Formation of Cyclobutylidenepyrazolines by Methanolysis of 6-(2,3,3-Trifluorocyclobutenyl)-4,5-diazaspiro[2.4]hept-4-ene

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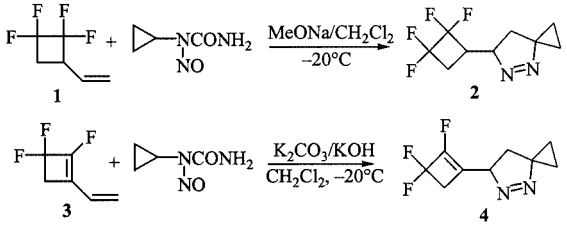
The reaction of 6-(2,3,3-trifluorocyclobutenyl)-4,5-diazaspiro[2.4]hept-4-ene with NaOMe in MeOH results in a mixture of isomeric (6*E*)- and (6*Z*)-6-(2-fluoro-3,3-dimethoxycyclobutylidene)-4,5-diazaspiro[2.4]hept-4-ene due to the formal substitution of methoxy groups for two geminal fluorine atoms. Both of the isomers selectively add acetyl chloride at the azo-olefin unit to give 4-acetyl-6-(1-chloro-2-fluoro-3,3-dimethoxycyclobutyl)-4,5-diazaspiro[2.4]hept-4-ene as the *trans*-isomer in greater than 95% yield.

Introduction

Previously[1,2] we reported that the interaction of 3-vinyl-1,1,2,2-tetrafluorocyclobutane (**1**) with diazocyclopropane, which was generated in situ by the decomposition of *N*-cyclopropyl-*N*-nitrosourea upon reaction with NaOMe at −20 °C, afforded a diastereomeric mixture of 6-(1,1,2,2-tetrafluorocyclobutyl)-4,5-diazaspiro[2.4]hept-4-enes (**2**) as a result of 1,3-dipolar cycloaddition. In this case, minor products (4−6%) were formed along with the main pyrazolines **2**, which were formed with a total yield of 48% (isomer ratio 2.3:1). According to preliminary data,[1,2] the structure of these minor products corresponds to the partial formal substitution of methoxy groups for fluorine atoms upon reaction with NaOMe. The nucleophilic substitution of fluorine atoms in fluorinated cyclobutanes has been reported previously;[3−5] these processes were described as addition-elimination processes. In our case, methoxy derivatives could be formed via either the partial dehydrofluorination of parent olefin **1** into 1-vinyl-2,3,3-trifluorocyclobutene (**3**) and its conversion into 6-(2,3,3-trifluoro-1-cyclobutenyl)-4,5-diazaspiro[2.4]hept-4-ene (**4**) by reaction with diazocyclopropane or the direct dehydrofluorination of tetrafluoride **2** into pyrazoline **4**, and further methanolysis of the latter. Indeed, we found previously[1] that unsaturated compound **3** reacts with diazocyclopropane, generated in situ by the decomposition of *N*-cyclopropyl-*N*-nitrosourea upon reaction with a mixture of KOH and K_2CO_3.



The aim of this work was to study the structure of the methoxy derivatives, to analyze the mechanisms of their formation, and to examine their reactions with acetyl chloride.

Results and Discussion

Initially, we found that the action of an excess of NaOMe in MeOH on compound **2** at −20 °C (i.e., under conditions[1] that were used for preparing pyrazoline **2** from olefin **1**) did not result in the formation of new products, such as methoxy derivatives, which were detected upon reaction with in situ generated diazocyclopropane on vinyltetrafluorocyclobutane (**1**; the reaction mixture was monitored by TLC for 2 h). In contrast, the reaction of olefin **1** with an equimolar amount of NaOMe in CD_2Cl_2 at −20 °C gave vinyltrifluorocyclobutene (**3**; approx. 30% after 1.5 h), which was detected in the reaction mixture by ^1H NMR spectroscopy. Compound **3** was found to react with diazocyclopropane, which was generated by the decomposition of *N*-cyclopropyl-*N*-nitrosourea with an excess of NaOMe

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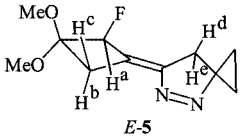
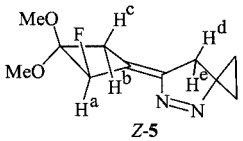
in MeOH (in contrast to the decomposition with a KOH/K_2CO_3 mixture), to afford only methoxy derivatives **5**. The ^{1}H NMR spectra of the obtained compounds were identical to those of the by-products of the reaction between compound **1** and diazocyclopropane in the presence of NaOMe. Thus, in the latter case, the formation of methoxy derivatives in small amounts resulted from partial conversion of tetrafluorovinylcyclobutane (**1**) into trifluorovinylcyclobutene (**3**). The subsequent addition of in situ generated diazocyclopropane to **3** gave pyrazoline **4**, which can be readily converted into methoxy derivatives upon reaction with NaOMe/MeOH.

