B_{12} vitamin and analogous compounds.[21] A pyrrolidin-2-one derivative is also found as a constituent of the peptide histrelin that has been used for the treatment of the precocious puberty showing superior activity than the commonly used hormones.[22] More recently, *N*-substituted 5-methyl-5-trifluoromethylpyrrolidin-2-ones were claimed to function as cognitive performance enhancers.[23,24]

Considering some of the important aspects summarized above concerning pyrrolidin-2-ones, we wish to report the synthesis of a new series of 5-hydroxy-5-trifluoromethylpyrrolidin-2-ones **2a**–**h** from the reaction of 1,1,1-trifluoro-4-alkoxyalk-3-en-2-ones **1a**–**h** with sodium cyanide in hydro-alcoholic medium. The synthetic potential of compounds **1** to yield a series of heterocycles of five,[25–31] six,[32–36] and seven membered rings,[37,38] and in Michael type reaction,[39] has been shown in previous publications of our group.

The synthesis of a series of 5-trifluoromethylpyrrolidin-2-ones **2a**–**h** was carried out from the reaction of ketones **1a**–**h** with sodium cyanide in hydro-alcoholic medium, at room temperature, according to Scheme 1.

The ketones **1a**–**h** were dissolved in methanol or ethanol and to this mixture a solution of sodium cyanide in water was added at room temperature. In order to try to improve the yields and/or the stereoselectivity, the reactions were



1a-h **2a-h**

Compound 1, 2	R^1	R^2	R
a	H	H	Et
b	Me	H	Me
c	H	Me	Et
d	H	$-(CH_2)_2-$	
e	H	$-(CH_2)_3-$	
f	Ph	H	Me
g	*p*-Me-Ph	H	Me
h	*p*-F-Ph	H	Me

Scheme 1

Synthesis 2002, No. 16, Print: 14 11 2002.
Art Id.1437-210X,E;2002,0,16,2404,2408,ftx,en;M05001SS.pdf.

ISSN 0039-7881

carried out at different temperatures ranging from 0 °C to the reflux of the solvent. Different solvents such as alcohols and THF were used. However, the most satisfactory condition was found when alcohols were used as solvent with the reaction carried out at room temperature. The reaction times were very dependent of the structure of the ketones **1a**–**h**, ranging from 4 hours for **1a**–**d**, 16 hours for **1e**,**g**, to 22 and 48 hours for the ketones **1h**,**f**. The only isolated products were the 3-alkoxy-5-hydroxy-5-trifluoromethylpyrrolidin-2-ones **2a**–**h**. Surprisingly, compounds **2a**–**h** resisted the dehydration under various conditions and an efficient method to convert them to the corresponding 5-trifluoromethyl-2-hydroxypyrroles, was not yet found.

The products were isolated by extraction of the reaction mixture with dichloromethane and the organic phase dried with anhydrous magnesium sulfate. Compounds **2a**–**d** were obtained as light yellow oils and compounds **2e**–**h** as solids. The solids were purified by recrystallization and the oils, which were isolated in satisfactory purity, were analyzed without further purification. Tentative purification of **2a**–**d** by silica column chromatography was not very successful.

According to Stevens et al.,[20] the formation of 3-alkoxy-5-hydroxy-5-trifluoromethylpyrrolidin-2-ones **2a**–**h** possibly resulted from a Michael addition of the cyanide ion to the β-carbon of ketones **1a**–**h** forming β-cyano ketone intermediates which were not isolated. Subsequent hydrolysis of the cyano group to amide followed by an intramolecular attack of the amide nitrogen to the α-trifluoro carbonyl furnished the compounds **2a**–**h** in moderate to good yields. The low yields observed for some products may be due to the partial solubility of these compounds in water. Yields, selected physical and spectral data are presented in Table 1.

