Synthesis of New Fluorinated 1,5-Benzoxazepine Derivatives

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Received April 29, 1997

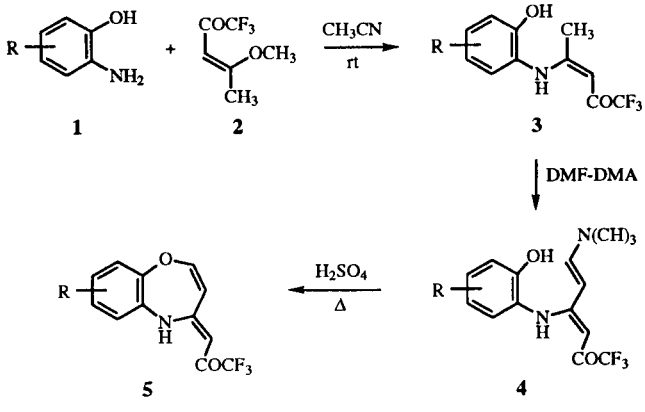
A simple approach to the fluorinated 1,5-benzoxazepine ring system is described. By reacting commercially accessible aminophenols **1** and the trifluoroacetylvinyl ether **2**, high yields of enaminones **3** were obtained. Functionalization of methyl group of compounds **3** gave rise to dieneamines **4** that were cyclized in acidic environment to benzoxazepine derivatives **5**.

J. Heterocyclic Chem., **34**, 1347 (1997).

In recent years, increasing attention has been directed toward benzoxazepine derivatives due to their useful pharmacological activities as angiotensin receptor modulators [1], sedatives [2] and analgesics [3].

As the introduction of a fluorinated moiety onto a bioactive molecule generally improves its pharmacological properties, the development of simple methods for the synthesis of fluorinated compounds has became one of the goals in organic chemistry. In connection with our studies on fluorinated heterocycles [4,5] we became interested in the synthesis and study of benzoxazepines bearing a trifluoromethyl moiety. In the present paper a useful approach to the preparation of new trifluoroacetylmethylene-1,5-benzoxazepines is described, starting from commercially available *o*-aminophenols **1** and 4-methoxy-1,1,1-trifluoro-3-penten-2-one **2**.

Scheme



1 **2** **3** **4** **5**

The fact that nucleophilic *O-N* exchange at olefinic carbon atoms activated by a trifluoroacetyl group proceeds easily under mild conditions [6,7], high yields of the expected enaminones **3** were obtained, when equimolecular amounts of enolether **2** and aminophenol **1** were allowed to react at room temperature in acetonitrile solution.

Complete characterization of compounds **3** is given in Tables 1 and 2. The ir spectra show the stretching absorption near 3200-3450 cm^{-1} due to NH and OH as well as that at 1620-1635 cm^{-1} for the conjugated carbonyl group. The ^1H nmr spectra of compounds **3** show two deuterium oxide exchangeable signals at 12.41-12.11 and 9.93-11.91 ppm that can be attributed to OH and NH groups and

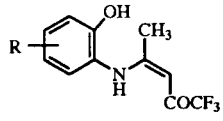
Table 1

Physical and Analytical Data of Enaminones **3**

Compound No.	R	Yield (%)	mp (°C) (Recrystallization Solvent)	Formula	Analysis (%) Calcd./Found C	H	N
3a	H	84	163-164 (Isopropyl ether)	$C_{11}H_{10}F_3NO_2$	53.88 53.83	4.11 4.09	5.71 5.78
3b	5-CH_3	93	175-176 (Benzene)	$C_{12}H_{12}F_3NO_2$	55.60 55.65	4.67 4.66	5.40 5.43
3c	4-CH_3	97	182-183 (Isopropyl ether)	$C_{12}H_{12}F_3NO_2$	55.60 55.54	4.67 4.68	5.40 5.38
3d	5-Cl	98	186-187 (Isopropyl ether)	$C_{11}H_9ClF_3NO_2$	47.24 47.18	3.24 3.25	5.01 4.97
3e	5-NO_2	91	214-215 (Benzene)	$C_{11}H_9F_3N_2O_4$	45.52 45.47	3.12 3.13	9.65 9.70
3f	4-NO_2	89	207-208 (2-Propanol)	$C_{11}H_9F_3N_2O_4$	45.52 45.57	3.12 3.11	9.65 9.62

