Synthesis of New Fluorine Containing Triazolo- and Tetrazolopyrimidines

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Abstract: The reaction of 1,1,1-trifluoro-4-(sulfonyl)-but-3-ene-2,2-dioles **1a**,**b** with corresponding aminoazoles was investigated. A new simple and efficient way for the regioselective synthesis of 5-CF_3 or 7-CF_3 triazolo- and tetrazolopyrimidines is described.

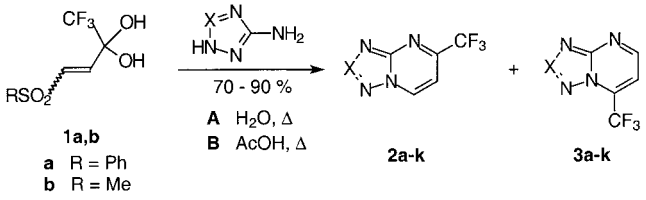
Key words: cycloaddition, heterocycles, triazolopyrimidine, tetrazolopyrimidine, sulfones

Fluorine containing heterocyclic compounds are a subject of continuous interest[1,2] due to their potent pharmacological properties. Some fluorinated pyrimidines were clinically evaluated as valuable anticancer agents.[3] It is known that incorporation of a fluorine atom or CF_3- group into bioactive molecule leads to increased lipid solubility and thereby enhances the rate of absorption and transport of that substance in vivo.[1]Also, many triazolopyrimidines have shown significant herbicidal,[4] fungicidal[5] activity and are well-known as new cardiovascular agents[6]. The reported methods for the synthesis of substituted azolopyrimidines usually involves cyclocondensation of aminotriazoles[5–12] or aminoterazoles[8,13] with three carbon 1,3-electrophilic fragments.[14] A drawback of these approaches is the formation of the mixture of isomers from the reaction of non-symmetrical systems with aminoazoles.[4,12] Paudler at al. obtained mixtures when treating triazolopyrimidine with phenyllithium.[15] Novel methods for the construction of the triazolopyrimidines nucleus involving reactions of vinylogous iminium salts and related analogs with 3-amino-1,2,4-triazoles have been reported last year.[16] An alternative synthetic route to different triazolopyrimidines is the reaction of 2-hydrazinopyrimidine with acylating agents and also the Dimroth-like rearrangement of triazolo[4,3-*a*]pyrimidines to triazolo[1,5-*a*]pyrimidines in acid or alkali.[5,17]

Thus, there is a limited amount of the regiospecific synthesis of 7- and 5-substituted azolopyrimidines.[7,16] There is a definite need to develop new methods for the regiospecific synthesis of this class of compounds.

In recent work, we have prepared some β-trifluoroacetylvinylsulfones.[18] We have found that alkenes **1a**,**b** are very reactive electrophiles, reacting with heteroarenes such as pyrrole, indole and furan.[19] Also, we have recently described a new simple and efficient way for the regiospecific formation of CF_3-containing imidazo[1,2-*a*]pyridines,[20] pyrazolo[1,5-*a*]pyrimidines,[21] 6,7-dihydro-5*H*-1,3,4-thiadiazolo[3,2-*a*]pyrimidines,[22] and 6,7-dihydro-5*H*-thiazolo[3,2-*a*]pyrimidines[23] by the reaction of sulfones **1a**,**b** with various aminoheterocycles. It was therefore considered that the reaction of diols **1a**,**b** with 3-amino-1,2,4-triazoles and 5-aminotetrazole might result in improved regioselectivity yielding only one regioisomer under a particular reaction condition.