To support this conclusion, we performed the methanolysis (−20 °C, 2 h) of pyrazoline **4** upon reaction with NaOMe in a CH_2Cl_2/MeOH mixture. The TLC separation of the reaction mixture on Al_2O_3 (eluent: heptane/diethyl ether, 4:5) afforded two individual compounds in an approximately equimolar ratio with a total yield of about 60%. Both of the separated compounds exhibited identical peaks due to molecular ions (M^+ 226) in the mass spectra and very similar sets of signals in the ^{1}H and ^{13}C NMR spectra. These data correspond to the products of formal substitution of methoxy groups for two geminal fluorine atoms, that is, to two isomeric forms of 6-(2-fluoro-3,3-dimethoxycyclobutylidene)-4,5-diazaspiro[2.4]hept-4-enes (**5**), in which the 4,5-diazaspiro[2.4]hept-4-ene unit remains unchanged. The ^{1}H and ^{19}F NMR spectra unambiguously indicate the occurrence of CHF units in both of the isomers ($^2J_{H,F}$ = 54−55 Hz), and ^{13}C NMR spectroscopic data suggest the presence of a tetrasubstituted double bond, whose signals appear as doublets at δ = 127−128 ppm ($^2J_{C,F}$ = 13−14 Hz) and δ = 157−160 ppm ($^3J_{C,F}$ = 2.7−3.4 Hz).

An additional NOESY study of these isomers revealed an interaction between the protons of the CH_2 group of the pyrazoline ring and the corresponding protons of the cyclopropane moiety. One of the isomers exhibits a proton-proton interaction of the CH_2 groups of the cyclobutane and pyrazoline moieties, whereas the other isomer exhibits an interaction of a proton of the CH_2 group of the pyrazoline ring with the methyne proton of the CHF unit. These results confirm that the above compounds are the *E*- and *Z*-isomers of spiro compounds **5**.



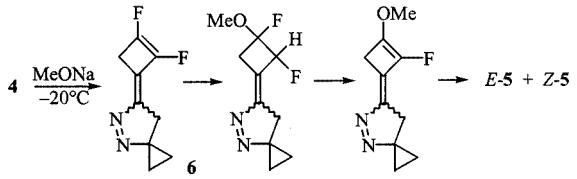
E-**5**



Z-**5**

Note that the H^d and H^e protons at C-7 atom in isomer *Z*-**5** have identical chemical shifts, whereas the signals of the corresponding protons in isomer *E*-**5** differ by 0.19 ppm. The only signal in the ^{19}F NMR spectrum of pyrazoline *E*-**5**, along with the geminal spin-spin coupling constant ($J_{H,F}$ = 54.3 Hz), allowed us to identify two other spin-spin coupling constants (J = 6.3−6.8 Hz), whereas the corresponding signal of the *Z*-isomer appears as a broadened doublet with unresolved constants.

It is likely that the initial step of the formation of spiro compounds **5** was the 1,4-dehydrohalogenation of pyrazoline **4** upon reaction with NaOMe followed by the addition of MeOH to the intermediate diene **6**. Next, the second molecule of HF was eliminated, and a MeOH molecule was added. The exocyclic double bond was retained in the reaction products, providing higher stability due to conjugation between the C=C bond and the azo group.



A tendency for the conversion of alkenyl derivatives of 4,5-diazaspiro[2.4]hept-4-ene into isomeric alkylidene-4,5-diazaspiro[2.4]hept-4-enes has been observed previously;[6] the reaction of in situ generated diazocyclopropane with 2-methylbutadiene is a good example.

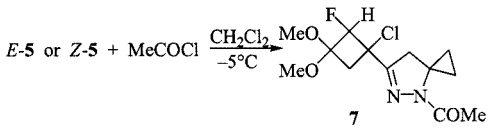
The fact that pyrazoline **2** did not undergo dehydrohalogenation to pyrazoline **4** under the above reaction conditions (NaOMe, −20 °C) suggests that the methyne protons in pyrazoline **2** are less labile than the allyl proton at C(3) of the pyrazoline ring in compound **4**.

