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SYNTHESIS OF 1,5-BENZODIAZEPINE HETEROCYCLES CONTAINING A TRIFLUOROMETHYL GROUP

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2,3-Dihydro-1,5-benzodiazepines containing a trifluoromethyl group were obtained by the reaction of α,β-unsaturated ketones $CF_3COCH=CR^1R^2$ with o-phenylenediamine.

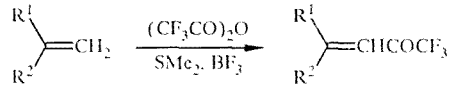
The introduction of fluorine into organic molecules often makes major changes in their properties and leads to the appearance of new, valuable qualities, in particular, the high physiological activity of fluorinated compounds [1, 2]. A considerable number of investigations have been devoted to the synthesis of heterocycles containing the trifluoromethyl group because many of them show physiological activity (trifluorothymidine and triftazin are widely used as medicines). Heterocycles of the benzodiazepine series have already found wide application in medical practice as tranquilizers, anticonvulsants, and carcinostatics [3].

Despite the fact that the reaction of α,β-unsaturated ketones with bifunctional nucleophiles has been widely used for the synthesis of heterocycles, this method has not been developed for the case of α,β-unsaturated ketones with a CF_3 group. There is the single example of a synthesis using acetylenic ketones obtained by the trifluoroacetylation of lithiated organic compounds [4]. This lack is apparently due to the low availability of α,β-unsaturated ketones with perfluorinated radicals.

The α,β-unsaturated ketones $R_fCOCH=CHR$, containing both a highly electrophillic double bond and an extremely active carbonyl group in the molecule, are extremely valuable synthons for the preparation of various fluorine-containing compounds. A promising method for the preparation of these ketones is the direct electrophillic perfluoroacylation of unsaturated hydrocarbons. However, up until recently, there was no such a synthetic method.

Trifluoroacetic anhydride reacts with alkenes containing an active double bond: eneamines [5], vinyl ethers [6], and vinyl thioethers [7]. However, trifluoroacetic anhydride does not react with unactivated alkenes and dienes because of the insufficient electrophillicity of the reagents used. Attempts to activate trifluoroacetic anhydride with Lewis acids leads to the cationic polymerization of the starting substrates.

Recently, we proposed a method for the direct electrophillic perfluorination of alkenes based on the use of trifluoroacetic anhydride (or other anhydrides of perfluorocarboxylic acids) in the presence of a complex of dimethyl sulfide with boron trifluoride [8]. This method allows one to prepare unsaturated ketones containing a perfluorinated substituent [9-12].



We have studied the reaction of trifluoroacetylenic derivatives of styrene, methylenecyclobutane, and methyleneadamantane, I-III, prepared previously [12], with o-phenylenediamine. The reaction was carried out in ethanol with boiling for several hours. As a result, we obtained substituted 2,3-dihydro-1,5-benzodiazepines IV-VI:

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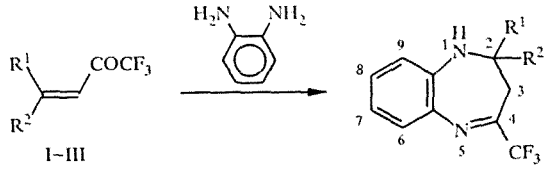

I-III

IV(86%), V(81%), VI(75%)

I, IV R^1=H, R^2=Ph; II, V R^1=R^2= $-CH_2CH_2CH_2-$; III, VI R^1=R^2=

In the PMR spectra of these compounds a system of signals appears in the 7.3-6.6 ppm region that is characteristic of the benzene nucleus. In the spectrum of compound IV there is a doublet of doublets at 4.66 ppm corresponding to the signal of 2-H, and signals of the 3-H protons at 2.96 (d.d.d.) and 2.83 (d.d.) ppm. In the PMR spectra of compounds V and VI, singlets are found at 2.78 and 2.72 ppm, respectively, corresponding to the 3-H protons.

