Reactions of α-fluorine-containing β-functionalized vinyl sulfides with N-nucleophiles

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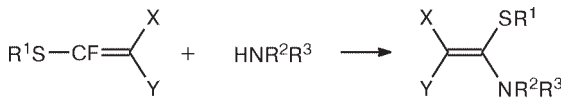
α-Fluorine-containing β-functionalized vinyl sulfides readily react with N-nucleophiles to form α-fluorine-substituted products. The reactions with phenylhydrazines and amidines of acids are accompanied by cyclization at the functional group. Thermal cyclization of cyanotrifluoromethylketene N,S-acetals proceeds at the trifluoromethyl group to give substituted 3-cyanoquinolin-4-ones.

Key words: vinyl sulfides, substitution, N-nucleophiles, cyclization.

Functionalized vinyl sulfides are not only of theoretical but also of practical interest because they can be used as precursors of various (including heterocyclic) compounds. Previously,[1] we have developed a one-step procedure for the synthesis of fluorine-containing vinyl sulfides bearing functional groups at the multiple bond due to which these compounds became accessible for the examination of their subsequent transformations, among them cyclization involving functional groups.

It is known that vinyl sulfides bearing the F atom at the multiple bond readily react with O-nucleophiles to give vinyl substitution products.[2,3] In particular, we have demonstrated that the products of the reactions of α-fluoro-α,β-unsaturated sulfenyl chlorides with enols and phenols underwent intramolecular cyclization to form substituted 1,3-oxathioles.[4,5] Analogous reactions with N-aryleneamines also exemplify the intramolecular N-nucleophilic vinyl substitution of the F atom.[6] In the present study, we investigated the reactions of α-fluorine-containing β-functionalized vinyl sulfides with various N-nucleophiles, including bifunctional nucleophiles, and examined the possibility of their use in the synthesis of heterocyclic compounds.

Scheme 1



1a—e **2a—n**

1,2	X	Y	R^1	R^2	R^3
1a	COOMe	CF_3	Bn	—	—
1b	COOMe	CF_3	Bu^t	—	—
1c	CN	CF_3	Bn	—	—
1d	CN	CF_3	Bu^t	—	—
1e	COOMe	COOMe	Bn	—	—
2a	COOMe	CF_3	Bn	H	H
2b	COOMe	CF_3	Bn	Et	Et
2c	COOMe	CF_3	Bn	H	4-C_6H_4Me
2d	COOMe	CF_3	Bn	H	4-C_6H_4OMe
2e	COOMe	CF_3	Bn	H	4-C_6H_4OPh
2f	COOMe	CF_3	Bu^t	H	4-C_6H_4Et
2g	CN	CF_3	Bn	H	Ph
2h	CN	CF_3	Bn	H	4-C_6H_4F
2i	CN	CF_3	Bn	H	4-C_6H_4Me
2j	CN	CF_3	Bn	H	4-C_6H_4OMe
2k	CN	CF_3	Bn	H	4-C_6H_4OPh
2l	CN	CF_3	Bu^t	H	4-C_6H_4OMe
2m	COOMe	COOMe	Bn	H	4-C_6H_4Et
2n	COOMe	COOMe	Bn	H	4-C_6H_4COOEt

Results and Discussion

Reactions with amines. In the case of activation with strong electron-withdrawing groups located in the β position, the α-vinyl F atom in vinyl sulfides (**1a—e**) is readily replaced in the reactions with ammonia, diethylamine, and primary arylamines to form the corresponding ketene N,S-acetals (**2a—n**) (Scheme 1).

The reactions were carried out at room temperature in ethereal solutions with the use of a twofold excess of amine serving both as the reagent and (simultaneously) acceptor of HF. Under the above-mentioned conditions, only vinyl sulfides containing two strong electron-withdrawing groups in the β position were involved in the reactions, whereas α,β-difluoro-β-(benzylthio)acrylonitrile (**1f**) did not react with anilines even upon heating. Sterically hindered *tert*-butyl sulfides reacted somewhat more slowly than their benzyl analogs. Substituents of various electronic nature located in the *para* position of aniline have no effect on the reaction rate.

According to the NMR data, compounds **2a—l** exist as enamines. Only the spectra of di(methoxycarbo-

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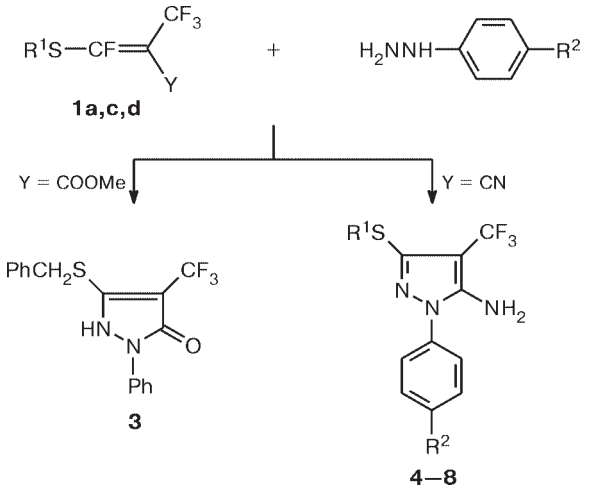
nyl)ketene aminothioacetals **2m** and **2n** have signals (up to 10%) of tautomeric imines resulting from the migration of the H atom from N to C. Previously,[7] it has been noted that the initially formed alkoxycarbonyltrifluoromethylketene aminoacetals are rather slowly rearranged into imino esters, the rearrangement being irreversible. The fact that this rearrangement did not take place in the case under consideration is attributable to the electronic effect of the S atom. The spectroscopic data also indicate that substituted acrylates **2a,c—f** exist as the only isomer due, apparently, to the presence of a hydrogen bond between the amino and methoxycarbonyl groups, whereas acrylonitriles **2g—l** in which this bond cannot occur exist as mixtures of the *E* and *Z* isomers.