Note that the action of NaOMe/MeOH on 3-(2,3,3-trifluorocyclobut-1-enyl)-1-pyrazoline, which was prepared previously[1] by the 1,3-dipolar cycloaddition of diazomethane to vinyltrifluorocyclobutene **3**, at −20 °C resulted in the intense resinification of the reaction mixture, and we failed to identify the expected products of the substitution of methoxy groups for fluorine atoms. This result is indicative of a specific effect of a spirocyclopropane unit on the stability of the resulting cyclobutylidenepyrazolines **5**, which remain unchanged at 0 °C for several months.

Thus, the action of NaOMe in MeOH on compound **4** was accompanied not only by double-bond migration to a position conjugated to the azo group but also formal substitution of methoxy groups for two geminal fluorine atoms. The isomerization of 1-pyrazoline into 2-pyrazoline was not observed under these conditions.

The occurrence of, on the one hand, a spiro-joined cyclopropane unit and, on the other hand, an exo-olefinic double bond in the vicinity of the azo group of compound **5** gave impetus to a study of its acylation. Previously,[7] it was found that the addition of AcCl to the azocyclopropane system of 4,5-diazaspiro[2.4]hept-4-enes readily occurred to give 1,5-addition products in high yields. In contrast, the addition of AcCl to the individual isomers *E*-**5** and *Z*-**5** occurred almost exclusively at the azo-olefin unit to afford the same product, *trans*-4-acetyl-6-(1-chloro-2-fluoro-3,3-dimethoxycyclobutyl)-4,5-diazaspiro[2.4]hept-4-ene (**7**), in greater than 95% yield. The observed reaction path results from a much higher polarizability of the conjugated azo-olefin group than that of the azo-cyclopropane group. It is likely that the chloride anion is added at the early stages of the generation of a carbocationic center in the cyclobutane

ring because the formation of carbocation deprotonation products would be expected in the case of the full generation of a carbocation.



7

The characteristic spin-spin coupling constant ($J_{H,F}$) of 50.2 Hz in the ^1H and ^{19}F NMR spectra suggests the presence of a CHF unit in spiro compound **7**. Signals due to cyclopropane protons oriented toward nitrogen atoms are shifted downfield with respect to those of initial diazaspiroheptenes **5** ($\Delta\delta \approx 0.3$ ppm) because of deshielding by the acetyl group. Methoxy groups manifest themselves as two signals, one of which exhibits a rarely occurring spin-spin splitting (doublet with $J = 1.3$ Hz), which is due to spatial interaction with a fluorine atom. It is likely that this interaction results from a change in the cyclobutane ring geometry upon the introduction of a chlorine atom.

Finally, the structure of compound **7** and, particularly, the trans arrangement of the halogen atoms in the cyclobutane moiety was proved from X-ray diffraction data: for example, the N(1)−N(2) and N(2)−N(3) bond lengths are 0.139 and 0.127 nm, respectively, and the dihedral angle F−C−C−Cl is 102°.

Thus, methanolysis of fluoro-containing cyclobutenyl 4,5-diazaspiro[2.4]hept-4-enes easily gives rise to a new structure in which the spirocyclopropane unit and exo-olefinic double bond are in the vicinity of the azo group. Acylation of compounds with this fragment takes place selectively at the azo-olefin unit.

Conclusion

Reaction of 6-(2,3,3-trifluorocyclobutenyl)-4,5-diazaspiro[2.4]hept-4-ene (**4)** with NaOMe resulted in a mixture of isomeric (6*E*)- and (6*Z*)-6-(2-fluoro-3,3-dimethoxycyclobutylidene)-4,5-diazaspiro[2.4]hept-4-enes (**5**) due to the formal substitution of two geminal fluorine atoms by methoxy groups. This result is indicative of the specific effect of a spirocyclopropane unit on the stability of the resulting spiro compounds **5**. Acylation of compound **5** takes place selectively at the azo-olefin unit to afford the same product, *trans*-4-acetyl-6-(1-chloro-2-fluoro-3,3-dimethoxycyclobutyl)-4,5-diazaspiro[2.4]hept-4-ene (**7**). The reaction path results from a much higher polarizability of the conjugated azo-olefin group than that of the azocyclopropane group.