The ^{13}C-NMR spectra of the 1,5-benzodiazepines contained the characteristic signal of the CF_3 group, a quadruplet at 120-125 ppm with $^1J_{C-F}$ of 280-300 Hz, and a signal from the $C_{(4)}$ carbon atom, a quadruplet at 151-155 ppm with $^2J_{C-F}$ of 33.0-33.7 Hz. The presence of the latter signal in the spectrum confirms the presence of a C=N double bond in the structure of the compounds prepared.

It is known that in many cases the trifluoromethyl group stabilizes a geminal amino alcohol group and no dehydration with the formation of a double bond occurs [13]. In this reaction, however, dehydration occurred in all cases. This may be explained by the favorable conjugation of the aromatic system of the benzene ring with C=N bond being formed.

Thus the reaction of unsaturated ketones containing perfluoroacyl group with o-phenylenediamine has been studied. On the basis of this reaction a method has been developed for preparing trifluoromethyl-containing heterocycles of the 1,5-benzodiazepine series.

EXPERIMENTAL

The ^{1}H-NMR spectra were recorded on Varian VXR-400 spectrometers in $CDCl_3$. The ^{13}C-NMR were recorded on Varian VXR-400 instruments (operating frequency 100 MHz), HMDS internal standard, chemical shifts given relative to TMS with a precision of 0.01 ppm. The chromato-mass spectral analyses were carried out on a Finnegan MAT-112S spectrometer, 80 eV ionization energy, 50 × 0.25 mm column with an SBP-5 immobile phase. The IR spectra were obtained on a UR-20 spectrometer in mineral oil. The TLC analyses were carried out on Silufol UV-254 plates developed with slightly acidic $KMnO_4$ solution and iodine vapor.

The elemental analyses for C, H, and N agreed with the calculated values. The α,β-unsaturated ketones I-III with a CF_3 group were synthesized by the method in [12].

1,5-Benzodiazepines (general method). To a solution of 0.01 moles of the appropriate ketone in 25 ml of ethanol is added 0.015 moles of o-phenylenediamine. The mixture is boiled for 6-9 h (monitored by TLC), 5 ml of water then added, and the mixture allowed to stand and crystallize. The benzodiazepine (IV-VI) that separates out is recrystallized from aqueous ethanol.

2,3-Dihydro-4-trifluoromethyl-2-phenyl-1H-1,5-benzodiazepine (IV, $C_{16}H_{13}F_3N_2$). Yield 86%, mp 123-124°C. ^{1}H-NMR spectrum ($CDCl_3$): 7.36 (1H, d.d., ^4J = 1.58, ^3J = 7.96 Hz, 6-H); 7.34-7.23 (5H, m, C_6H_5); 7.06 (1H, d.d.d., ^4J = 1.58, ^3J = 8.03, ^3J = 7.96 Hz, 7-H); 6.86 (1H, d.d.d., ^4J = 1.36, ^3J = 8.40, ^3J = 7.96 Hz, 8-H); 6.65 (1H, d.d., ^4J = 1.36, ^3J = 8.03 Hz, 9-H); 4.66 (1H, d.d., ^3J = 2.71, ^3J = 8.63 Hz, 2-H); 4.12 (1H, ex.b.s, NH); 2.96 (1H, d.d.d., ^3J = 2.71, ^2J = 15.59, $^4J_{H-NH}$ = 1.35 Hz, 3e-H); 2.83 ppm (1H, d.d., ^3J = 8.63, ^2J = 15.59 Hz, 3a-H). ^{13}C-NMR spectrum ($CDCl_3$): 151.30 (q, $^2J_{C-F}$ = 33.68 Hz, $C_{(4)}$); 141.13 (C_{arom}, C_6H_5); 138.69 ($C_{(9a)}$); 130.99 ($C_{(6)}$ or $C_{(8)}$); 130.25 ($C_{(5a)}$); 127.55 ($C_{(8)}$ or $C_{(6)}$); 127.23 ($2C_{arom}$, C_6H_5); 126.54 (C_{arom}, C_6H_5); 124.12 ($2C_{arom}$, C_6H_5); 118.39 (q, $^1J_{C-F}$ = 277.39 Hz, CF_3); 118.19 ($C_{(7)}$ or $C_{(9)}$); 117.53 ($C_{(7)}$ or $C_{(9)}$); 61.54 ($C_{(2)}$); 37.02 ($C_{(3)}$). Mass spectrum (*m/z*, (I, %)): 290 (7, $(M)^+$), 213 (25); 186 (10), 104 (100). IR spectrum: 3410 (NH); 1610 (C=N); 1000-1300 cm^{-1} (CF_3).