Upon heating to 150 °C, the reactions of vinyl sulfides of interest with tertiary amines, for example, with *N*,*N*-dimethylaniline, in the absence of solvents afforded only resinous products.

Reactions with phenylhydrazines and amidines. In spite of the fact that functionalized fluoroolefins, in particular, derivatives of perfluoromethacrylic acid,[8] were extensively studied beginning in 1970s, examples of their cyclization at the functional group are scarce. We found that the reactions of compounds **1a,s,d** with phenylhydrazines were accompanied by intramolecular cyclization at the β-functional group to form the corresponding substituted pyrazoles **3—8** (Scheme 2).

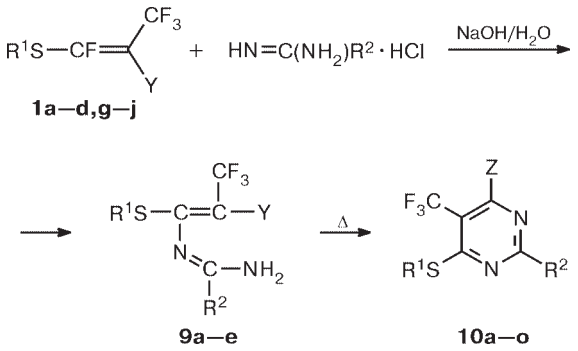
Scheme 2

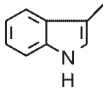
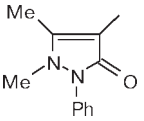
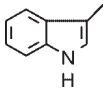
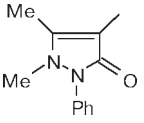
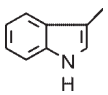
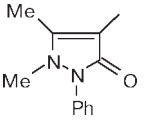


R^1 = $PhCH_2$, R^2 = H (**4**), Cl (**5**), F (**6**), CF_3 (**7**);
R^1 = Bu^t, R^2 = H (**8**)

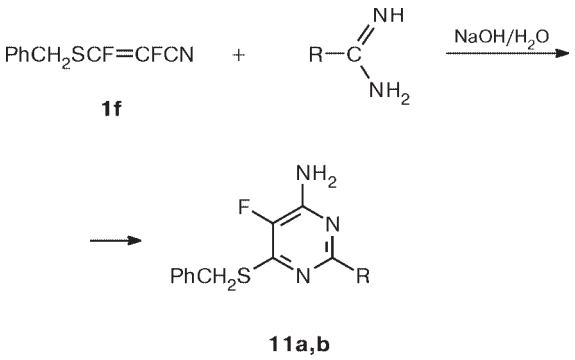
Undoubtedly, the above-considered reaction began with the nucleophilic displacement of the vinyl F atom although we failed to isolate intermediates. To the contrary, heterocyclization in the reactions of vinyl sulfides **1** with *N*-unsubstituted carbamidines occurred only upon

Scheme 3



	Y	Z	R^1	R^2
1,9,10				
1g	COOMe	—	4-$Me_2NC_6H_4$	—
1h	COOMe	—		—
1i	COOMe	—		—
1j	COOMe	—		—
9a,10a	CN	NH_2	Bn	Me
9b,10b	CN	NH_2	Bu^t	Me
9c,10c	CN	NH_2	Bn	Ph
9d,10d	CN	NH_2	Bu^t	Ph
10e	COOMe	OH	Bn	Me
10f	COOMe	OH	Bu^t	Me
10g	COOMe	OH	4-$Me_2NC_6H_4$	Me
10h	COOMe	OH		Me
10i	COOMe	OH		Me
10j	COOMe	OH		Me
10k	COOMe	OH	Bn	Ph
10l	COOMe	OH	4-$Me_2NC_6H_4$	Ph
10m	COOMe	OH		Ph
10n	COOMe	OH		Ph
10o	COOMe	OH		Ph

Scheme 4

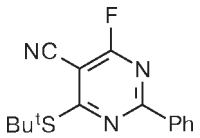


R = Me (**11a**), Ph (**11b**)

heating. For this reason, the isolation of intermediate products of the F atom replacement presents no problems as exemplified by the isolation of substituted amidines **9a—e**. Thermolysis of compounds of this type gave rise to pyrimidines **10** (Scheme 3).

Acetamidine and benzamidine were used in the reactions as hydrochlorides. An aqueous solution of NaOH was used as an acceptor of HCl and HF. Heterocyclization at the nitrile group proceeded more difficultly than that at the methoxycarbonyl group and was completed upon refluxing in toluene in 4—5 h. Under analogous conditions, α,β-difluoro-β-benzylthioacrylonitrile (**1f**) also reacted with amidines to produce the corresponding 4-amino-5-fluoropyrimidines **11a,b**.

Cyclization of β-(*tert*-butylthio)perfluoromethacrylonitrile with benzamidine afforded a minor product, *viz.*, 6-*tert*-butylthio-5-cyano-4-fluoro-2-phenylpyrimidine (**12**), which was isolated by column chromatography and characterized by spectroscopic data. Compound **12** was formed through cyclization involving the trifluoromethyl and amino groups.