Treatment of **1a**,**b** with different 3-amino-1,2,4-triazoles and 5-aminotetrazole in acetic acid at reflux gave a mixture of cycloadducts **2a**–**k** and **3a**–**k** in 70–90% isolated yields (Scheme 1, Table 1). It is worth mentioning, that in water, under reflux, no significant difference of the ratio of regioisomer was observed. The reaction of **1a**,**b** with aminotriazoles at room temperature afforded only 5% conversion after 10 days. It should be noted that the yields and ratio of 5- and 7-CF_3 substituted azolopyrimdines do not depend significantly on reagents **1a** or **1b**. Moreover, the reaction with triazoles bearing both aliphatic and aromatic substituents as a rule gives a mixture of isomeric azolopyrimdines. Only in the case of aryltriazoles **f**–**h** the highly regioselectively formation of 7-CF_3 azolopyrimdines is observed.



Scheme 1

Nevertheless, simple modification of reaction conditions allowed us to obtain 5-CF_3 triazolo[1,5-*a*]pyrimidines **2** as a pure regioisomer. We have observed that the reaction of sulfones **1a**,**b** with 3-amino-1,2,4-triazoles in acetonitrile at room temperature yields exclusively the 5-CF_3 isomer of tetrahydro[1,2,4]triazolo[1,5-*a*]pyrimidine (**4**). Compound **4** precipitated from the reaction mixture. None of the isomeric 7-CF_3 isomer could be detected in the reaction. Moreover, this reaction proceeds stereoselectively to give **2**, the only diastereomer of triazolo[1,5-*a*]pyrimidines having diaxially oriented sulfonyl and hydroxyl groups. Earlier, we observed the same arrangement of these groups in analogous tetrahydropyrimidines system[22,23] and have confirmed this by X-ray crystallography.[22] We presume that, it is connected with the formation

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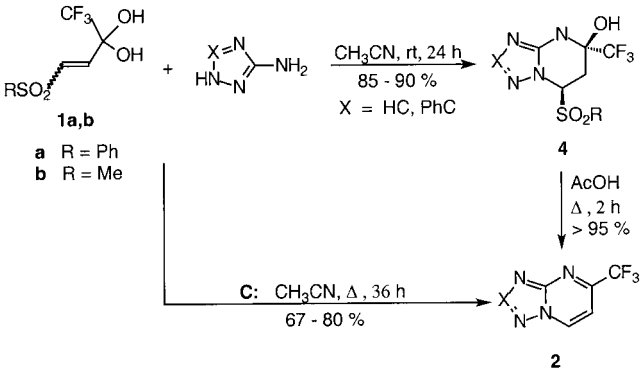
Table 1 Yields and Regioisomeric Ratio of Cycloadducts **2** and **3**

X	Entry	Method	from **1a**		from **1b**	
			2:**3** [a]	Yield %	**2**:**3** [a]	Yield %
HC	**a**	**A**	100:10	83	100:44	80
		B	100:15	86	100:50	82
MeC	**b**	**B**	88:100	80	95:100	75
CF_3C	**c**	**B**	28:100	74	59:100	70
(1-Ad)C	**d**	**B**	10:100	78	38:100	74
t-BuC	**e**	**B**	15:100	76	44:100	76
PhC	**f**	**B**	5:100	83	24:100	78
4-$MeOC_6H_4C$	**g**	**B**	0:100	70	3:100	72
4-ClC_6H_4C	**h**	**B**	2:100	93	13:100	90
2-BrC_6H_4C	**i**	**B**	19:100	81	37:100	76
MeOOCC	**j**	**B**	100:7	87	100:23	86
N	**k**	**B**	3:100	72	16:100	72

[a] Structure and ratios of products were determined by ^{1}H NMR

of intramolecular hydrogen bond between sulfonyl and hydroxyl group in **4**.

Further aromatization of **4** at reflux in acetic acid provides 5-CF_3 triazolo[1,5-*a*]pyrimidines **2** as one regioisomer quantitatively. We have also investigated one-pot synthesis of 5-CF_3 triazolo[1,5-*a*]pyrimidines **2** in acetonitrile at reflux (method **C**, Scheme 2, Table 2). This approach provides a simple way to obtain 5-CF_3 triazolo[1,5-*a*]pyrimidines. We reason that, in this case the reaction is autocatalyzed by the eliminated sulfinic acid. In spite of slighly lower yields, the one-pot technique is attractive due to its simplicity.