2,3-Dihydro-2,2-trimethylene-4-trifluoromethyl-1H-1,5-benzodiazepine (V, $C_{13}H_{13}F_3N_2$). Yield, 81%, mp 60-61°C. ^{1}H-NMR spectrum ($CDCl_3$): 7.32 (1H, d.d., ^4J = 1.10, ^3J = 7.81 Hz, 6-H); 7.04 (1H, t.d., ^4J = 1.39, ^3J = 7.81 Hz, 7-H); 6.79 (1H, t.d., ^4J = 1.10, ^3J = 7.81 Hz, 8-H); 6.60 (1H, d.d., ^4J = 1.39, ^3J = 7.81 Hz, 9-H); 4.21 (1H, ex.b.s., NH); 2.78 (2H, s, 3-H); 2.10-2.00 (4H, m, $2CH_{2cyclobut.}$); 1.85-1.70 ppm (2H, m, $CH_{2cyclobut.}$). ^{13}C-NMR spectrum ($CDCl_3$): 152.40 (q, J_{C-F} = 33.65 Hz, $C_{(4)}$); 139.21 ($C_{(9a)}$); 133.18 ($C_{(6)}$ of $C_{(8)}$); 131.63 ($C_{(5a)}$); 129.51 ($C_{(8)}$ or $C_{(6)}$); 120.45 (q, $^1J_{C-F}$ = 277.38 Hz, CF_3); 110.48 ($C_{(7)}$ or $C_{(9)}$); 119.21 ($C_{(7)}$ or $C_{(9)}$); 62.66 ($C_{(2)}$); 39.90 ($C_{(3)}$); 37.82 ($2CH_{2cyclobut.}$); 12.88 ppm ($CH_{2cyclobut.}$). IR spectrum: 3300-3500 (NH), 1610 (C=N), 1000-1300 cm^{-1} (CF_3).

2′,3′-Dihydro-4′-trifluoromethylspiro(adamantane-2,2′-1H-1,5-benzodiaxepine) (VI, $C_{19}H_{21}F_3N_2$). Yield, 75%, mp 78-79°C. ^{1}H-NMR spectrum ($CDCl_3$): 7.30 (1H, d.d., ^4J = 1.40, ^3J = 7.62 Hz, 6-H); 7.07 (1H, t.d., ^4J = 1.35, ^3J = 7.62 Hz, 7-H); 6.91 (1H, t.d., ^4J = 1.40, ^3J = 7.62 Hz, 8-H); 6.76 (1H, d.d., ^4J = 1.35, ^3J = 7.62 Hz, 9-H); 4.39 (1H, ex.b.s., NH); 2.72 (2H, s, 3-H); 2.05-1.60 ppm (14H, m, adamant. group). ^{13}C-NMR spectrum ($CDCl_3$): 155.20 (q, $^2J_{C-F}$ = 33.06 Hz, $C_{(4)}$); 138.79 ($C_{(9a)}$); 135.78 ($C_{(5a)}$); 131.08 ($C_{(6)}$ or $C_{(8)}$); 128.96 ($C_{(8)}$ or $C_{(6)}$); 121.56 ($C_{(7)}$ or $C_{(9)}$); 121.22 ($C_{(7)}$ or $C_{(9)}$); 120.52 (q, $^1J_{C-F}$ = 277.56 Hz, CF_3); 69.81 ($C_{(2)}$); 38.55 ($C_{(3)}$); 37.56 (CH_2); 36.22 (2CH); 33.83 ($2CH_2$); 32.90 ($2CH_2$); 27.15 (CH); 26.93 ppm (CH)(adamant. group). IR spectrum: 3450 (NH), 1610 (C=N), 1000-1300 cm^{-1} (CF_3).

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