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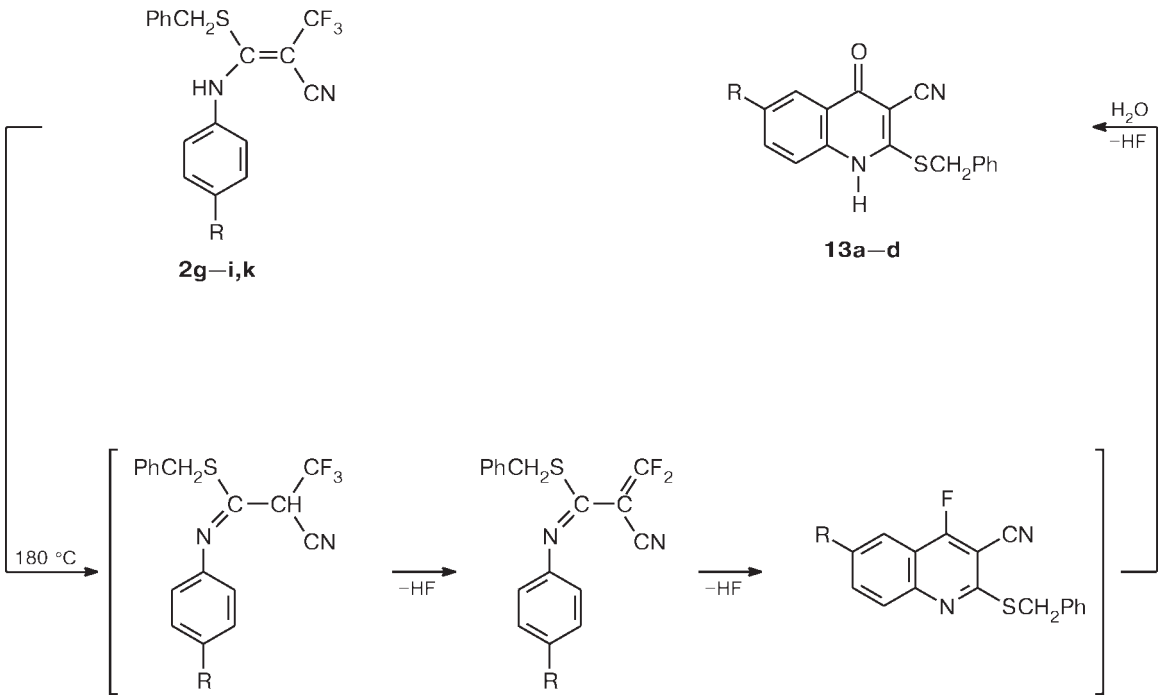
Thermal cyclization of N,S-acetals. Cyclization at the trifluoromethyl group also occurs upon heating of (trifluoromethyl)cyanoketene N,S-acetals in diphenyl oxide. Generally, heating of these compounds to ~250 °C leads to their cyclization at the nitrile group to form an aromatic ring. Unexpectedly, the reactions of compounds **2g—j,k** proceeded even at 180 °C and were accompanied by HF evolution. Apparently, the first step involves the migration of the proton from the N atom to the C_α atom, dehydrofluorination of the resulting CH-acid, and cyclization giving rise to an aromatic ring. Unfortunately, attempts to isolate 4-fluoroquinolines (which were presumably generated) in the individual form failed due to their high hydrolytic lability. The formation of these compounds was evidenced by the presence of a singlet at δ −70 in the ^{19}F NMR spectra of the reaction mixtures.

Scheme 5



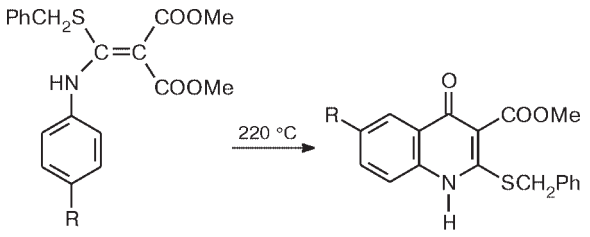
13: R = H (**a**), F (**b**), Me (**c**), PhO (**d**)

Alkaline hydrolysis of the reaction products afforded the corresponding 3-cyanoquinolin-4-ones **13a—d**, which were characterized by NMR spectroscopy (Scheme 5).

The data on the involvement of the trifluoromethyl group in cyclization to form an aromatic ring are available in the literature.[9] These transformations require an additional assistance of bases. In this case, the reaction proceeded in the absence of bases and, hence, can be considered as the first example of thermal reactions of this type.

Upon heating in diphenyl oxide, cyclization of compounds **2m,n** proceeded in a usual fashion to produce quinolone derivatives **14a,b** (Scheme 6).

Scheme 6



2m,n **14a,b**

R = Et (**14a**), COOEt (**14b**)

Thermal cyclization of trifluoromethyl(methoxycarbonyl)ketene N,S-acetals proceeded ambiguously (due, apparently, to competitive cyclizations at the methoxycarbonyl and trifluoromethyl groups) and was accompanied by substantial resinification of the reaction mixture.

The above-considered approaches to the preparation of heteroaromatic derivatives bearing sulfur-containing fragments in the side chain are of interest as applied to the synthesis of biologically active compounds.

Experimental

The ^{19}F NMR spectra were recorded on a Bruker AC-200F spectrometer (188.31 MHz). The ^{1}H NMR spectra were measured on a Bruker AC-300SF instrument (300.13 MHz). The chemical shifts (δ) are given relative to CF_3COOH (^{19}F, external standard) and Me_4Si (^{1}H, internal standard). The mass spectra (EI) of the reaction products were obtained on an HP-5890 gas chromatograph equipped with an HP-5972 mass-selective detector; the energy of ionizing electrons was 70 eV. The course of the reactions and the purities of the resulting compounds were monitored by TLC on Merck 60F-254 plates in an acetone—CCl_4 system.

The starting vinyl sulfides **1** were synthesized according to a procedure reported previously.[1]

The yields, physicochemical properties, spectroscopic characteristics, and data from elemental analysis for the resulting compounds are given in Table 1.

Methyl 3-amino-3-benzylthio-2-(trifluoromethyl)acrylate (2a). A stream of dry ammonia (excess) was passed through a solution of methyl 3-benzylthio-3-fluoro-2-(trifluoromethyl)acrylate (**1a**) (2.9 g, 0.01 mol) in ether (10 mL). The mixture was kept at 0 °C for 10 h, the residue was filtered off at this temperature, the solvent was removed *in vacuo*, and the residue was recrystallized from hexane.