The pyrrolidinones **2a**,**b**,**f**–**h** have two asymmetric carbons and two diastereoisomers were formed. The reactions showed little stereoselectivity giving a pair of stereoisomers in a ratio of approximately 60:40% as determined from both ^{1}H NMR integrals and GC/MS. The mixture of diastereoisomers were confirmed by the observation of two sets of signals in both ^{1}H and ^{13}C NMR spectra and two chromatographic peaks with different retention times but with superimposed mass spectra in the GC/MS. The minor isomer of the pyrrolidinone **2h** was lost during the crystallization process. The reactions, however, were highly regioselective furnishing only the pyrrolidinones **2** with the exclusion of 4-alkoxy-5-imino-2-trifluoromethyltetrahydrofuran-2-ols.[40]

The pyrrolidinones **2c**–**e** have three asymmetric carbons, and four diastereoisomers could be formed. Indeed, compound **2c** showed to be comprised of 4 stereoisomers in a ratio of 60:30:8:2 determined by GC/MS, but **2e** showed three stereoisomers in a ratio of 60:34:6 and **2d** exhibited only a single compound.

A NOESY experiment of **2d** showed a strong cross peak between H-3 and H-4. This indicates that H-3 and H-4 are close in space, which suggests that the pyrrolidinone ring closure was accomplished with *cis* configuration with respect to the tetrahydrofuran ring. The coupling constant of H-3 and H-4 of 7.8 Hz further supports this conclusion. So the most probable structure for **2d** presents the pyrrolidinone ring closure in *cis* configuration with respect to the tetrahydrofuran ring and the CF_3 group is *cis* to the H-4 and *trans* to the CH_2 of the tratrahydrofuran moiety.

The mixture of isomers made the ^{1}H NMR spectra very complex. The ^{13}C NMR spectra, however, were simpler

Table 1 Reaction Times and Selected Physical and Spectral Data for **2a**–**h**[a]

Compound	Reaction Time (h)	Yield[b] (%)	Mp[b] (°C)	IR[c] (cm^{-1})	MS[d] (%), EI (70 ev)
2a	4	48	oil	3250, 1717	169 (100), 100 (50), 73 (18), 56 (38)
2b	4	65	oil	3180, 1703	183 (100), 155 (17), 101 (22), 72 (43)
2c	4	73	oil	3237, 1731	183 (94), 168 (100), 114 (20), 70 (59)
2d	4	74	oil	3282, 1732	211 (12), 164 (63), 99 (100), 71 (97)
2e	16	48	146–148	3441, 1720	181 (100), 169 (34), 125 (29), 83 (29),
2f	48	62	128–132[e], 150–154[f]	3284, 1690	245 (100), 231 (37), 133 (24), 105 (46), 103 (41), 77 (31)
2g	16	55	152–155[e], 189–191[f]	3285, 1717	257 (42), 188 (100), 142 (40), 115 (34)
2h	22	42	158–160	3239, 1716	263 (100), 249 (24), 151 (28), 123 (59), 121 (42), 95 (19)

[a] Satisfactory elemental analysis C ± 0.50, H ± 0.40, N ± 0.40, except for: **2a**, C ± 0.6; **2c**, C ± 1.1, H ± 0.7; **2f**, H ± 0.5; 2**g**, H ± 0.7.
[b] Yields of compounds **2a**–**d** after extraction and yields of **2e**–**f** after recrystallization.
[c] Stretching frequencies of OH/NH and C=O, respectively.
[d] Compounds **2a**,**c**,**e** showed M – 44 (MOEt) while **2b**,**f**–**h** showed M – 30 (M – OMe) as the molecular ion.
[e] Melting point for the minor isomer.
[f] Melting point for the major isomer.

and very useful to assign these structures. All compounds have been fully analyzed by ^{1}H and ^{13}C NMR as well as 2D experiments[41] such as COSY-HH, HMQC and HMBC to provide unambiguous assignments of the mixture of isomers. ^{1}H NMR spectral data of **2a**–**h** are presented in Table 2 and their ^{13}C NMR spectral data are presented in Table 3. The NMR data of the two minor isomers of **2c** (**2c**′′ and **2c**′′′) and the minor isomer of **2e** (**2e**′′) were not presented because the low signal to noise ratio did not allow the correct assignment.