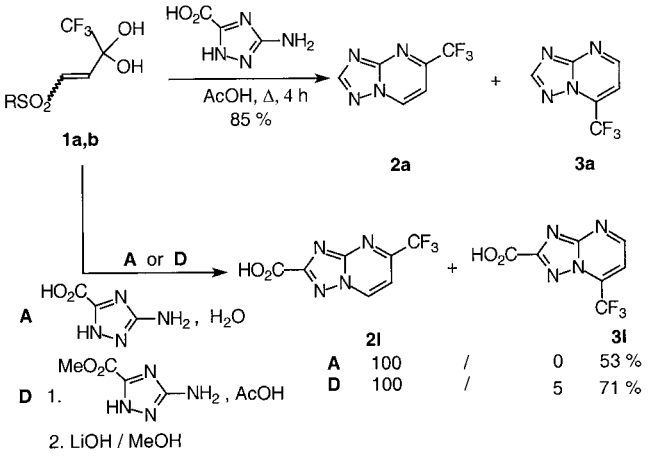


Scheme 2

Introduction of a polar group, such as the carboxylic acid, at position 2 of triazolopyrimidines resulted in a greater solubility of new potential biologically active CF_3- containing azolopyrimdines and therefore has increased interest in this class of compounds.[9] In the reaction of the sulfones **1a**,**b** with 3-amino-1*H*-1,2,4-triazole-5-carboxylic acid in acetic acid under reflux, a mixture of triazolopyrimidines **2a**,**3a** was obtained in good yield instead of the expected product. Moreover, the ratio of isomers **2a**:**3a** is the same as for the reaction with unsubstituted 3-amino-1,2,4-triazole. We believe that decarboxylation of 3-amino-1*H*-1,2,4-triazole-5-carboxylic acid precedes the step of heterocyclization. To avoid decarboxylation, we performed the reaction of **1a**,**b** with the corresponding ester of [1,2,4]triazolo[1,5-*a*]pyrimidine-2-carboxylic acid. Initially formed cycloadducts **2j**,**3j** can be smoothly converted to [1,2,4]triazolo[1,5-*a*]pyrimidine-2-carboxylic acid **2l**,**3l** (Scheme 3) by hydrolysis with lithium hydroxide in methanol (method **D**). Alternatively, carboxylic acid **2l** can be prepared by the reaction of sulfones **1a**,**b** with the 3-amino-1*H*-1,2,4-triazole-5-carboxylic acid in water at reflux (method **A**).

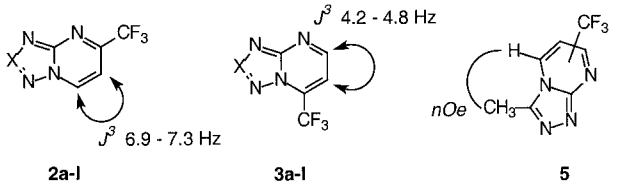
Table 2 Yields of Cycloadducts **4**, and **2** Obtained by Method **C**

X	from **1a**		from **1b**	
	entry	Yield %	entry	Yield %
HC	**4a**	85	**4b**	86
PhC	**4c**	88	**4d**	90
HC	**2a**	70	**2a**	65
(1-Ad)C	**2d**	68	**2d**	72
t-BuC	**2e**	64	**2e**	66
PhC	**2f**	75	**2f**	70
2,4-$Cl_2C_6H_3C$	**2m**	61	**2m**	63
2-BrC_6H_4C	**2i**	65	**2i**	66



