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α-Aminoazoles in the Synthesis of Heterocycles: V.* Synthesis of Azolo[1,5-*a*]pyrimidines from 2-Ethoxyvinyl Trifluoromethyl Ketones and 2,2-Diethoxyvinyl Trifluoromethyl Ketone

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Abstract—A procedure was proposed for the synthesis of 7-trifluoromethylazolo[1,5-*a*]pyrimidines by reactions of 2-ethoxyvinyl trifluoromethyl ketones and 2,2-diethoxyvinyl trifluoromethyl ketone with 5(3)-aminoazoles. The reactions occurred under mild conditions, and the products were formed with high yield and regioselectivity.

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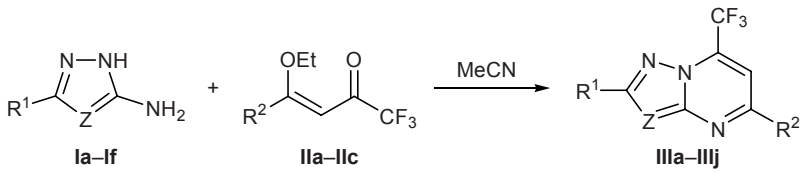
Functionally substituted pyrazolo[1,5-*a*]pyrimidines exhibit a broad spectrum of biological and pharmacological activity [2–5]. Some pyrazolo[1,5-*a*]-pyrimidines, namely Zaleplon, Indiplon, and Ocinaplon [6] that belong to non-benzodiazepine sedative and hypnotic agents, are used in medical practice. Therefore, studies in this field of synthetic organic chemistry continuously attract researchers' attention and imply both development of new procedures and modification of already known ones.

We previously proposed an effective regioselective method for the synthesis of 7-trifluoromethyl-substituted azolopyrimidines from trifluoroacetylvinyl ethers. The latter were also used as starting compounds in regioselective syntheses of trifluoromethyl-containing β-acylvinylamines [7–9], 2-trifluoromethylpyrazolo-[1,5-*a*]pyrimidines [10], pyrido[3,4-*b*]pyrimidines, and pyrazolo[3,4-*b*]pyridines [11]. Hojo et al. [8, 9] showed that O–N exchange follows vinylic substitution pattern (replacement of the alkoxy group by amino). It is known that introduction of a trifluoromethyl group into organic molecules often increases their lipophilicity and decreases toxicity, which could modify or enhance their biological activity [12].

In the present work we examined reactions of 4-ethoxy-1,1,1-trifluoropent-3-en-2-one (**IIa**), 4-ethoxy-1,1,1-trifluoro-4-phenylbut-3-en-2-one (**IIb**), and 4,4-diethoxy-1,1,1-trifluoropent-3-en-2-one (**IIc**) with 5(3)-aminopyrazoles **Ia**–**Ie** and 5-amino-1,2,4-triazole (**If**) (Scheme 1). The reactions occurred under mild conditions to give compounds **IIIa**–**IIIj** as the only products. It should be noted that the cyclocondensation of aminotriazole **If** with 1,1,1-trifluoromethyl-4-phenylbutane-2,4-dione was reported to afford a mixture of regioisomeric triazolopyrimidines [13]. Unlike known schemes for the introduction of an ethoxy group into

Scheme 1.

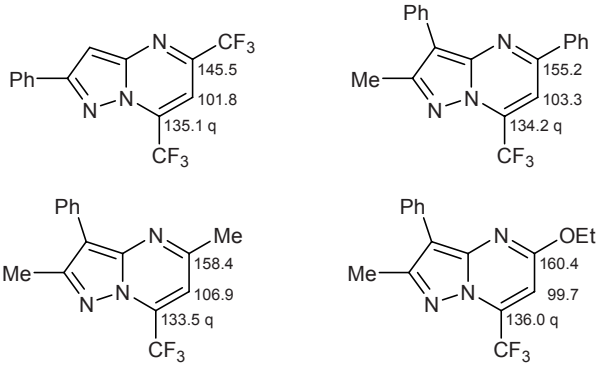


Ia–If **IIa–IIc** **IIIa–IIIj**

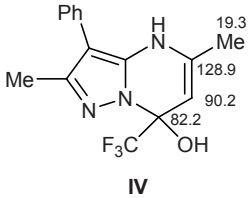
I, Z = CH, R^1 = Me (**a**), 4-ClC_6H_4 (**b**); Z = CPh, R^1 = Me (**c**); Z = CCN, R^1 = H (**d**); Z = CBr, R^1 = Me (**e**); Z = N, R^1 = H (**f**); **II**, R^2 = Me (**a**), Ph (**b**), EtO (**c**); **III**, Z = CH: R^1 = Me, R^2 = OEt (**a**); R^1 = 4-ClC_6H_4, R^2 = Me (**b**), Ph (**c**), EtO (**d**); Z = CPh, R^1 = R^2 = Me (**e**), Ph (**f**), EtO (**g**); Z = CCN, R^1 = H, R^2 = EtO (**h**); Z = CBr, R^1 = Me, R^2 = EtO (**i**); Z = N, R^1 = H, R^2 = Ph (**j**).