Unless otherwise indicated all common reagents and solvents were used as obtained from commercial suppliers without further purification. The 1,1,1-trifluoro-4-alkoxy-alk-3-en-2-ones (**1**) were prepared according to references.[26,42] Mps were determined on a Reichert Thermovar apparatus and are uncorrected. ^{1}H, ^{13}C and 2D-NMR spectra were acquired on a Bruker DPX 400 spectrometer (^{1}H at 400.13 MHz and ^{13}C at 100.62 MHz) or on a Bruker DPX 200 spectrometer (^{1}H at 200.13 MHz and ^{13}C at 50.32 MHz) in $CDCl_3$ or DMSO-d_6, using TMS as the internal reference. IR spectra were recorded on a Bruker IFS 28 FT-IR spectrometer in film for the oils and KBr disks for the solid compounds. Elemental analysis was performed on a Vario EL Elementar Analysensysteme. Mass spectra were registered on a HP 5973 MSD connected to a HP 6890 GC and interfaced by a pentium PC. The GC was equipped with a split-splitless injector, autosampler, cross-linked HP-5 capillary column (30 m, 0.32 mm of internal diameter), and helium was used as the carrier gas.

3-Alkoxy-5-hydroxy-5-trifluoromethylpyrrolidin-2-ones (2a–h); General Procedure

To a solution of ketones **1a**–**h** (5 mmol) in MeOH or EtOH (3 mL), a solution of NaCN (5 mmol, 0.25 g in 3 mL of H_2O) was added at r.t. under magnetic stirring, from 4 to 48 h (see Table 1). After half of the reaction time, another equiv of sodium cyanide solution (5 mmol, 0.25 g in 3 mL of H_2O) was added. A second addition of NaCN improved the yields of 10–25%. The reaction was extracted with CH_2Cl_2 (3 × 20 mL), washed with distilled H_2O (1 × 20 mL), and the organic layer was dried ($MgSO_4$). Evaporation of the solvent under vacuum resulted in light yellow oils for **2a**–**d** and white solids for **2e**–**h**. The oils were analyzed without further purification since tentative purification using column chromatography (30 g of silica gel 60 for 0.5 g of the product) were unsuccessful. The solid products **2e**–**h** were recrystallized from MeOH in $CHCl_3$ (10%). Yields and selected physical and spectroscopic data are presented in Table 1. ^{1}H and ^{13}C NMR data are presented in Table 2 and Table 3, respectively.

Acknowledgment

The authors thank the Conselho Nacional de Desenvolvimento Científico e Tecnológico (CNPq), PADCT-III/CNPq 62.0228/97-0 – QEQ, and Fundação de Apoio a Pesquisa do Estado do Rio Grande do Sul (FAPERGS) for financial support. Fellowships from CAPES (L. S. R. and M. F. M. C.) and CNPq (S. B.) are also acknowledged.

References

(1) Song, L.; Chu, Q.; Zhu, S. *J. Fluorine Chem.* **2001**, *107*, 107.
(2) Zhu, S.; Qin, C.; Wang, Y.-L.; Chu, Q. *J. Fluorine Chem.* **1999**, *99*, 183.
(3) Zhu, S.; Qin, C.; Xu, G.; Chu, Q.; Huang, Q. *J. Fluorine Chem.* **1999**, *99*, 141.