Scheme 3

The regiochemistry of 5- and 7-CF_3 substituted compounds **2**,**3** can be established by ^{1}H NMR spectroscopy. The cycloadducts having 5-CF_3-substitution have J^3_{HH} 6.9−7.3 Hz, while those with a 7-CF_3-substitution have J^3_{HH} 4.2−4.8 Hz. (Scheme 4).[7,17]



Scheme 4

Two types of heterocyclization in reactions of 1,3-bielectrophiles with aminotriazoles to form triazolo[1,5-*a*]pyrimidines or triazolo[4,3-*a*]pyrimidines system are described in literature. Calculations of total energy of basic states showed that triazolo[1,5-*a*]pyrimidines are more stable than isomeric triazolo[4,3-*a*]pyrimidines.[24] Kawase[25] and Bouillon[26] showed NH_2-4-N ring atom cyclization with the formation of [1,2,4]triazolo[4,3-*a*]pyrimidine ring by only an NOE experiment[25] or by questionable comparison of UV-VIS and ^{13}C NMR data. Others attribute the formation of [1,2,4]triazolo[1,5-*a*]pyrimidine in the reaction of 1,2,4-triazol-3-amines to 1,3-bielectrophiles and some authentic X-ray diffraction analysis[12] or by independent synthesis.[7,8b,16] In order to confirm the formation of the pair of **2**,**3** isomers instead of isomers of **5**, we performed an NOE experiment for the mixture of **2b**:**3b** (95:100) isomers and have not observed this effect in both isomers. Therefore, at least in our case, the formation of triazolo[1,5-*a*]pyrimidines system takes place.

In summary, the reaction of 1,1,1-trifluoro-4-(sulfonyl)-but-3-ene-2,2-dioles **1a**,**b** with 3-amino-1,2,4-triazoles and 5-aminotetrazole was investigated. The reaction in acetic acid leads to the mixture of 5- and 7-CF_3- isomers. We have developed a novel regiospecific technique with simple experimental layout which allows for the preparation of pure 5-CF_3-azolo[1,2-*a*]pyrimidines in high yields.

Melting points were determined in sealed capillaries and are uncorrected. NMR spectra were recorded on Varian VXR-400 spectrometer with TMS as an internal standard. The IR spectra were obtained with UR-20 spectrometer as films. Column chromatography was performed on silica gel (63−200 mesh, Merck). All solvents used were dried and distilled according to standard procedures. Silica gel Merck 60 and Merck $60F_{254}$ plates were used for conventional and analytical (TLC) chromatography, respectively.

Azolopyrimidines 2,3; General Procedure

To a solution of vinylsulfone **1a**,**b** (1 mmol) in H_2O (10 mL) (method **A**), in AcOH (5 mL) (method **B**) or in CH_3CN (method **C**) the corresponding aminoazole (1.1 mmol) was added. The mixture was stirred at reflux at the appropriate time. Removal of the solvent under reduced pressure afforded products, which were purified by column chromatography over silica gel using CH_2Cl_2 as eluent.

5-(Trifluoromethyl) [1,2,4]triazolo[1,5-*a*]pyrimidine-2-carboxylic acid (2l)

Method **A**: To a solution of vinylsulfone **1a**,**b** (1 mmol) in H_2O (25 mL) the 3-amino-1*H*-1,2,4-triazole-5-carboxylic acid (1.1 mmol) was added. The mixture was stirred for 10 h at reflux. The solution was cooled and the pH adjusted to 2.0 with HCl (10%). The white precipitate of **2l** was filtered, washed by H_2O (2 × 5 mL) and air dried. Yield 53%.

Method **D**: 1. As the common technique. 2. To a solution of methyl [1,2,4]triazolo[1,5-*a*]pyrimidine-2-carboxylate (**2j**, 0.5 mmol) in MeOH (5 mL) the solution of LiOH (1.1 equiv) in MeOH was added. The mixture was stirred at r.t. for 24 h. Removal of the solvent under reduced pressure afforded products, which was dissloved in H_2O (5 mL) and the pH adjusted to 2.0 with HCl (10%). The white precipitate of **2l** was filtered, washed by H_2O (2 × 5 mL) and dried on air; yield 71%; white solid; mp 120−123 °C.