Experimental Section

General Remarks: The ^1H, ^{13}C and ^{19}F NMR spectra, ^{13}C COSY/proton and NOESY decoupled experiments were recorded with Bruker AC-200 (^1H, 200 MHz, ^{19}F, 188.3 MHz and ^{13}C, 50.3 MHz), Bruker AM-300 (^1H, 300 MHz and ^{13}C, 75.5 MHz) and Bruker DRX-500 (^1H, 500 MHz and ^{13}C, 125.8 MHz). Mass spectra were obtained using a Finnigan MAT INCOS-50 instrument (EI, 70 eV, direct injection). The preparative TLC was carried out on 20 × 20 cm plates with a nonfixed layer of neutral Al_2O_3; analytical TLC was performed on plates with Al_2O_3 GF_{254} (Chemapol). Starting compounds: 2,3,3-trifluoro-1-vinylcyclobutene (**3**), 6-(2,2,3,3-tetrafluorocyclobutyl)-4,5-diazaspiro[2.4]hept-4-ene (**2**), 6-(2,3,3-trifluoro-1-cyclobutenyl)-4,5-diazaspiro[2.4]hept-4-ene (**4**) and 3-(2,3,3-trifluorocyclobut-1-enyl)-1-pyrazoline were prepared by known methods;[1] *N*-cyclopropyl-*N*-nitrosourea was obtained according to a known procedure.[8]

All solvents used were of commercial quality and were additionally distilled.

Procedure for the Preparation of (6*E*)- and (6*Z*)-6-(2-Fluoro-3,3-dimethoxycyclobutylidene)-4,5-diazaspiro[2.4]hept-4-enes [(*E*)- and (*Z*)-5]. a) From 3 and *N*-Cyclopropyl-*N*-nitrosourea upon Reaction with NaOMe in MeOH: A solution of NaOMe (270 mg, 5.0 mmol) in 1.0 mL of MeOH was added whilst stirring during 5 min to a mixture of 2,3,3-trifluoro-1-vinylcyclobutene (**3**; 940 mg, 7.0 mmol) and *N*-cyclopropyl-*N*-nitrosourea (478 mg, 3.7 mmol) in 4 mL of CH_2Cl_2 at −20 °C and the mixture was stirred for 0.5 h at this temperature. Then, a solution of NaOMe (163 mg, 3.0 mmol) in 0.6 mL of MeOH was added and the mixture was stirred for 0.5 h at −20 °C. After warming to room temperature the reaction mixture was passed through a thin layer of Al_2O_3 (1.0 cm) and washed with CH_2Cl_2. The solvent was evaporated in vacuo and the resulting oily yellow liquid (530 mg) was separated by preparative TLC (two portions, hexane/diethyl ether, 4:5). Two fractions (214 mg, $R_f = 0.54$ and 205 mg, $R_f = 0.47$), corresponding to *E*- and *Z*-isomers of spiro compounds **5** were obtained in a total yield of about 50%.

b) From 4 with NaOMe/MeOH: A solution of NaOMe (21.6 mg, 0.4 mmol) in 0.08 mL of MeOH was added at −20 °C to a solution of diazaspiroheptene **4** (40.5 mg, 0.2 mmol) in 0.4 mL of CD_2Cl_2, and the mixture was shaken and kept at −20 °C (reaction was controlled by ^1H NMR spectroscopy). After 2 h the signals of the starting spiro compound had practically disappeared and signals of the isomeric compounds ***E*-5** and ***Z*-5** (ca. 1:1) appeared. The reaction mixture was then passed through a thin layer of Al_2O_3 (0.3 cm), washed with CH_2Cl_2 and the solvent was evaporated. The residue was separated by TLC on Al_2O_3 with hexane/diethyl ether (4:5) as eluent, and two fractions (13.7 mg and 13.4 mg), corresponding to the *E*- and *Z*-isomers of spiro compounds **5**, were obtained in a total yield of about 60%.