Table 2 ^{1}H NMR Spectral Data of Compounds **2a**–**h**

Compound	^{1}H NMR,[a] δ, *J* (Hz)
2a[b]	1.23 (t, 3 H, $^3J_{HH}$ = 7.0, CH_3), 2.15 (dd, H, $^2J_{H4'-H4}$ = 14.4, $^3J_{H4'-H3}$ = 8.0, H-4′), 2.93 (dd, 1 H, $^2J_{H4-H4'}$ = 14.4, $^3J_{H4-H3}$ = 8.0 Hz, H-4), 3.60–3.80 (m, 2 H, OCH_2), 4.14 (t, 1 H, $^3J_{H3-H4H4'}$ = 8.0, H-3), 8.40 (s, 1 H, OH), 9.41 (br s, 1 H, NH)[d]
2a	1.23 (t, 3 H, $^3J_{H-H}$ = 7.0, CH_3), 2.29 (dd, 1 H, $^2J_{H4'-H4}$ = 14.4, $^3J_{H4'-H3}$ = 8.0, H-4′), 2.57 (dd, 1 H, $^2J_{H4-H4'}$ = 14.4, $^3J_{H4-H3}$ = 8.0, H-4), 3.60–3.80 (m, 2 H, OCH_2), 4.40 (t, 1 H, $^3J_{H3-H4H4'}$ = 8.0, H-3), 8.32 (s, 1 H, OH), 9.41 (br s, 1 H, NH)[d]
2b[c]	1.27 (s, 3 H, CH_3), 1.98 (d, 1 H, $^2J_{H4'-H4}$ = 15.5, H-4′), 2.41 (d, 1 H, $^2J_{H4-H4'}$ = 15.5, H-4), 3.20 (s, 3 H, OCH_3), 7.30 (br s, 1 H, OH), 9.20 (br s, 1 H, NH)[d]
2b′	1.39 (s, 3 H, CH_3), 1.72 (d, 1 H, $^2J_{H4'-H4}$ = 14.5, H-4′), 2.56 (d, 1 H, $^2J_{H4-H4'}$ = 14.5, H-4), 3.15 (s, 3 H, OCH_3), 7.30 (br s, 1 H, OH), 9.20 (br s, 1 H, NH)[d]
2c[c]	1.13 (d, 3 H, $^3J_{H-H4}$ = 7.2, CH_3), 1.14 (t, 3 H, $^3J_{H-H}$ = 7.0, CH_3), 2.26 (dq, 1 H, $^3J_{H4-H3}$ = 8.6, $^3J_{H4-CH3}$ = 7.2, H-4), 3.55–3.65 (m, 2 H, OCH_2), 3.79 (d, 1 H, $^3J_{H3-H4}$ = 8.6, H-3), 7.75 (s, 1 H, OH), 9.20 (br s, 1 H, NH)
2c′	0.95 (d, 3 H, $^3J_{H-H4}$ = 7.2, CH_3), 1.14 (t, 3 H, $^3J_{H-H}$ = 7.0, CH_3), 2.74 (quin, 1 H, $^3J_{H4-H3}$ = 7.2, $^3J_{H4-CH3}$ = 7.2, H-4), 3.55–3.65 (m, 2 H, OCH_2), 3.92 (d, 1 H, $^3J_{H3-H4}$ = 7.2, H-3), 8.11 (s, 1 H, OH), 9.08 (br s, 1 H, NH)
2d[c]	1.80–1.90 (m, 1 H, CH_2), 2.25–2.30 (m, 1 H, CH_2), 3.00 (m, 1 H, H-4), 3.54 (ddd, 1 H, $^2J_{OCH2}$ = 15.6, $^3J_{OCH2-CH2}$ = 8.2, $^3J_{OCH2-CH2}$,[e] OCH_2), 3.82 (m, 1 H, OCH_2), 4.42 (d, 1 H, $^3J_{H3-H4}$ = 7.8, H-3), 6.08 (br s, 2 H, OH, NH)
2e[b]	1.64–1.88 (m, 2 H, CH_2), 1.88–2.27 (m, 2 H, CH_2), 2.20–2.27 (m, 1 H, H-4), 3.36–3.86 (m, 2 H, OCH_2), 4.15 (d, 1 H, $^3J_{H3-H4}$ = 9.7, H-3), 7.28 (s, 1 H, OH), 9.24 (br s, 1 H, NH)
2e′	1.64–1.88 (m, 2 H, CH_2), 1.88–2.27 (m, 2 H, CH_2), 2.33–2.42 (m, 1 H, H-4), 3.36–3.86 (m, 2 H, OCH_2), 4.00 (d, 1 H, $^3J_{H3-H4}$ = 9.7, H-3), 7.60 (s, 1 H, OH), 9.11 (br s, 1 H, NH)
2f[b]	2.52–2.78 (m, 2 H, H-4), 3.32 (OCH_3), 7.03–7.93 (Ph)[f]
2f′	2.52–2.78 (m, 2 H, H-4), 3.25 (OCH_3), 7.03–7.93 (Ph)[f]
2g[c]	2.36 (CH_3), 2.55–2.75 (m, 2 H, H-4), 3.24 (OCH_3), 6.99–7.80 (4-CH_3Ph), 7.00 (s, 1 H, OH), 8.76 (br s, 1 H, NH)
2g′	2.34 (CH_3), 2.55–2.75 (m, 2 H, H-4), 3.30 (OCH_3), 6.99–7.80 (4-CH_3Ph), 7.50 (s, 1 H, OH), 8.90 (br s, 1 H, NH)
2h[b]	2.53–2.73 (m, 1 H, H-4), 3.22 (OCH_3), 6.89–7.96 (4-FPh)[f]
2h′	2.53–2.73 (m, 2 H, H-4), 3.18 (OCH_3), 6.89–7.96 (4-FPh)[f]

[a] The minor isomer of each compound was designated with a prime. Compounds **2a**,**c**–**f**,**h** were registered at 400 MHz and **2b**,**g** were registered at 200 MHz.
[b] Spectrum registered in $CDCl_3$–TMS.
[c] Spectrum registered in DMSO-d_6–TMS.
[d] H-4 and H-4′ may be interconverted.
[e] Coupling constant could not be measured.
[f] Signal of OH and NH superimposed with the aromatic hydrogens.