IR: 1770 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.78 (1 H, d, CH-6, *J* = 7.1 Hz), 9.24 (1 H, d, CH-7, *J* = 7.1 Hz).

^{13}C NMR (100 MHz, DCl_3) δ = 110.5, 128.9 (q, *J* = 277.0 Hz, CF_3), 142.3, 153.7, 156.5, 158.3, 159.9 (q, *J* = 40, 1 Hz, C-CF_3).

Anal. Calcd for $C_{14}H_{13}F_3O_3S$: C, 36.22; H, 1.30. Found: C, 36.11; H, 1.19.

4,5,6,7-Tetrahydro[1,2,4]triazolo[1,5-*a*]pyrimidines (4)

To a solution of vinylsulfone **1a**,**b** (1 mmol) in CH_3CN (7 mL) the corresponding aminoazoles (1.1 mmol) was added. The mixture was stirred for 12 h at r.t. The precipitate was filtered, washed by CH_3CN (2 × 3 mL) and dried on air.

7-(Phenylsulfonyl)-5-(trifluoromethyl)-4,5,6,7-tetrahydro-[1,2,4]triazolo[1,5-*a*]pyrimidin-5-ol (4a)

White solid; mp 136−138 °C.

IR: 2920, 1374 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 2.29 (1 H, dd, CH-6, *J* = 12.4, 13.5 Hz), 2.63 (1 H, dd, CH-6, *J* = 4.8, 13.5 Hz), 5.62 (1 H, dd, CH-7, *J* = 4.8, 12.4 Hz), 7.40 (1 H, m, Ph), 7.70 (2 H, m, Ph), 7.79 (2 H, m, Ph), 9.02 (1 H, br s, CH-2).

^{13}C NMR (100 MHz, $CDCl_3$): 26.7, 67.8, 79.5 (COH, *J* = 41.2 Hz), 123.7 (CF_3, *J* = 285.8 Hz), 129.7, 132.0, 133.0, 140.6, 150.6, 152.3.

Anal. Calcd for $C_{12}H_{11}F_3N_4O_3S$: C, 41.38; H, 3.18. Found: C, 41.21; H, 3.19.

7-(Methylsulfonyl)-5-(trifluoromethyl)-4,5,6,7-tetrahydro-[1,2,4]triazolo[1,5-*a*]pyrimidin-5-ol (4b)

White solid; mp 151−153 °C.

IR: 2924, 1382 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 2.10 (1 H, m, CH-6), 2.67 (1 H, m, CH-6), 3.34 (3 H, s, CH_3), 5.90 (1 H, br t, CH-7, *J* = 6.7 Hz), 9.0 (1 H, br s, CH-2).

^{13}C NMR (100 MHz, DCl_3): δ = 26.4, 41.2, 67.7, 79.1 (COH, *J* = 41.4 Hz), 124.0 (CF_3, *J* = 286.0 Hz), 150.6, 152.3.

Anal. Calcd for $C_{79}F_3N_4O_3S$: C, 29.37; H, 3.17. Found: C, 29.29; H, 3.12.

2-Phenyl-7-(phenylsulfonyl)-5-(trifluoromethyl)-4,5,6,7-tetrahydro[1,2,4] triazolo[1,5-*a*]pyrimidin-5-ol (4c)

White solid; mp 177−179 °C.