Table 2

IR and ^1H NMR Data of Enaminones **3**



Compound No.	IR	^1H NMR
3a	3300, 1620, 1585	2.12 (s, 3H, CH_3), 5.58 (s, 1H, CH), 6.80, 6.96, 7.12, 7.28 (m, 4H, Ar), 10.24 (s, 1H, NH), 12.32 (s, 1H, OH)
3b	3320, 1620, 1575	2.07 (s, 3H, CH_3), 2.13 (s, 3H, CH_3), 5.52 (s, 1H, CH), 6.77, 6.87, 7.03 (m, 3H, Ar), 9.93 (s, 1H, NH), 12.24 (s, 1H, OH)
3c	3210, 1615, 1570	2.08 (s, 3H, CH_3), 2.19 (s, 3H, CH_3), 5.54 (s, 1H, CH), 6.62, 6.74, 7.12 (m, 3H, Ar), 10.11 (s, 1H, NH), 12.25 (s, 1H, OH)
3d	3330, 1620, 1580	2.13 (s, 3H, CH_3), 5.59 (s, 1H, CH), 6.94, 7.17, 7.40 (m, 3H, Ar), 10.55 (s, 1H, NH), 12.20 (s, 1H, OH)
3e	3240, 1610, 1590	2.20 (s, 3H, CH_3), 5.65 (s, 1H, CH), 7.08, 7.30, 8.05, 8.20 (m, 3H, Ar), 11.91 (s, 1H, NH), 12.24 (s, 1H, OH)
3f	3280, 1630, 1590	2.28 (s, 3H, CH_3), 5.63 (s, 1H, CH), 7.50, 7.66 (m, 3H, Ar), 11.33 (s, 1H, NH), 12.41 (s, 1H, OH)

single signals at ~2 ppm for the methyl and at ~5.5 ppm for the olefinic protons. We can therefore affirm that only a geometrical isomer is present, in the *Z* configuration with intramolecular hydrogen bonding as indicated by the downfield NH resonance.

Further functionalization of enaminones **3** was achieved by heating with an excess of *N,N*-dimethylformamide dimethyl acetal. Thus the corresponding dieneamines **4**, in which the presence of a dimethylamino group should increase the reactivity, were easily obtained. In the reactions of compounds **3e** and **3f**, after diluition of the reaction mixture with water, dieneamines **4e** and **4f** were obtained as the main products. When the basic solutions were acidified further product separated which were identified as the corresponding *N*-methyl derivatives **4g** and **4h**.

The structure of compounds **4a-f** was assigned from the ^1H nmr spectra: the AB system with doublets at 4.83-5.11 and 7.82-8.04 ppm ($J_{5,6}$ = 12.7), the single signal at (5.7 ppm for H-3 and the much deshielded peak of amino proton by hydrogen bonding between NH and CO, account for the presence of a single geometrical isomer with 3,4 (*Z*)-5,6 (*E*) configuration.

Cyclization of the resulting adducts **4a-f** with aqueous sulfuric acid, at 70°, occured smootly between C-6 and the phenolic group to give the fluorinated 1,5-benzoxazepine derivatives **5** in good yields.

Structural assignments were made on the basis of analytical and spectroscopic data. The ir spectrum of compound **5a** shows a broad signal at 2400-2500 cm^{-1} and a sharp absorbance band at 1630 cm^{-1}. In the ^1H nmr spectrum, a deuterium oxide exchangeable signal at 10.42 ppm due to NH and a singlet at 6.69 ppm due to the exocyclic proton are observed. Moreover an AB system with J = 7.3 Hz at 7.64 and 6.28 ppm for H-2 and H-3 respectively was also present.