Compound (*E*)-5: ^1H NMR (500 MHz, $CDCl_3$, 25 °C): δ = 1.20 (m, 2 H, 1-H and 2-H directed away from the N atom of the heterocycle), 1.81 (m, 2 H, 1-H and 2-H oriented toward the N atom of the heterocycle), 2.48 (m, $^2J = 17.8$ Hz, 1 H, H^e), 2.68 (m, $^2J = 17.8$ Hz, 1 H, H^d), 2.89 (m, 1 H, H^b), 3.35 and 3.41 (two s, 2 × 3 H, 2 OMe), 3.47 (m, 1 H, H^c), 5.47 (m, $^2J_{H,F} = 55.7$ Hz, 1 H, H^a) ppm. ^{13}C NMR (50.3 MHz, $CDCl_3$, 25 °C): δ = 15.7 and 15.8 (C-1 and C-2), 28.0 (C-7), 35.3 (d, $^3J_{C,F} = 9.3$ Hz, C-4′), 50.2 and 50.3 (2 OMe), 68.4 (C-3), 91.7 (d, $^1J_{C,F} = 228.0$ Hz, C-2′), 101.8 (d, $^2J_{C,F} = 16.6$ Hz, C-3′), 128.1 (d, $^2J_{C,F} = 13.3$ Hz, C-1′), 157.5 (d, $^3J_{C,F} = 2.7$ Hz, C-6) ppm. ^{19}F NMR (188.3 MHz, $CDCl_3$, CCl_3F, 25 °C): δ = −190.9 (br. d, $^2J_{H,F} = 55.7$ Hz, CHF) ppm. EIMS (probe, 70 eV): *m/z* (%) = 226 $[M]^+$ (2), 211 $[M - Me]^+$ (30), 195 $[M - OMe]^+$ (38), 179 $[M - MeOH - Me]^+$ (26), 167 $[M - OMe - N_2]^+$ (35), 151 $[M - MeOH - Me - N_2]^+$ (55), 131 $[M - MeOH - Me - N_2 - HF]^+$ (70), 123 (25), 109 (31), 84 (40), 77 (48), 59 (85), 51 (48), 39 $[C_3H_3]^+$ (100). $C_{11}H_{15}FN_2O_2$ (226.1): calcd. C 58.40, H 6.68; found C 58.81, H 6.79.

Compound (*Z*)-5: ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 1.17 (m, 2 H, 1-H and 2-H directed away from the N atom of the heterocycle), 1.82 (m, 2 H, 1-H and 2-H oriented toward the N atom of the heterocycle), 2.43 (m, 2 H, H^d and H^e), 2.70 (m, 1 H, H^b), 2.91 (m, 1 H, H^c), 3.33 and 3.41 (two s, 2 × 3 H, 2 OMe), 5.75 (m, $^2J_{H,F}$ = 54.3 Hz, 1 H, H^a) ppm. ^{13}C NMR (75.5 MHz, $CDCl_3$, 25 °C): δ = 15.7 and 15.8 (C-1 and C-2), 28.6 (C-7), 35.9 (d, $^3J_{C,F}$ = 7.30 Hz, C-4′), 50.1 and 50.6 (2 OMe), 67.8 (C-3), 91.6 (d, $^1J_{C,F}$ = 226.0 Hz, C-2′), 101.7 (d, $^2J_{C,F}$ = 17.8 Hz, C-3′), 128.5 (d, $^2J_{C,F}$ = 13.3 Hz, C-1′), 159.5 (d, $^3J_{C,F}$ = 2.7 Hz, C-6) ppm. ^{19}F NMR (188.3 MHz,. $CDCl_3$, CCl_3F, 25 °C): δ = −181.0 (ddd, $^2J_{H,F}$ = 54.3, ^4J = 6.8 Hz; ^4J = 6.3 Hz, CHF) ppm. EIMS (probe, 70 eV): *m*/*z* (%) = 226 $[M]^+$ (2), 211 $[M - Me]^+$ (30), 195 $[M - OMe]^+$ (38), 179 $[M - MeOH - Me]^+$ (26), 167 $[M - MeO - N_2]^+$ (35), 151 $[M - MeOH - Me - N_2]^+$ (55), 131 $[M - MeOH - Me - N_2 - HF]^+$ (70), 123 (25), 109 (31), 84 (40), 77 (48), 59 (85), 51 (48), 39 $[C_3H_3]^+$ (100). $C_{11}H_{15}FN_2O_2$ (226.1): calcd. C 58.40, H 6.68; found C 58.75, H 6.82.

Reaction of 1 with NaOMe in MeOH: A solution of NaOMe (21.6 mg, 0.4 mmol) in 0.08 mL of MeOH was added at −20 °C to a solution of compound **1** (61 mg, 0.4 mmol) in 0.5 mL of CD_2Cl_2. The mixture was shaken and kept for 1.5 h at this temperature. With the help of ^{1}H NMR spectrum at −20 °C it was found that the reaction mixture consisted of initial compound **1** and the dehydrofluorination product **4** in a ratio of about 2.3:1.