Methyl 3-benzylthio-3-diethylamino-2-(trifluoromethyl)acrylate (2b) was prepared analogously from the same ester and diethylamine. MS, *m/z*: 347 $[M]^+$.

Reactions of α-fluorovinyl sulfides with anilines (general procedure). A solution of the corresponding aniline (0.02 mol) in ether (20 mL) was added dropwise with stirring to a solution of vinyl sulfide (0.01 mol) in ether (10 mL). The reaction mixture was kept at 20 °C for 25—30 h and washed with a 5—10% HCl solution. The organic layer was separated and dried over Na_2SO_4. The solvent was removed *in vacuo* and the residue was recrystallized from hexane. This procedure was used for the preparation of methyl 3-benzylthio-3-(4-methylphenylamino)-2-(trifluoromethyl)acrylate (**2c**); methyl 3-benzylthio-3-(4-methoxyphenylamino)-2-(trifluoromethyl)acrylate (**2d**); methyl 3-benzylthio-3-(4-phenoxyphenylamino)-2-(trifluoromethyl)acrylate (**2e**); methyl 3-*tert*-butylthio-3-(4-ethylphenylamino)-2-(trifluoromethyl)acrylate (**2f**), MS, *m/z*: 361 $[M]^+$; nitrile of 3-benzylthio-3-phenylamino-2-(trifluoromethyl)acrylic acid (**2g**); nitrile of 3-benzylthio-3-(4-fluorophenylamino)-2-(trifluoromethyl)acrylic acid (**2h**); nitrile of 3-benzylthio-3-(4-methylphenylamino)-2-(trifluoromethyl)acrylic acid (**2i**); nitrile of 3-benzylthio-3-(4-methoxyphenylamino)-2-(trifluoromethyl)acrylic acid (**2j**); nitrile of 3-benzylthio-3-(4-phenoxyphenylamino)-2-(trifluoromethyl)acrylic acid (**2k**); nitrile of 3-*tert*-butylthio-3-(4-methoxyphenylamino)-2-(trifluoromethyl)acrylic acid (**2l**); methyl 3-benzylthio-3-(4-ethylphenylamino)-2-methoxycarbonylacrylate (**2m**), and methyl 3-benzylthio-3-(4-ethoxycarbonylphenylamino)-2-(methoxycarbonyl)acrylate (**2n**).

Reactions of α-fluorovinyl sulfides with arylhydrazines (general procedure). A solution of vinyl sulfide (0.01 mol) in ether (10 mL) was added dropwise with stirring and cooling to 10 °C to a solution of the corresponding hydrazine (0.02 mol) in ether (10 mL). The reaction mixture was kept at 20 °C for 15—20 h. The precipitate that formed was filtered off, the filtrate was concentrated, and the residue was recrystallized from alcohol. This procedure was used for the preparation of 3-benzylthio-1-phenyl-4-trifluoromethyl-3-pyrazol-5-one (**3**); 5-amino-3-benzylthio-1-phenyl-4-(trifluoromethyl)pyrazole (**4**); 5-amino-3-benzylthio-1-(4-chlorophenyl)-4-(trifluoromethyl)pyrazole (**5**), MS, *m/z*: 383 $[M]^+$; 5-amino-3-benzylthio-1-(4-fluorophenyl)-4-(trifluoromethyl)pyrazole (**6**); 5-amino-3-benzylthio-4-trifluoromethyl-1-(4-trifluoromethylphenyl)pyrazole (**7**), and 5-amino-3-*tert*-butylthio-1-phenyl-4-(trifluoromethyl)pyrazole (**8**).

Reactions of α-fluorovinyl sulfides with amidines (general procedure). A 40% aqueous solution of NaOH (0.02 mol) was added portionwise with vigorous stirring to a suspension of the corresponding α-fluorovinyl sulfide (0.01 mol) and the corresponding amidine hydrochloride (0.01 mol) in benzene (20 mL). The reaction mixture was kept at ~20 °C for 30 min and then hexane (10 mL) was added. The precipitate that formed was filtered off, washed on a filter with water and hexane, and dried in air. This procedure was used for the preparation of

Table 1. Yields, physicochemical properties, spectroscopic characteristics, and data from elemental analysis for the compounds synthesized