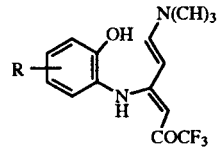
Table 3

Physical and Analytical Data of Dieneamines **4**

Compound No.	R	Yield (%)	mp (°C) (Recrystallization Solvent)	Formula	Analysis (%) Calcd./Found C	H	N
4a	H	64	226-228 (Acetonitrile)	$C_{14}H_{15}F_3N_2O_2$	56.00 56.08	5.04 5.09	9.33 9.23
4b	5-CH_3	46	224-225 (2-Propanol)	$C_{15}H_{17}F_3N_2O_2$	57.31 57.36	5.45 5.44	8.91 8.86
4c	4-CH_3	76	214-215 (2-Propanol)	$C_{15}H_{17}F_3N_2O_2$	57.31 57.27	5.45 5.46	8.91 8.94
4d	5-Cl	69	204-205 (2-Propanol)	$C_{14}H_{14}ClF_3N_2O_2$	50.24 50.30	4.22 4.23	8.37 8.34
4e	5-NO_2	56	216-217 (Ethanol)	$C_{14}H_{14}F_3N_3O_4$	48.70 48.76	4.09 4.13	12.17 12.21
4f	4-NO_2	63	245-246 (Ethanol)	$C_{14}H_{14}F_3N_3O_4$	48.70 48.63	4.09 4.06	12.17 12.13

Table 4

IR and ^1H NMR Data of Dieneamines **4**



Compound No.	IR	^1H NMR
4a	3120, 1630, 1570	2.66 (s, 3H, CH_3), 3.11 (s, 3H, CH_3), 4.85 (d, J = 12.7, 1H, H-5), 5.68 (s, 1H, H-3), 6.77, 6.93, 7.05 7.23 (m, 4H, Ar), 7.82 (d, J = 12.7, 1H, H-6), 9.94 (s, 1H, NH), 12.40 (s, 1H, OH)
4b	3200, 1620, 1570	2.17 (s, 3H, CH_3), 2.67 (s, 3H, CH_3), 3.11 (s, 3H, CH_3), 4.84 (d, J = 12.7, 1H, H-5), 5. 66 (s, 1H, H-3), 6.83, 7.02 (m, 3H, Ar), 7.82 (d, J = 12.7, 1H, H-6), 9.64 (s, 1H, NH), 12.36 (s, 1H, OH)
4c	3040, 1620, 1570	2.22 (s, 3H, CH_3), 2.68 (s, 3H, CH_3), 3.12 (s, 3H, CH_3), 4.83 (d, J = 12.7, 1H, H-5), 5.67 (s, 1H, H-3), 6.63, 6.75, 7.09 (m, 3H, Ar), 7.82 (d, J = 12.7, 1H, H-6), 9.80 (s, 1H, NH), 12.34 (s, 1H, OH)
4d	3120, 1620, 1560	2.74 (s, 3H, CH_3), 3.16 (s, 3H, CH_3), 4.85 (d, J = 12.7, 1H, H-5), 5.72 (s, 1H, H-3), 6.94, 7.11, 7.36 (m, 3H, Ar), 7.90 (d, J = 12.7, 1H, H-6), 10.27 (s, 1H, NH), 12.41 (s, 1H, OH)
4e	1630, 1600, 1570	2.74 (s, 3H, CH_3), 3.16 (s, 3H, CH_3), 4.99 (d, J = 12.7, 1H, H-5), 5.75 (s, 1H, H-3), 7.06-8.16 (m, 4H, Ar + H-6), 11.68 (s, 1H, NH), 12.52 (s, 1H, OH)
4f	3100, 1625, 1550	2.82 (s, 3H, CH_3), 3.18 (s, 3H, CH_3), 5.11 (d, J = 12.2, 1H, H-5), 5.77 (s, 1H, H-3),7.59, 7.68, 7.85 (m, 3H, Ar), 8.04 (d, J = 12.2, 1H, H-6), 11.14 (brs, 1H, NH), 12.60 (s, 1H, OH)