Table 3 ^{13}C NMR Spectral Data of Compounds **2a**–**h**

Compound	^{13}C NMR, δ, J_{CF} (Hz)[a]
2a[b]	14.87 (CH_3), 37.80 (C-4), 67.04 (OCH_2), 75.20 (C-3), 84.31 (q, $^2J_{CF}$ = 34, C-5), 123.38 (q, $^1J_{CF}$ = 284, CF_3), 175.39 (C-2)
2a′	14.72 (CH_3), 36.30 (C-4), 66.35 (OCH_2), 74.34 (C-3), 84.22 (q, $^2J_{CF}$ = 34, C-5), 123.78 (q, $^1J_{CF}$ = 285, CF_3), 176.82 (C-2)
2b[c]	22.80 (CH_3), 40.50 (C-4), 51.29 (OCH_3), 78.50 (C-3), 82.63 (q, $^2J_{CF}$ = 32, C-5), 124.22 (q, $^1J_{CF}$ = 285, CF_3), 175.09 (C-2)
2b′	23.40 (CH_3), 39.65 (C-4), 50.90 (OCH_3), 78.09 (C-3), 82.54 (q, $^2J_{CF}$ = 33, C-5), 122.95 (q, $^1J_{CF}$ = 285, CF_3), 175.86 (C-2)
2c[c]	11.72 (CH_3), 15.28 (CH_3), 40.52 (C-4), 67.21 (OCH_2), 80.73 (C-3), 92.50 (q, $^2J_{CF}$ = 32, C-5), 122.84 (q, $^1J_{CF}$ = 290, CF_3), 174.66 (C-2)
2c′	8.14 (CH_3), 15.07 (CH_3), 38.38 (C-4), 67.65 (OCH_2), 77.55 (C-3), 83.45 (q, $^2J_{CF}$ = 31, C-5), 123.66 (q, $^1J_{CF}$ = 285, CF_3), 173.60 (C-2)
2d[c]	26.80 (CH_2), 42.91 (C-4), 68.03 (OCH_2), 79.98 (C-3), 84.58 (q, $^2J_{CF}$ = 32, C-5), 124.32 (q, $^1J_{CF}$ = 287, CF_3), 173.09 (C-2)
2e[b]	21.97 (CH_2), 24.77 (CH_2), 36.56 (C-4), 63.77 (OCH_2), 75.89 (C-3), 85.24 (q, $^2J_{CF}$ = 32, C-5), 124.45 (q, $^1J_{CF}$ = 287, CF_3), 172.69 (C-2)
2e′	19.70 (CH_2), 25.72 (CH_2), 44.72 (C-4), 68.77 (OCH_2), 72.83 (C-3), 83.06 (q, $^2J_{CF}$ = 32, C-5), 123.48 (q, $^1J_{CF}$ = 285, CF_3), 172.47 (C-2)
2f[b]	43.81 (C-4), 52.33 (OCH_3), 82.13 (C-3), 84.47 (q, $^2J_{CF}$ = 33, C-5), 123.42 (q, $^1J_{CF}$ = 286, CF_3), 126–130 (Ph), 170.53 (C-2)
2f′	40.80 (C-4), 51.58 (OCH_3), 79.12 (C-3), 83.02 (q, $^2J_{CF}$ = 33, C-5), 123.90 (q, $^1J_{CF}$ = 286, CF_3), 126–130 (Ph), 173.33 (C-2)
2g[c]	20.58 (CH_3), 44.12 (C-4), 52.13 (OCH_3), 81.53 (C-3), 83.95 (q, $^2J_{CF}$ = 33, C-5), 119.83 (q, $^1J_{CF}$ = 285, CF_3), 125.50–138.82 ($PhCH_3$), 170.43 (C-2)
2g′	20.29 (CH_3), 44.12 (C-4), 51.40 (OCH_3), 81.53 (C-3), 82.39 (q, $^2J_{CF}$ = 33, C-5), 119.83 (q, $^1J_{CF}$ = 285, CF_3), 125.50–138.82 ($PhCH_3$), 173.32 (C-2)
2h[b]	44.72 (C-4), 52.93 (OCH_3), 81.77 (C-3), 83.02 (q, $^2J_{CF}$ = 33, C-5), 123.43 (q, $^1J_{CF}$ = 285, CF_3), 114.84–134.34 (PhF), 162.22 (d, $^1J_{CF}$ = 247, CF), 173.56 (C-2).
2h′	41.19 (C-4), 52.09 (OCH_3), 81.77 (C-3), 83.02 (q, $^2J_{CF}$ = 33, C-5), 123.43 (q, $^1J_{CF}$ = 285, CF_3), 114.84–134.34 (PhF), 162.22 (d, $^1J_{CF}$ = 247, CF), 173.56 (C-2)