Compound	Yield (%)	M.p. /°C	Found / Calculated (%) C	Found / Calculated (%) H	Molecular formula	NMR (δ, *J*/Hz)* ^{19}F	NMR (δ, *J*/Hz)* ^{1}H
2a	55	103—105	51.77 51.61	4.35 4.30	$C_{12}H_{12}F_3NO_2S$	21.2 (s, CF_3)	3.75 (s, 3 H, OMe); 4.25 (s, 2 H, CH_2); 7.40 (m, 5 H, Ph); 5.70, 9.50 (both br.s, 1 H each, NH_2)
2b	53	34—36	55.39 55.33	5.75 5.76	$C_{16}H_{20}F_3NO_2S$	24.5, 20.9 (both s, CF_3, 5 : 1)	1.19 (m, 6 H, 2 Me); 3.59 (m, 7 H, 2 CH_2 and OMe); 4.06 (s, 2 H, CH_2); 7.29 (m, 5 H, Ph)
2c	85	60—62	59.88 59.84	4.71 4.72	$C_{19}H_{18}F_3NO_2S$	—	2.30 (s, 3 H, Me); 3.72 (s, 3 H, OMe); 4.31 (s, 2 H, CH_2); 4.81 (br.s, 1 H, NH); 6.60, 7.16 (both d, 2 H each, J = 8); 7.29 (m, 5 H, Ph)
2d	80	52—54	57.49 57.43	4.50 4.53	$C_{19}H_{18}F_3NO_3S$	—	3.76 (s, 6 H, 2 OMe); 4.30 (s, 2 H, CH_2); 4.83 (br.s, 1 H, NH); 6.78 (m, 4 H); 7.32 (m, 5 H)
2e	62	50—52	62.78 62.75	4.38 4.36	$C_{24}H_{20}F_3NO_3S$	—	3.75 (s, 3 H, 2 OMe); 4.31 (s, 2 H, CH_2); 4.98 (br.s, 1 H, NH); 6.70—7.40 (m, 14 H)
2f	60	38—40	56.56 56.51	6.10 6.09	$C_{17}H_{22}F_3NO_2S$	19.3 (s, CF_3)	1.58 (s, 9 H, Bu^t); 2.28 (t, 3 H, Me, J = 7.0); 2.65 (q, 2 H, CH_2, J = 7.0); 3.81 (s, 3 H, OMe); 4.69 (br.s, 1 H, NH); 6.65, 7.18 (both d, 2 H each, J = 8)
2g	85	68—70	61.13 61.08	3.91 3.89	$C_{17}H_{13}F_3N_2S$	—	3.86, 3.96 (both s, 2 H, CH_2, 1 : 1); 7.14—7.28 (m, 10 H, 2 Ph); 9.51, 9.98 (both br.s, 1 H, NH, 1 : 1)
2h	84	104—106	57.99 57.95	3.38 3.41	$C_{17}H_{12}F_4N_2S$	−33.9, −33.5 (both s, 1 F, CF, 4 : 3); 27.1, 32.5 (both s, 3 F, CF_3, 3 : 4)	3.90, 4.03 (both s, 2 H, CH_2, 3 : 4); 7.06 (m, 4 H); 7.22 (m, 5 H); 9.57, 9.90 (both br.s, 1 H, NH, 3 : 4)
2i	85	69—71	62.12 62.07	4.29 4.31	$C_{18}H_{15}F_3N_2S$	—	2.36 (s, 3 H, Me); 3.90, 4.02 (both s, 2 H, CH_2, 1 : 1); 7.00 (m, 2 H); 7.21 (m, 7 H); 9.63, 9.94 (both br.s, 1 H, NH, 1 : 1)
2j	71	75—77	59.27 59.34	4.10 4.12	$C_{18}H_{15}F_3N_2OS$	—	3.73 (s, 3 H, OMe); 3.87, 3.96 (both s, 2 H, CH_2, 3 : 4); 7.09 (m, 2 H); 7.37 (m, 2 H); 9.50, 9.78 (both br.s, 1 H, NH, 3 : 4)
2k	60	93—95	64.87 64.79	3.97 3.99	$C_{23}H_{17}F_3N_2OS$	—	3.92, 4.03 (both s, 2 H, CH_2, 3 : 4); 6.96 (m, 4 H); 7.09 (m, 3 H); 7.27 (m, 7 H); 9.57, 9.90 (both br.s, 1 H, NH, 3 : 4)
2l	67	65—67	54.63 54.55	5.16 5.15	$C_{15}H_{17}F_3N_2OS$		1.30, 1.41 (both s, 9 H, Bu^t, 1 : 1); 3.79 (s, 3 H, OMe); 6.89 (m, 2 H); 7.13 (m, 2 H); 7.27 (m, 2 H); 9.52 (br.s, 1 H, NH)
2m	71	63—65	65.54 65.45	5.95 5.97	$C_{21}H_{23}NO_4S$	—	1.29 (m, 3 H, Me); 2.69 (m, 2 H, CH_2); 3.68 (m, 8 H, 2 OMe and CH_2); 7.20 (m, 9 H); 4.14, 10.30 (both s, 1 H, CH : NH = 1 : 9)
2n	73	69—71	61.70 61.54	5.33 5.36	$C_{22}H_{23}NO_6S$	—	Enamine: 1.36 (t, 3 H, Me, J = 7.0); 3.59 (s, 6 H, 2 OMe); 3.80 (s, 2 H, CH_2); 4.30 (q, 2 H, CH_2, J = 7.0); 7.21 (m, 7 H); 7.91 (m, 2 H); 9.89 (s, 1 H, NH); imine: 1.33 (m, 3 H, Me); 3.68 (s, 2 H, CH_2); 3.71 (s, 6 H, 2 OMe); 4.27 (s, 1 H, CH); 4.29 (m, 2 H, CH_2); 7.20 (m, 7 H); 7.92 (m, 2 H)
3	41	155—157	58.37 58.29	3.69 3.71	$C_{17}H_{13}F_3N_2OS$	—	3.80 (s, 2 H, CH_2); 6.92 (m, 2 H); 7.21 (m, 5 H); 7.41 (m, 3 H); 10.95 (br.s, 1 H, NH)
4	44	68—70	58.40 58.45	3.97 4.01	$C_{17}H_{14}F_3N_3S$	—	4.25 (s, 2 H, CH_2); 7.25 (m, 3 H); 7.40 (m, 3 H); 7.52 (m, 4 H)
5	53	140—142	53.27 53.19	3.36 3.39	$C_{17}H_{13}ClF_3N_3S$	—	4.25 (s, 2 H, CH_2); 7.25 (m, 3 H); 7.38 (m, 2 H); 7.50 (m, 4 H)

(*to be continued*)

Table 1 (*continued*)