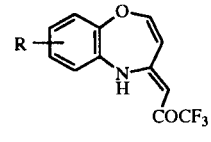
Table 5

Physical and Analytical Data of 1,5-Benzoxazepines **5**

Compound No.	R	Yield (%)	mp (°C) (Recrystallization Solvent)	Formula	Analysis (%) Calcd./Found C	H	N
5a	H	71	206-207 (Isopropyl ether)	$C_{12}H_8F_3NO_2$	56.47 56.52	3.16 3.15	5.49 5.43
5b	7-CH_3	56	177-178 (2-Propanol)	$C_{13}H_{10}F_3NO_2$	57.99 58.03	3.74 3.73	5.20 5.17
5c	8-CH_3	53	204-205 (2-Propanol)	$C_{13}H_{10}F_3NO_2$	57.99 57.93	3.74 3.75	5.20 5.23
5d	7-Cl	51	220-222 (2-Propanol)	$C_{12}H_7ClF_3NO_2$	49.76 49.85	2.44 2.43	4.84 4.87
5e	7-NO_2	55	269-270 (Ethanol)	$C_{12}H_7F_3N_2O_4$	48.01 48.08	2.35 2.36	9.33 9.37
5f	8-NO_2	49	284-285 (2-Propanol)	$C_{12}H_7F_3N_2O_4$	48.01 47.95	2.35 2.34	9.33 9.28

Table 6

Ir and ^1H nmr Data of 1,5-Benzoxazepines **5**



Compound No.	IR	^1H NMR
5a	3080, 2500, 1630, 1555	6.28 (d, J = 7.3, 1H, H-3), 6.69 (s, 1H, H-1'), 6.86 - 7.66 (m, 5H, Ph + H-2), 10.42 (s, 1H deuterium oxide exchangeable)
5b	3060, 2560, 1635, 1560	2.20 (s, 3H, CH_3), 6.28 (d, J = 6.3, 1H, H-3), 6.69 (s, 1H, H-1'), 6.87 - 7.66 (m, 4H, Ph + H-2), 10.14 (s, 1H deuterium oxide exchangeable)
5c	3060, 2550, 1635, 1560	2.24 (s, 3H, CH_3), 6.25 (d, J = 7.3, 1H, H-3), 6.78 (s, 1H, H-1'), 6.65 - 7.59 (m, 4H, Ph + H-2), 10.25 (s, 1H deuterium oxide exchangeable)
5d	3060, 2460, 1635, 1545	6.28 (d, J = 6.3, 1H, H-3), 6.68 (s, 1H, H-1'), 6.98 - 7.68 (m, 4H, Ph + H-2), 10.77 (s, 1H deuterium oxide exchangeable)

Table 6 (continued)

Compound No.	IR	^{1}H NMR
5e	3080, 2540, 1635, 1600, 1550	6.34 (d, J = 7.8, 1H, H-3), 6.74 (s, 1H, H-1'), 7.18 - 8.55 (m, 4H, Ph + H-2), 12.19 (brs, 1H deuterium oxide exchangeable)
5f	3050, 2550, 1630, 1560	6.33 (d, J = 7.3, 1H, H-3), 6.74 (s, 1H, H-1'), 7.70 - 7.76 (m, 4H, Ph + H-2), 11.60 (s, 1H deuterium oxide exchangeable)

In conclusion, we have developed an effective route to obtain new fluorinated 1,5-benzoxazepines. Furthemore, we suggest that the enaminones **3** and dieneamines **4** could be usefully employed in synthetic procedures to other heterocyclic systems.