IR: 2921, 1373 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 2.24 (1 H, dd, CH-6, *J* = 12.4, 13.4 Hz), 2.60 (1 H, dd, CH-6, *J* = 4.8, 13.4 Hz), 5.60 (1 H, dd, CH-7, *J* = 4.8, 12.4 Hz), 7.40 (2 H, m, Ph), 7.48 (2 H, m, Ph), 7.70 (3 H, m, Ph), 7.79 (3 H, m, Ph), 9.11 (1 H, br s, CH-2).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 26.9, 67.7, 79.0 (COH, *J* = 41.3 Hz), 124.0 (CF_3, *J* = 284.1 Hz), 129.5, 132.1, 133.0, 133.6, 137.8, 140.1, 140.6, 142.4, 150.6, 152.3.

Table 3 Spectroscopic Data

^{1}H NMR (DMSO-d_6/TMS) δ, *J* (Hz)	^{13}C NMR (DMSO-d_6/TMS) δ, *J* (Hz)	Mp, °C
2a: 7.48 (d, 1 H, *J* = 7.1 Hz, CH-6), 8.67 (s, 1 H, CH-8), 9.11 (d, 1 H, *J* = 7.1 Hz, CH-7) **3a**: 7.48 (d, 1 H, *J* = 4.3 Hz, CH-6), 8.66 (s, 1 H, CH-8), 9.01 (d, 1 H, *J* = 4.3 Hz, CH-5)	Major isomer **2a**: 105.5, 119.8 (q, *J* = 277.1 Hz, CF_3), 138.8, 150.5 (q, *J* = 37.0 Hz, C-CF_3), 154.5, 156.8	128–130
2b: 2.60 (s, 3 H, CH_3), 7.51 (d, 1 H, *J* = 7.1 Hz, CH-6), 9.15 (d, 1 H, *J* = 7.1 Hz, CH-7) **3b**: 2.60 (s, 3 H, CH_3), 7.54 (d, 1 H, *J* = 4.2 Hz, CH-6), 8.91 (d, 1 H, *J* = 4.2 Hz, CH-5)	**2b**: 15.2, 107.5, 120.2 (q, *J* = 277.9 Hz, CF_3), 139.4, 155.8 (q, *J* = 38.3 Hz, C-CF_3), 140.4, 156.5 **3b**: 15.3, 110.0, 123.8 (q, *J* = 276.7 Hz, CF_3), 149.4 (q, *J* = 37.7 Hz, CCF_3), 150.8, 154.8, 169.0	142–144
2c: 7.80 (d, 1 H, *J* = 7.2 Hz, CH-6), 9.39 (d, 1 H, *J* = 7.2 Hz, CH-7) **3c**: 7.84 (d, 1 H, *J* = 4.5 Hz, CH-6), 9.18 (d, 1 H, *J* = 4.5 Hz, CH-5)	Major isomer **3c**: 110.6, 120.0 (q, *J* = 274.8 Hz, CF_3), 121.4 (q, *J* = 277.2 Hz, CF_3), 142.9 (q, *J* = 37.2 Hz, C-CF_3), 151.0, 151.4 (q, *J* = 38.0 Hz, C-CF_3), 154.4	84–86
2d: 1.65−2.18 (m, 15 H, Ad), 7.53 (d, 1 H, *J* = 7.1 Hz, CH-6), 9.21 (d, 1 H, *J* = 7.1 Hz, CH-7) **3d**: 1.65−2.18 (m, 15 H, Ad), 7.55 (d, 1 H, *J* = 4.3 Hz, CH-6), 8.92 (d, 1 H, *J* = 4.3 Hz, CH-5)	Major isomer **3d**: 20.7, 29.1, 37.1, 41.8, 109.8, 120.8 (q, *J* = 277.7 Hz, CF_3), 140.1, 149.1 (q, *J* = 38.5 Hz, C-CF_3), 156.4, 175.3	101–103
2e: 1.46 (s, 9 H, 3 CH_3), 7.51 (d, 1 H, *J* = 7.1 Hz, CH-6), 9.16 (d, 1 H, *J* = 7.1 Hz, CH-7) **3e**: 1.46 (s, 9 H, 3 CH_3), 7.53 (d, 1H, *J* = 4.4 Hz, CH-6), 8.91 (d, 1 H, *J* = 4.4 Hz, CH-5)	Major isomer **3e**: 29.7, 35.7, 109.6, 121.2 (q, *J* = 277.0 Hz, CF_3), 140.0, 149.3 (q, *J* = 37.9 Hz, C-CF_3), 154.6, 178.1	113–115