Compound	Yield (%)	M.p. /°C	Found / Calculated (%) C	Found / Calculated (%) H	Molecular formula	NMR (δ, *J*/Hz)* ^{19}F	NMR (δ, *J*/Hz)* ^{1}H
6	57	74—76	55.67 55.59	3.55 3.54	$C_{17}H_{13}F_4N_3S$	−30.9 (s, 1 F, CF); 28.9 (s, 3 F, CF_3)	4.27 (s, 2 H, CH_2); 5.90 (br.s, 2 H, NH_2); 7.30 (m, 7 H); 7.55 (m, 2 H)
7	63	68—70	51.88 51.80	3.15 3.12	$C_{18}H_{13}F_6N_3S$	21.7 (s, CF_3); 28.8 (s, CF_3)	4.27 (s, 2 H, CH_2); 5.89 (br.s, 2 H, NH_2); 7.27 (m, 3 H); 7.40 (m, 2 H); 7.81 (m, 4 H)
8	59	82—84	53.40 53.33	5.07 5.08	$C_{14}H_{16}F_3N_3S$	—	1.45 (s, 9 H, Bu^t); 5.51 (br.s, 2 H, NH_2); 7.44 (m, 1 H); 7.52 (m, 4 H)
9a	68	86—88	52.27 52.17	3.99 4.01	$C_{13}H_{12}F_3N_3S$	—	1.79, 1.89 (both s, 3 H, CH_3, 1 : 2); 3.98, 4.09 (both s, 2 H, CH_2, 1 : 2); 7.30 (m, 7 H, 5 CH + NH_2)
9b	74	132—134	47.42 47.31	5.70 5.73	$C_{11}H_{16}F_3N_3S$	—	1.47 (s, 9 H, Bu^t); 1.93, 1.99 (both s, 3 H, Me, 5 : 2); 7.25 (br.s, 2 H, NH_2)
9c	77	124—126	59.91 59.83	3.90 3.88	$C_{18}H_{14}F_3N_3S$	—	3.93, 4.08 (both s, 2 H, CH_2, 5 : 1); 7.24 (m, 5 H); 7.48 (m, 3 H); 7.91 (m, 2 H)
9d	69	116—118	55.13 55.05	4.87 4.89	$C_{15}H_{16}F_3N_3S$	25.6, 28.1 (both s, CF_3, 1 : 4)	1.42, 1.47 (both s, 9 H, Bu^t, 4 : 1); 7.49 (m, 5 H, 3 CH + NH_2); 7.90 (m, 2 H)
9e	65	80—82	57.97 57.89	4.28 4.31	$C_{19}H_{17}F_3N_2O_2S$	—	3.58 (s, 3 H, OMe); 3.80 (s, 2 H, CH_2); 7.07 (br.s, 2 H, NH_2); 7.24 (m, 5 H); 7.45 (m, 3 H); 7.91 (m, 2 H)
10a	70	93—95	52.25 52.17	4.00 4.01	$C_{12}H_{12}F_3N_3S$	26.7 (s, CF_3)	2.40 (s, 3 H, Me); 4.40 (s, 2 H, CH_2); 6.58 (br.s, 2 H, NH_2); 7.25 (m, 3 H); 7.37 (m, 2 H)
10b	72	98—100	45.37 45.28	5.24 5.28	$C_{10}H_{14}F_3N_3S$	—	1.58 (s, 9 H, Bu^t); 2.35 (s, 3 H, Me); 7.25 (br.s, 2 H, NH_2)
10c	77	78—80	60.01 59.83	3.94 3.89	$C_{18}H_{14}F_3N_3S$		4.60 (s, 2 H, CH_2); 6.75 (br.s, 2 H, NH_2); 7.25 (m, 3 H); 7.43 (m, 5 H); 8.34 (m, 2 H)
10d	51	101—103	55.16 55.05	4.85 4.89	$C_{15}H_{16}F_3N_3S$	28.1 (s, CF_3)	1.68 (s, 9 H, Bu^t); 7.20 (br.s, 2 H, NH_2); 7.55 (m, 3 H); 8.31 (m, 2 H)
10e	64	208—210	52.11 52.00	3.64 3.67	$C_{13}H_{11}F_3N_2OS$	26.3 (s, CF_3)	2.38 (s, 3 H, Me); 4.45 (s, 2 H, CH_2); 7.30 (m, 3 H); 7.40 (m, 2 H)
10f	66	83—85	45.20 45.11	4.84 4.89	$C_{10}H_{13}F_3N_2OS$	—	1.67 (s, 9 H, Bu^t); 2.25 (s, 3 H, Me); 12.90 (br.s, 1 H, OH)
10g	69	247—249 (with decomp.)	51.16 51.06	4.24 4.26	$C_{14}H_{14}F_3N_3OS$	—	2.08 (s, 3 H, Me); 3.00 (s, 6 H, 2 NCH_3); 6.67 (m, 2 H); 7.22 (m, 2 H)
10h	71	243—245 (with decomp.)	45.79 45.67	3.44 3.46	$C_{11}H_{10}F_3N_3OS$	—	2.10 (s, 3 H, Me); 3.52 (s, 3 H, NCH_3); 6.10 (m, 1 H); 6.40 (m, 1 H); 7.10 (m, 1 H); 12.95 (br.s, 1 H, OH)
10i	55	273—275	51.77 51.69	3.10 3.08	$C_{14}H_{10}F_3N_3OS$	26.9 (s, CF_3)	1.90 (s, 3 H, Me); 7.10 (m, 2 H); 7.40 (m, 2 H); 7.65 (m, 1 H); 11.57 (br.s, 1 H, NH)
10j	58	308—310	51.63 51.52	3.76 3.79	$C_{17}H_{15}F_3N_4O_2S$	—	2.20 (s, 3 H, Me); 2.30 (s, 3 H, Me); 3.30 (s, 3 H, NCH_3); 7.32 (m, 3 H); 7.50 (m, 2 H)
10k	65	260—262	59.74 59.67	3.58 3.59	$C_{18}H_{13}F_3N_2OS$	—	4.59 (s, 2 H, CH_2); 7.30 (m, 3 H); 7.40 (m, 2 H); 7.55 (m, 2 H); 7.64 (m, 1 H); 8.18 (m, 2 H)
10l	53	278—280 (with decomp.)	58.39 58.31	4.07 4.09	$C_{19}H_{16}F_3N_3OS$	—	3.05 (s, 6 H, 2 NCH_3); 6.78 (m, 2 H); 7.30 (m, 4 H); 7.51 (m, 1 H); 7.79 (d, 2 H, J = 9)
10m	59	252—254	54.81 54.70	3.44 3.42	$C_{16}H_{12}F_3N_3OS$	26.2 (s, CF_3)	3.57 (s, 3 H, NCH_3); 6.20 (m, 1 H); 6.43 (m, 1 H); 7.12 (s, 1 H); 7.38 (m, 2 H); 7.54 (m, 1 H); 7.80 (m, 2 H)
10n	47	286—288	59.03 58.91	3.11 3.10	$C_{19}H_{12}F_3N_3OS$	—	7.15 (m, 4 H); 7.40 (m, 4 H); 7.55 (m, 1 H); 7.74 (s, 1 H); 11.65 (br.s, 1 H, NH)
10o	51	332—334	57.74 57.64	3.69 3.71	$C_{22}H_{17}F_3N_4O_2S$	—	2.33 (s, 3 H, Me); 3.30 (s, 3 H, NCH_3); 7.35 (m, 5 H); 7.55 (m, 3 H); 7.93 (d, 2 H, J = 9)