[a] The minor isomer of each compound was designated with a prime. Compounds **2a**,**c**–**f**,**h** were registered at 100 MHz and **2b**,**g** were registered at 50 MHz.
[b] Spectrum registered in $CDCl_3$/TMS.
[c] Spectrum registered in DMSO-d_6/TMS.

(4) Kruchok, I. S.; Gerus, I. I.; Kukhar, V. P. *Tetrahedron* **2000**, *56*, 6533.
(5) Andrew, R. J.; Mellor, J. M.; Reid, G. *Tetrahedron* **2000**, *56*, 7255.
(6) Andrew, R. J.; Mellor, J. M. *Tetrahedron* **2000**, *56*, 7267.
(7) Coles, J. S.; Mellor, J. M.; El-Sagheer, A. F.; Salem, E. E.-D.; Metwally, R. N. *Tetrahedron* **2000**, *56*, 10057.
(8) Chi, K.-W.; Furin, G. G.; Gatilov, Y. V.; Bagryanskay, I. Y.; Zhuzhgov, E. L. *J. Fluorine Chem.* **2000**, *103*, 105.
(9) Krasovsky, A. L.; Nenajdenko, V. G.; Balenkova, E. S. *Tetrahedron* **2001**, *57*, 201.
(10) Nenajdenko, V. G.; Statsuk, A. V.; Balenkova, E. S. *Tetrahedron* **2000**, *56*, 6549.
(11) Nenajdenko, V. G.; Sanin, A. V.; Balenkova, E. S. *Molecules* **1997**, *2*, 186.
(12) Pierce, M. E.; Parsons, R. L.; Radesca, L. A.; Lo, Y. S.; Silverman, S.; Moore, J. R.; Islam, Q.; Choudhury, A.; Fortunak, J. M. D.; Nguyen, D.; Luo, C.; Morgan, S. J.; Davis, W. P.; Confalone, P. N.; Chen, C.; Tillyer, R. D.; Frey, L.; Tan, L.; Xu, F.; Zhao, D.; Thompson, A. S.; Corley, E. G.; Grobowski, E. J. J.; Reamer, R.; Reider, P. J. *J. Org. Chem.* **1998**, *63*, 8536.
(13) Welch, J. T. *Tetrahedron* **1987**, *43*, 3123.
(14) Zanatta, N.; Rosa, L. S.; Loro, E.; Bonacorso, H. G.; Martins, M. A. P. *J. Fluorine Chem.* **2001**, *107*, 149.
(15) Miller, R. D.; Goelitz, P. *J. Org. Chem.* **1981**, *46*, 1366.
(16) Tamura, Y.; Maeda, H.; Akai, S.; Ishiyama, K.; Ishibashi, H. *Tetrahedron Lett.* **1981**, *22*, 4301.
(17) Kochlar, K. S.; Pinnick, H. W. *J. Org. Chem.* **1984**, *49*, 3222.
(18) Vedejs, E.; Meier, G. P. *Tetrahedron Lett.* **1979**, 4185.
(19) Stamm, H. *Chem. Ber.* **1966**, *99*, 556.
(20) Stevens, R. V.; Christensen, C. G.; Edmonson, W. L.; Kaplan, M.; Reid, E. B.; Wentland, M. P. *J. Am. Chem. Soc.* **1971**, *93*, 6629.
(21) Bertele, E.; Boss, H.; Dunitz, J. D.; Elsinger, F.; Eschenmoser, A.; Felner, I.; Grib, H. P.; Gschwend, H.; Meyer, E. F.; Pesaro, M.; Scheffold, R. *Angew. Chem., Int. Ed. Engl.* **1964**, *76*, 393.
(22) Cheng, X. M. In *Annual Reports in Medicinal Chemistry*, Vol. 29; Bristol, J. A., Ed.; Academic Press: New York, **1994**, 43.
(23) Lui, N.; Baasner, B. Ger. Offen. DE 4 441 984, **1996**; *Chem. Abstr*. **1996**, *125*, 114474n.
(24) Lui, N.; Negele, M.; Baasner, B.; Jonge, M.; Schuurman, T. Ger. Offen. DE 4 433 266, **1996**; *Chem. Abstr*. **1996**, *124*, 343105q.
(25) Colla, A.; Clar, G.; Martins, M. A. P.; Krimmer, S.; Fischer, P. *Synthesis* **1991**, 483.
(26) Martins, M. A. P.; Zoch, A. N.; Flores, A. F. C.; Clar, G.; Zanatta, N.; Bonacorso, H. G. *J. Heterocycl. Chem.* **1995**, *32*, 739.
(27) Martins, M. A. P.; Siqueira, G.; Bastos, G. P.; Zanatta, N. *J. Heterocycl. Chem.* **1996**, *33*, 1223.
(28) Martins, M. A. P.; Freitag, R.; Flores, A. F. C.; Zanatta, N. *J. Heterocycl. Chem.* **1996**, *33*, 1619.
(29) Martins, M. A. P.; Flores, A. F. C.; Bastos, G. P.; Sinhorin, A.; Bonacorso, H. G.; Zanatta, N. *Tetrahedron Lett.* **2000**, *41*, 293.
(30) Martins, M. A. P.; Freitag, R.; Flores, A. F. C.; Zanatta, N. *J. Heterocycl. Chem.* **1995**, *32*, 1491.
(31) Bonacorso, H. G.; Oliveira, M. R.; Wentz, A. P.; Oliveira, A. B.; Hörner, M.; Zanatta, N.; Martins, M. A. P. *Tetrahedron* **1999**, *55*, 345.
(32) Pacholski, I. L.; Blanco, I.; Zanatta, N.; Martins, M. A. P. *J. Braz. Chem. Soc.* **1992**, *2*, 118.