EXPERIMENTAL

Melting points were determined on a Kofler hot stage and are uncorrected. The ir spectra were obtained in Nujol with a Perkin-Elmer 398 spectrophotometer. The ^{1}H nmr spectra were recorded in hexadeuteriodimethyl sulfoxide solution on a Varian Unity 300 spectrometer, the chemical shifts are given in δ (ppm) downfield from the internal standard hexamethyldisiloxane and coupling costants in Hz. Elemental analyses were carried out with a Carlo Erba Model 1106 Elemental Analyzer. Trifluoroacetylvinyl ether **2** was prepared by a previously described procedure [6].

General Procedure for the Preparation of 4-(2-Hydroxyarylamino)-1,1,1-trifluoro-3-penten-2-ones **3**.

A solution of *o*-aminophenol **1** (10 mmoles) and enol ether **2** (1.68 g, 10 mmoles) in dry acetonitrile (20 ml) was stirred at room temperature for 24 hours. The reaction mixture was then evaporated to dryness in *vacuo* and the residue collected and crystallized to give enaminones **3** (Tables 1 and 2).

General Procedure for the Preparation of 6-Dimethylamino-4-(2-hydroxyarylamino)-1,1,1-trifluoro-3,5-hexadien-2-ones **4**.

A mixture of compound **3** (5 mmoles) and *N,N*-dimethylformamide dimethyl acetal (2 ml, 15 mmoles) was stirred at 75-80° for 4 hours. After the rection mixture was allowed to stand overnigth at room temperature, water was added and the precipitate was filtered, dried and crystallized to give the dieneamines **4**. In the cases of enaminones **3e** and **3f** by acidification of the aqueous solution dieneamines **4g** and **4h** were also obtained respectively.

6-Dimethylamino-4-[methyl(2-hydroxy-5-nitrophenyl)amino]-1,1,1-trifluoro-3,5-hexadien-2-one (**4g**).

This compound was obtained in 36% yield, mp 248-250° (from acetonitrile); ^{1}H nmr: δ 2.74 (s, 3H, CH_3), 3.16 (s, 3H, CH_3), 3.94 (s, 3H, CH_3), 4.99 (d, J = 12.7, 1H, H-5), 5.76 (s, 1H, H-3), 7.32, 8.08, 8.11 (m, 3H, Ar), 7.98 (d, J = 12.7, 1H, H-6), 12.61 (s, 1H, OH); ir: 3140, 1625, 1595, 1500 cm^{-1}.

Anal. Calcd. for $C_{15}H_{16}F_3N_3O_4$: C, 50.14; H, 4.49; N, 11.69. Found: C, 50.19; H, 4.48; N, 11.72.

6-Dimethylamino-4-[methyl(2-hydroxy-4-nitrophenyl)amino]-1,1,1-trifluoro-3,5-hexadien-2-one (**4h**).

This compound was obtained in 21% yield, mp 214-215° (from ethanol); ^{1}H nmr: δ 2.83 (s, 3H, CH_3), 3.19 (s, 3H, CH_3), 3.96 (s, 3H, CH_3), 5.13 (d, J = 12.7, 1H, H-5), 5.81 (s, 1H, H-3), 7.70, 7.85 (m, 3H, Ar), 8.05 (d, J = 12.7, 1H, H-6), 12.63 (s, 1H, OH); ir: 1625, 1595, 1570 cm^{-1}.

Anal. Calcd. for $C_{15}H_{16}F_3N_3O_4$: C, 50.14; H, 4.49; N, 11.69. Found: C, 50.10; H, 4.48; N, 11.66.

General Procedure for the Preparation of 4,5-Dihydro-4-(trifluoroacetylmethylene)-1,5-benzoxazepines **5**.

A mixture of dieneamine **4a-f** (2 mmoles) in 5 ml of 6*M* sulfuric acid was stirred at 70° for 1.5 hours. After cooling, 10 ml of water was added and the mixture was neutralized with 10% sodium hydroxide solution. The precipitate was then filtered, dried and crystallized to give 1,5-benzoxazepines **5**.

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