(*to be continued*)

Table 1 (*continued*)

Compound	Yield (%)	M.p. /°C	Found / Calculated (%) C	Found / Calculated (%) H	Molecular formula	NMR (δ, *J*/Hz)* ^{19}F	NMR (δ, *J*/Hz)* ^{1}H
11a	48	91—93	57.90 / 57.83	4.84 / 4.82	$C_{12}H_{12}FN_3S$	−75.2 (s, CF)	2.37 (s, 3 H, Me); 4.39 (s, 2 H, CH_2); 6.40 (br.s, 2 H, NH_2); 7.23 (m, 3 H); 7.36 (m, 2 H)
11b	49	111—113	65.68 / 65.59	4.47 / 4.50	$C_{17}H_{14}FN_3S$	—	4.58 (s, 2 H, CH_2); 6.85 (br.s, 2 H, NH_2); 7.27 (m, 3 H); 7.41 (m, 5 H); 8.29 (m, 2 H)
12	15	174—176	62.85 / 62.72	4.87 / 4.88	$C_{15}H_{14}FN_3S$	−65.6 (s, CF)	1.26 (s, 9 H, Bu^t); 7.67 (m, 3 H); 8.36 (m, 2 H)
13a	69	256—258	69.96 / 69.86	4.09 / 4.11	$C_{17}H_{12}N_2OS$	—	4.69 (s, 2 H, CH_2); 7.34 (m, 6 H); 7.78 (m, 2 H); 8.07 (m, 1 H); 12.52 (br.s, 1 H, NH)
13b	65	268—270	65.94 / 65.81	3.57 / 3.55	$C_{17}H_{11}FN_2OS$	−33.2 (s, CF)	4.65 (s, 2 H, CH_2); 7.37 (m, 5 H); 7.70 (m, 2 H); 7.81 (m, 1 H); 12.58 (br.s, 1 H, NH)
13c	72	270—272	70.70 / 70.59	4.55 / 4.58	$C_{18}H_{14}N_2OS$	—	2.40 (s, 3 H, Me); 4.64 (s, 2 H, CH_2); 7.29 (m, 5 H); 7.63 (m, 2 H); 7.88 (m, 1 H); 12.46 (br.s, 1 H, NH)
13d	64	285—287	71.97 / 71.88	4.14 / 4.17	$C_{23}H_{16}N_2O_2S$	—	4.67 (s, 2 H, CH_2); 7.09 (m, 2 H); 7.38 (m, 10 H); 7.80 (m, 1 H); 12.56 (br.s, 1 H, NH)
14a	52	224—226	68.11 / 67.99	5.34 / 5.38	$C_{20}H_{19}NO_3S$	—	1.25 (t, 3 H, Me, J = 7); 2.76 (q, 2 H, CH_2, J = 7); 3.75 (s, 3 H, OMe); 4.48 (s, 2 H, CH_2); 7.29 (m, 5 H); 7.60 (m, 2 H); 7.88 (m, 1 H); 11.82 (br.s, 1 H, NH)
14b	47	246—248	63.53 / 63.48	4.81 / 4.79	$C_{21}H_{19}NO_5S$	—	1.35 (t, 3 H, Me, J = 7); 3.75 (s, 3 H, OMe); 4.37 (q, 2 H, CH_2, J = 7); 4.53 (s, 2 H, CH_2); 7.30 (m, 5 H); 7.79 (m, 1 H); 8.22 (m, 1 H); 8.64 (m, 1 H); 12.19 (br.s, 1 H, NH)

* The spectra of all compounds were recorded in DMSO-d_6, except for compound **2a** (in $CDCl_3$).

N-(1-benzylthio-2-cyano-2-trifluoromethylvinyl)acetamidine (**9a**), MS, *m/z*: 299 $[M]^+$; *N*-(1-*tert*-butylthio-2-cyano-2-trifluoromethylvinyl)acetamidine (**9b**); *N*-(1-benzylthio-2-cyano-2-trifluoromethylvinyl)benzamidine (**9c**), MS, *m/z*: 361 $[M]^+$; *N*-(1-*tert*-butylthio-2-cyano-2-trifluoromethylvinyl)benzamidine (**9d**), and *N*-(1-benzylthio-2-methoxycarbonyl-2-trifluoromethylvinyl)benzamidine (**9e**).