(33) Zanatta, N.; Madruga, C. C.; Marisco, P. C.; Flores, D. C.; Bonacorso, H. G.; Martins, M. A. P. *J. Heterocycl. Chem.* **2000**, *37*, 1213.
(34) Zanatta, N.; Madruga, C. C.; Clerice, E.; Martins, M. A. P. *J. Heterocycl. Chem.* **1995**, *32*, 735.
(35) Zanatta, N.; Cortelini, M. F.; Carpes, M. J. S.; Bonacorso, H. G.; Martins, M. A. P. *J. Heterocycl. Chem.* **1997**, *34*, 509.
(36) Zanatta, N.; Fagundes, M. B.; Hellensohn, R.; Martins, M. A. P.; Bonacorso, H. G. *J. Heterocycl. Chem.* **1998**, *35*, 451.
(37) Bonacorso, H. G.; Bittencourt, S. R. T.; Wastowski, A. D.; Wentz, A. P.; Zanatta, N.; Martins, M. A. P. *Tetrahedron Lett.* **1996**, *37*, 9155.
(38) Bonacorso, H. G.; Bittencourt, S. R. T.; Wastowski, A. D.; Wentz, A. P.; Zanatta, N.; Martins, M. A. P. *J. Heterocycl. Chem.* **1999**, *36*, 45.
(39) Zanatta, N.; Barichello, R.; Bonacorso, H. G.; Martins, M. A. P. *Synthesis* **1999**, 765.
(40) Lee, H.-S.; Kim, K. *Tetrahedron Lett.* **1998**, *39*, 6895.
(41) Sanders, J. K. M.; Hunter, B. K. *Modern NMR Spectroscopy: A Guide for Chemists*, 2nd ed.; Oxford: New York, **1994**, 97–153.
(42) Martins, M. A. P.; Siqueira, G. M.; Flores, A. F. C.; Clar, G.; Zanatta, N. *Química Nova* **1994**, *17*, 24.