* For communication IV, see [1].

pyrazolopyrimidines [14–16], the proposed procedure ensures regioselective preparation of 5-ethoxy-7-trifluoromethylpyrazolopyrimidines **IIIa**–**IIIj** in one step. The ^{1}H and ^{13}C NMR spectra and physical constants of compounds **IIIb**, **IIIc**, **IIIe**, and **IIIf** coincided with those reported previously for the same compounds synthesized by reactions of 1,1,1-trifluoropentane-2,4-dione and 4,4,4-trifluoro-1-phenylbutane-1,3-dione with the corresponding aminoazoles [17]. The structure of compounds **IIIa**, **IIId**, and **IIIg**–**IIIi** was determined by comparing chemical shifts of the carbon atoms contiguous to the CF_3 group (δ_C 134–135 ppm, ^2J = 37–38 Hz) with those typical of pyrazolopyrimidines and pyrazolopyridines [δ_C 134 ppm, =**C**(CF_3)N=; 145.5 ppm [–**C**(CF_3)=N–] which were determined with account taken of long-range couplings [1, 17].



^{1}H and ^{13}C NMR monitoring of the reaction of 3(5)-methyl-4-phenyl-1*H*-pyrazol-5(3)-amine (**Ia**) with 4-ethoxy-1,1,1-trifluoropent-3-en-2-one (**IIa**) in $CDCl_3$ allowed us to detect only one intermediate product, 2,5-dimethyl-7-trifluoromethyl-3-phenyl-4,7-dihydropyrazolo[1,5-*a*]pyrimidin-7-ol (**IV**) having C^5=C^6 double bond in the pyrimidine ring; intermediate **IV** was gradually transformed into pyrazolo[1,5-*a*]pyrimidine (**IIIe**).

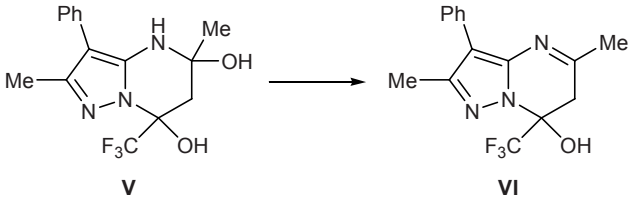


IV

^{1}H NMR spectrum, δ, ppm: 4.55 (6-H), 9.31 (4-H), 1.97 (5-CH_3)

On the other hand, the formation of pyrazolo[1,5-*a*]pyrimidines from 5(3)-aminopyrazoles and 1,1,1-trifluoropentane-2,4-dione was mediated by other species, stable diol **V** [18] and spectrally detectable 2,5-dimethyl-7-trifluoromethyl-3-phenyl-6,7-dihydropyrazolo[1,5-*a*]pyrimidin-7-ol (**VI**) having N^4=C^5 double bond [19] (Scheme 2). Compound **VI** is isomeric to intermediate **IV**.

Scheme 2.



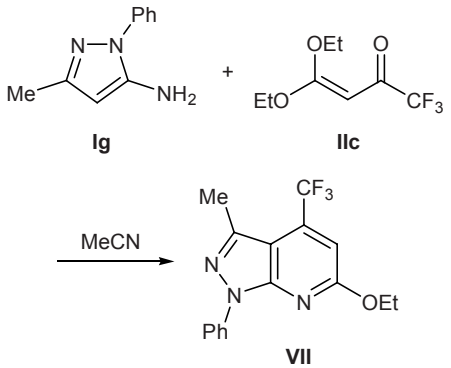
V **VI**

^{1}H NMR spectrum, δ, ppm: 2.25 and 2.42 (CH_2, *AB* system, J_{AB} = 13.7 Hz)

^{1}H NMR spectrum, δ, ppm: 2.95 and 3.20 (CH_2, AB *system*, J_{AB} = 18.9 Hz)

4,4-Diethoxy-1,1,1-trifluoropent-3-en-2-one (**IIc**) was brought into reaction with 3-methyl-1-phenyl-1*H*-pyrazol-5-amine (**Ig**) to obtain 4-trifluoromethylpyrazolo[3,4-*b*]pyridine (**VII**) (Scheme 3). The reaction was carried out both in acetonitrile and under the conditions reported in [11] (a mixture of toluene and acetic acid). Comparison of the ^{13}C chemical shifts for the **C**–CF_3 fragment in **VII** [δ_C 133.7 q (**C**^{4}CF_3), 160.0 ppm (C^6)] with those reported by us previously [1, 17] for trifluoromethyl-substituted pyrazolo[3,4-*b*]-pyridines {δ_C ~147.5 [**C**^{6}(CF_3)=N], ~132–133 ppm [**C**^{4}(CF_3)=C]} allowed us to unambiguously identify compound **VII** as 6-ethoxy-3-methyl-1-phenyl-4-trifluoromethylpyrazolo[3,4-*b*]pyridine. The ^{1}H and ^{13}C NMR spectra of **VII** coincided with the data given in [11] for the product which was erroneously assigned the structure of 6-ethoxy-3-methyl-1-phenyl-6-trifluoromethylpyrazolo[3,4-*b*]pyridine.