4-Amino-6-benzylthio-2-methyl-5-(trifluoromethyl)pyrimidine (10a). A solution of amidine **9a** (1 g) in toluene (10 mL) was refluxed for 5 h and then cooled to 20 °C. The crystals that precipitated were filtered off. Compound **10a** was obtained in a yield of 0.7 g, MS, *m/z*: 299 $[M]^+$.

4-Amino-6-*tert*-butylthio-2-methyl-5-(trifluoromethyl)pyrimidine (**10b**) and 4-amino-6-benzylthio-2-phenyl-5-(trifluoromethyl)pyrimidine (**10c**) were prepared analogously.

4-Amino-6-*tert*-butylthio-2-phenyl-5-(trifluoromethyl)pyrimidine (10d) and 6-*tert*-butylthio-5-cyano-4-fluoro-2-phenylpyrimidine (12). A solution of amidine **9d** (1 g) in toluene (10 mL) was refluxed for 5 h, the solvent was removed *in vacuo*, and the residue was chromatographed on a column with silica gel (150 g) using a 1 : 2 ethyl acetate—hexane mixture as the eluent. Pyrimidine **10d** was obtained in a yield of 0.51 g, MS, *m/z*: 327 $[M]^+$. Pyrimidine **12** was obtained in a yield of 0.15 g, MS, *m/z*: 287 $[M]^+$.

Synthesis of 4-hydroxypyrimidines (general procedure). A 40% aqueous solution of NaOH (0.02 mol) was added portionwise with vigorous stirring to a suspension of the corresponding methyl acrylate (0.01 mol) and the corresponding amidine hydrochloride (0.01 mol) in benzene (20 mL). The reaction mixture was kept at ~20 °C for 30 min, refluxed for 1 h, and cooled to 20 °C. The precipitate that formed was filtered off, washed on a filter with water and benzene, and dried in air. This procedure was used for the preparation of 6-benzylthio-4-hydroxy-2-methyl-5-(trifluoromethyl)pyrimidine (**10e**); 6-*tert*-butylthio-4-hydroxy-2-methyl-5-(trifluoromethyl)pyrimidine (**10f**); 6-(4-dimethylaminophenylthio)-4-hydroxy-2-methyl-5-(trifluoromethyl)pyrimidine (**10g**); 4-hydroxy-2-methyl-6-[2-(*N*-methyl)pyrrolylthio]-5-(trifluoromethyl)pyrimidine (**10h**); 4-hydroxy-6-(3-indolylthio)-2-methyl-5-(trifluoromethyl)pyrimidine (**10i**); 4-hydroxy-6-[4-(2,3-dimethyl-5-oxo-1-phenyl)pyrazolylthio]-2-methyl-5-(trifluoromethyl)pyrimidine (**10j**); 6-benzylthio-4-hydroxy-2-phenyl-5-(trifluoromethyl)pyrimidine (**10k**); 4-hydroxy-6-(4-dimethylaminophenylthio)-2-phenyl-5-(trifluoromethyl)pyrimidine (**10l**); 4-hydroxy-6-[2-(*N*-methyl)pyrrolylthio]-2-phenyl-5-(trifluoromethyl)pyrimidine (**10m**); 4-hydroxy-6-(3-indolylthio)-2-phenyl-5-(trifluoromethyl)pyrimidine (**10n**), and 6-[4-(2,3-dimethyl-5-oxo-1-phenyl)pyrazolylthio]-4-hydroxy-2-phenyl-5-(trifluoromethyl)pyrimidine (**10o**).

4-Amino-6-benzylthio-5-fluoro-2-methylpyrimidine (11a). A solution of NaOH (0.8 g, 0.02 mol) in water (1.2 mL) was added with vigorous stirring to a suspension of 2-benzylthio-1,2-difluoroacrylonitrile (**1f**) (2.1 g, 0.01 mol) and acetamidine hydrochloride (0.95 g, 0.01 mol) in toluene (20 mL). The reaction mixture was kept at 20 °C for 30 min, refluxed for 5 h, and cooled. The residue was filtered off and recrystallized from benzene. Pyrimidine **11a** was obtained in a yield of 1.2 g, MS, *m/z*: 249 $[M]^+$.

4-Amino-6-benzylthio-5-fluoro-2-phenylpyrimidine (**11b**) was prepared analogously from benzamidine hydrochloride.

2-Benzylthio-3-cyanoquinolin-4-one (13a). A solution of acrylonitrile **2g** (1 g) in diphenyl oxide (5 mL) was heated at 180 °C for 30 min. The reacton was accompanied by gas evolution. The mixture was cooled to 50 °C and the precipitate that formed was filtered off, washed on a filter with benzene, and dissolved in a 10% aqueous solution of NaOH. The crystals that formed after neutralization with a solution of HCl were filtered off and dried in air. Quinolin-4-one (**13a**) was obtained in a yield of 0.6 g.

2-Benzylthio-3-cyano-6-fluoroquinolin-4-one (**13b**), MS, *m/z*: 310 $[M]^+$; 2-benzylthio-3-cyano-6-methylquinolin-4-one (**13c**), and 2-benzylthio-3-cyano-6-phenoxyquinolin-4-one (**13d**) were synthesized analogously.

2-Benzylthio-6-ethyl-3-(methoxycarbonyl)quinolin-4-one (14a). A solution of diether **2m** (1 g) in diphenyl oxide (5 mL) was heated at 220 °C for 30 min. The reaction was accompanied by precipitation. The mixture was cooled to 50 °C. The precipitate was filtered off and washed on a filter with benzene and hexane. Quinolinone **14a** was obtained in a yield of 0.48 g.

2-Benzylthio-6-ethoxycarbonyl-3-(methoxycarbonyl)quinolin-4-one (**14b**) was prepared analogously from diether **2n**.

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