2f: 7.54−7.58 (m, 4 H, Ar + CH-6), 8.30−8.33 (m, 2 H, Ar), 9.24 (d, 1 H, *J* = 7.1 Hz, CH-7) **3f**: 7.54−7.58 (m, 3 H, Ar), 7.60 (d, 1 H, *J* = 4.3 Hz, CH-6), 8.30−8.33 (m, 2 H, Ar), 8.98 (d, 1 H, *J* = 4.3 Hz, CH-5)	**2f**: 113.0, 120.2 (q, *J* = 277.8 Hz, CF_3), 130.5, 130.9, 135.1, 135.9, 150.4, 157.9, 164.0 (q, *J* = 40.0 Hz, C-CF_3), 170.1 **3f**: 110.7, 118.9 (q, *J* = 276.6 Hz, CF_3), 129.0, 130.7, 133.0, 135.8, 150.2, 157.2, 159.4 (q, *J* = 39.5 Hz, C-CF_3), 172.8	180–182
2g: 3.85 (s, 3 H, CH_3), 6.95 (d, 2 H, Ar), 7.54 (d, 1 H, *J* = 7.0 Hz, CH-6), 7.94 (d, 2 H, Ar), 9.18 (d, 1 H, *J* = 7.0 Hz, CH-7) **3g**: 3.83 (s, 3 H, CH_3), 7.05 (d, 2 H, Ar), 7.56 (d, 1 H, *J* = 4.4 Hz, CH-6), 8.21 (d, 2 H, Ar), 8.91 (d, 1 H, *J* = 4.4 Hz, CH-5)	Major isomer **3g**: 56.46, 111.2, 116.7, 118.8 (q, *J* = 280.1 Hz, CF_3), 129.0, 130.0, 157.6, 158.0, 159.6 (q, *J* = 41.0 Hz, C-CF_3), 164.5, 175.7	195–197
2h: 7.55 (d, 2 H, Ar), 7.58 (d, 1 H, *J* = 6.9 Hz, CH-6), 7.96 (d, 2 H, Ar), 9.23 (d, 1 H, *J* = 6.9 Hz, CH-7) **3h**: 7.55 (d, 2 H Ar), 7.61 (d, 1 H, *J* = 4.3 Hz, CH-6), 8.27 (d, 2 H, Ar), 8.98 (d, 1 H, *J* = 4.3 Hz, CH-5)	Major isomer **3h**: 111.0, 118.9 (q, *J* = 277.4 Hz, CF_3), 129.4, 132.3, 132.8, 135.6, 154.2, 156.6, 159.1 (q, *J* = 39.7 Hz, C-CF_3), 170.8	168–170
2i: 7.43 (m, 1 H, Ar), 7.53 (m, 1 H, Ar), 7.62 (d, *J* = 7.0 Hz, CH-6), 7.80 (m, 1 H, Ar), 7.96 (m, 1 H, Ar), 9.29 (d, 1 H, *J* = 7.0 Hz, CH-7) **3i**: 7.43 (m, 1 H, Ar), 7.53 (m, 1 H, Ar), 7.64 (d, *J* = 4.3 Hz, CH-6), 7.80 (m, 1 H, Ar), 7.96 (m, 1 H, Ar), 9.02 (d, 1 H, *J* = 4.3 Hz, CH-5)	Major isomer **3i**: 110.1, 120.8 (q, *J* = 275.2 Hz, CF_3), 129.5, 130.3, 132.9, 133.5, 134.0, 135.9, 141.0, 157.3, 160.2 (q, *J* = 39.9 Hz, C-CF_3), 173.7	123–125
2j: 4.00 (s, 3 H, CH_3), 7.73 (d, 1 H, *J* = 7.1 Hz, CH-6), 9.36 (d, 1 H, *J* = 7.1 Hz, CH-7) **3j**: 4.00 (s, 3 H, CH_3), 7.77 (d, 1 H, *J* = 4.4 Hz, CH-6), 9.11 (d, 1 H, *J* = 4.4 Hz, CH-5)	Major isomer **2j**: 54.0, 109.9, 129.7 (q, *J* = 276.1 Hz, CF_3), 142.2, 154.9, 156.2, 158.8, 161.3 (q, *J* = 40.4 Hz, C-CF_3)	170–171
2k: 7.66 (d, 1 H, *J* = 7.3 Hz, CH-6), 9.43 (d, 1 H, *J* = 7.3 Hz, CH-7) **3k**: 7.42 (d, 1 H, *J* = 4.8 Hz, CH-6), 8.81 (d, 1 H, *J* = 4.8 Hz, CH-5)	Major isomer **3k**: 108.7, 121.2 (q, *J* = 277.0 Hz, CF_3), 156.2 (q, *J* = 39.9 Hz, C-CF_3), 156.2, 162.7	120–122
2m:[b] 7.48 (d, 2 H, Ar), 7.63 (d, 2 H, Ar), 7.82 (d, 1 H, *J* = 6.9 Hz, CH-6), 7.84 (d, 2 H, Ar), 9.40 (d, 1 H, *J* = 6.9 Hz, CH-7)	**2m**: 109.6, 114.3 (q, *J* = 283.3 Hz, CF_3), 120.7, 123.7, 128.1, 131.2, 132.9, 134.4, 139.5, 151.7, 155.3 (q, *J* = 39.7 Hz, C-CF_3), 162.4	160–162