Scheme 3.



Ig **IIc**

VII

We can conclude that cyclocondensation of α-aminoazoles with 2-ethoxyvinyl trifluoromethyl

ketones and 2,2-diethoxyvinyl trifluoromethyl ketone occurs strictly regioselectively via replacement of the ethoxy group at the vinylic double bond by the amino group in the azole and reaction of the trifluoroacetyl group at the endocyclic nitrogen atom. Analogous scheme was proposed previously for the reaction of 3(5)-aminoazoles with trifluoromethyl-containing 1,3-diketones [16, 17].

Probable biological activity of the synthesized compounds was predicted using PASS program. This program makes it possible to predict 3300 kinds of biological activity with an average accuracy of ~95% on the basis of the structure of a chemical compound [20–22]. The results showed that pyrazolopyrimidines **III** could inhibit cyclic AMP phosphodiesterase, cyclic GMP phosphodiesterase, and cyclooxygenase, act as interleucin-5 antagonists, and exhibit analgesic, antiarthritic, and anxiolytic properties.

Thus we have proposed an efficient procedure for the synthesis of 5-alkoxy-7-trifluoromethylpyrazolo- and 5-alkoxy-7-trifluoromethyltriazolo[1,5-*a*]pyrimidines with high yield and regioselectivity and simple isolation of the products.

EXPERIMENTAL

The ^{1}H and ^{13}C NMR spectra were recorded at 22°C on a Bruker DPX-300 spectrometer (300.13 and 75.47 MHz, respectively); the chemical shifts were measured relative to the residual proton or carbon signals of deuterated solvents ($CDCl_3$, δ 7.28 ppm, δ_C 76.90 ppm; DMSO-d_6, δ 2.50 ppm, δ_C 39.50 ppm). 1*H*-1,2,4-Triazol-3-amine (**Ic**) was commercial product (Acros Organics). 5(3)-Aminopyrazoles **Ia** and **Ib** were synthesized according to the procedures reported in [23, 24]. Trifluoromethyl ketones **IIa**–**IIc** were prepared by trifluoroacetylation of the corresponding ketone diethyl acetals [7]. The physical constants and spectral parameters of pyrazolo[1,5-*a*]pyrimidines **IIIb**, **IIIc**, **IIIe**, and **IIIf** were consistent with published data [16].

Azolopyrimidines IIIa–IIIj (*general procedure***).** A solution of 5 mmol of 5(3)-aminoazole **Ia**–**Ie** and 5.5 mmol of trifluoromethyl ketone **IIa**–**IIc** in 10 ml of acetonitrile or chloroform was stirred for 1 h at room temperature and was then heated for 1 h under reflux. The solvent was distilled off under reduced pressure, and the residue was recrystallized from ethanol.

5-Ethoxy-2-methyl-7-trifluoromethylpyrazolo-[1,5-*a*]pyrimidine (IIIa). Yield 91%, mp 80°C. ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 1.41 t (3H, CH_3, J = 7.0 Hz), 2.42 s (3H, 2-CH_3), 4.42 q (2H, OCH_2, J = 7.0 Hz), 6.20 s (1H, 3-H), 6.72 s (1H, 6-H). ^{13}C NMR spectrum (DMSO-d_6), δ_C, ppm: 13.78 (CH_3), 14.10 (2-CH_3), 62.61 (OCH_2), 98.17 q (C^6, $^3J_{CF}$ = 4.0 Hz), 94.55 (C^3), 118.78 q (CF_3, J_{CF} = 274.3 Hz), 134.62 q (C^7, $^2J_{CF}$ = 36.9 Hz), 148.23 (C^{3a}), 154.87 (C^2), 162.12 (C^5). Found, %: C 48.72; H 4.27. $C_{10}H_{10}F_3N_3O$. Calculated, %: C 48.98; H 4.11.