Attempted Reaction of 3-(2,3,3-Trifluorocyclobut-1-enyl)-1-pyrazoline with NaOMe in MeOH: A solution of NaOMe (216 mg, 4 mmol) in 0.8 mL of MeOH was added at −25 °C to a solution of 3-(2,3,3-trifluorocyclobut-1-enyl)-1-pyrazoline[1] (353 mg, 2 mmol) in 1 mL of CH_2Cl_2. The mixture was shaken for 15 min at this temperature. Then, the temperature was increased to 20 °C, the reaction mixture was passed through a thin layer of Al_2O_3 and was concentrated by evaporation of the solvents in vacuo with 1 mL of CCl_4. The TLC and ^{1}H NMR spectroscopic data showed a strong resination of the mixture, and methoxy derivatives analogous to isomeric compounds **5** were not detected.

4-Acetyl-6-(1-chloro-2-fluoro-3,3-dimethoxycyclobutyl)-4,5-diazaspiro[2.4]hept-4-ene (7): A solution of MeCOCl (13.5 mg, 0.17 mmol) in 0.6 mL of CH_2Cl_2 was added at −5 °C during 5 min to a solution of compound *Z*-**5** (or *E*-**5**; 38.4 mg, 0.17 mmol) in 1.0 mL of CH_2Cl_2 and the mixture was stirred for 30 min. Then, the solvent was evaporated in vacuo and the residue (51 mg) was found to be spiro compound **7** in about 96% purity by ^{1}H NMR spectroscopy. TLC showed R_f = 0.70 on SiO_2 with hexane/diethyl ether (4:5) as eluent, m.p. 56−58 °C. ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 0.66 (m, 2 H, 1-H and 2-H directed away from the N atom of the heterocycle), 2.11 (m, 2 H, 1-H and 2-H oriented toward the N atom of the heterocycle), 2.24 (c, 3 H, COMe), 2.29 (ddd, ^2J = 13.5, $^4J_{H,F}$ = 3.1, ^4J = 1.9 Hz, 1 H, 4′-H), 3.08 (dd, ^2J = 18.0, J = 1.9 Hz, 1 H, 7-H), 3.28 (d, ^2J = 18.0 Hz, 1 H, 7-H), 3.29 (s, 3 H, OMe), 3.30 (d, J = 1.3 Hz, 3 H, OMe), 3.69 (ddd, ^2J = 13.5, $^4J_{H,F}$ = 12.0, ^4J = 1.4 Hz, 1 H, 4′-H), 5.16 (ddd, $^2J_{H,F}$ = 50.2, ^4J = 1.9, ^4J = 1.4 Hz, 1 H, 2′-H) ppm. ^{13}C NMR (75.5 MHz, $CDCl_3$, 25 °C): δ = 11.2 and 11.3 (C-1 and C-2), 23.2 (Me), 38.1 (d, J = 10 Hz, C-4′), 42.8 (d, J = 4.2 Hz, C-7), 45.2 (C-3), 49.1 and 50.2 (2 OMe), 60.2 (d, J = 23 Hz, C-1′), 98.6 (d, J = 246 Hz, C-2′), 99.5 (d, J = 18 Hz, C-3′), 151.3 (C-6), 169.4 (CO) ppm. ^{19}F NMR (188.3 MHz, $CDCl_3$, CCl_3F, 25 °C): δ = −187.6 (br. dd, $^2J_{H,F}$ = 50.2, J = 12.0 Hz, CHF) ppm. EIMS (probe, 70 eV): *m*/*z* (%) = 304 and 306 $[M]^+$ (8 and 3), 269 $[M - Cl]^+$ (30), 237 $[M - Cl - MeOH]^+$ (10), 236 $[M - HCl - MeOH]^+$ (21), 226 $[M - Cl - MeCO]^+$ (16), 195 (27), 194 $[M - Cl - MeOH - MeCO]^+$ (39), 193 (18), 179 (18), 43 $[COMe]^+$ (100). $C_{13}H_{18}ClFN_2O_3$ (304.5): calcd. C 51.24, H 5.95; found C 51.61, H 6.13.

CCDC-191223 (**7**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge at www.ccdc.cam.ac.uk/conts/retrieving.html [or from the Cambridge Crystallographic Data Centre, 12, Union Road, Cambridge CB2 1EZ, UK; fax: (internat.) +44−1223/336-033; E-mail: deposit@ccdc.cam.ac.uk].

Acknowledgments

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