[a] Satisfactory microanalyses were obtained: C ± 0.28, H ± 0.25.
[b] In $CDCl_3$/CF_3COOH.

Anal. Calcd for $C_{18}H_{15}F_3N_4O_3S$: C, 50.94; H, 3.56. Found: C, 51.03; H, 3.49.

2-Phenyl-7-(methylsulfonyl)-5-(trifluoromethyl)-4,5,6,7-tetrahydro[1,2,4] triazolo[1,5-*a*]pyrimidin-5-ol (4d)
White solid; mp 184−186 °C.

IR: 2926, 1384 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 2.18 (1 H, dd, CH-6, *J* = 12.6, 13.3 Hz), 2.67 (1 H, dd, CH-6, *J* = 4.6, 13.3 Hz), 3.32 (3 H, s, CH_3), 5.90 (1 H, dd, CH-7, *J* = 4.6, 12.6 Hz), 7.46 (2 H, m, Ph), 7.69 (1 H, m, Ph), 7.80 (2 H, m, Ph), 9.08 (1 H, br s, CH-2).

^{13}C NMR (100 MHz, DCl_3): δ = 26.6, 41.4, 67.7, 80.1 (C-OH, *J* = 41.0 Hz), 124.2 (CF_3, *J* = 286.6 Hz), 133.7, 140.4, 140.8, 142.8, 150.6, 152.3.

Anal. Calcd for $C_7H_9F_3N_4O_3S$: C, 29.37; H, 3.17. Found: C, 29.29; H, 3.12.

Azolopyrimidines 2 from 4; General Procedure
The corresponding 4,5,6,7-tetrahydro[1,2,4]triazolo[1,5-*a*]pyrimidine **4** (0.5 mmol) was dissolved in HOAc (10 mL). The mixture was stirred for 1 h under reflux. The solvent was evaporated under reduced pressure. The residue was purified by column chromatography over silica gel using CH_2Cl_2 as eluent; yield 95−98%.

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