2-(4-Chlorophenyl)-5-ethoxy-7-trifluoromethylpyrazolo[1,5-*a*]pyrimidine (IIId). Yield 93%, mp 176°C. ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 1.47 t (3H, CH_3, J = 6.5 Hz), 4.50 q (2H, OCH_2, J = 6.5 Hz), 6.69 s (1H), 6.72 s (1H), 7.42–7.94 m (4H, C_6H_4). ^{13}C NMR spectrum ($CDCl_3$), δ_C, ppm: 14.12 (CH_3), 63.39 (OCH_2), 92.54 (C^3), 99.66 q (C^6, $^3J_{CF}$ = 3.9 Hz), 119.10 q (CF_3, J_{CF} = 274.2 Hz), 135.97 q (C^7, $^2J_{CF}$ = 37.6 Hz), 149.46 (C^{3a}), 155.64 (C^2), 160.40 (C^5); 127.78, 128.88, 131.00, 134.94 (C_6H_4). Found, %: C 52.55; H 3.50. $C_{15}H_{11}ClF_3N_3O$. Calculated, %: C 52.72; H 3.24.

5-Ethoxy-2-methyl-3-phenyl-7-trifluoromethylpyrazolo[1,5-*a*]pyrimidine (IIIg). Yield 91%, mp 146°C. ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 1.45 t (3H, CH_3, J = 6.5 Hz), 2.65 s (3H, 2-CH_3), 4.49 q (2H, OCH_2, J = 6.5 Hz), 6.67 s (1H), 7.31–7.72 m (5H, Ph). ^{13}C NMR spectrum ($CDCl_3$), δ_C, ppm: 14.05 (CH_3), 14.56 (2-CH_3), 63.27 (OCH_2), 98.91 q (C^6, $^3J_{CF}$ = 3.9 Hz), 108.24 (C^3), 119.18 q (CF_3, J_{CF} = 274.9 Hz), 135.65 q (C^7, $^2J_{CF}$ = 36.6 Hz), 145.56 (C^{3a}), 153.70 (C^2), 160.32 (C^5), 126.21, 128.21, 128.50, 131.98 (Ph). Found, %: C 59.60; H 4.60. $C_{16}H_{14}F_3N_3O$. Calculated, %: C 59.81; H 4.39.

5-Ethoxy-7-trifluoromethylpyrazolo[1,5-*a*]pyrimidine-3-carbonitrile (IIIh). Yield 74%, mp 148°C. ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 1.47 t (3H, CH_3, J = 7.0 Hz), 4.60 q (2H, OCH_2, J = 7.0 Hz), 7.22 s (1H, 6-H), 8.54 s (1H, 2-H). ^{13}C NMR spectrum (DMSO-d_6), δ_C, ppm: 13.72 (CH_3), 64.46 (OCH_2), 81.17 (C^3), 102.86 q (C^6, $^3J_{CF}$ = 5.0 Hz), 111.20 (CN), 118.39 q (CF_3, J_{CF} = 275.3 Hz), 136.10 q (C^7, $^2J_{CF}$ = 38.9 Hz), 147.02 (C^{3a}), 150.30 (C^2), 162.99 (C^5). Found, %: C 46.61; H 2.86. $C_{10}H_7F_3N_4O$. Calculated, %: C 46.88; H 2.75.

3-Bromo-5-ethoxy-2-methyl-7-trifluoromethylpyrazolo[1,5-*a*]pyrimidine (IIIi). Yield 91%, mp 80°C. ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 1.43 t (3H, CH_3, J = 7.0 Hz), 2.40 s (3H, 2-CH_3), 4.52 q (2H, OCH_2, J = 7.0 Hz), 6.80 s (1H, 6-H). ^{13}C NMR spectrum (DMSO-d_6), δ_C, ppm: 12.74 (2-CH_3), 13.70 (CH_3), 63.17 (OCH_2), 83.04 (C^3), 99.62 q (C^6, $^3J_{CF}$ = 4.0 Hz), 118.48 q (CF_3, J_{CF} = 273.2 Hz), 135.12 q (C^7, $^2J_{CF}$ =

37.9 Hz), 144.70 (C^{3a}), 153.05 (C^2), 160.44 (C^5). Found, %: C 36.83; H 3.40. $C_{10}H_9BrF_3N_3O$. Calculated, %: C 37.06; H 2.80.

5-Phenyl-7-trifluoromethyl[1,2,4]triazolo[1,5-*a*]-pyrimidine (IIIj). Yield 79%, mp 143–146°C (sublimes). ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 8.38 s (1H, 6-H), 7.60–8.32 m (5H, C_6H_5), 8.80 s (1H, 2-H). ^{13}C NMR spectrum (DMSO-d_6), δ_C, ppm: 107.12 (C^6), 119.18 (CF_3, J_{CF} = 273.1 Hz), 134.60 (C^7, $^2J_{CF}$ = 38.5 Hz), 155.89 (C^2), 157.08 (C^{3a}), 161.59 (C^5); 128.26, 129.38, 132.34, 135.24 (C_6H_5). Found, %: C 54.63; H 2.82. $C_{12}H_7F_3N_4$. Calculated, %: C 54.55; H 2.67.

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