Electron-Rich Amino Heterocycles for Regiospecific Synthesis of Trifluoromethyl-Containing Fused Pyridines

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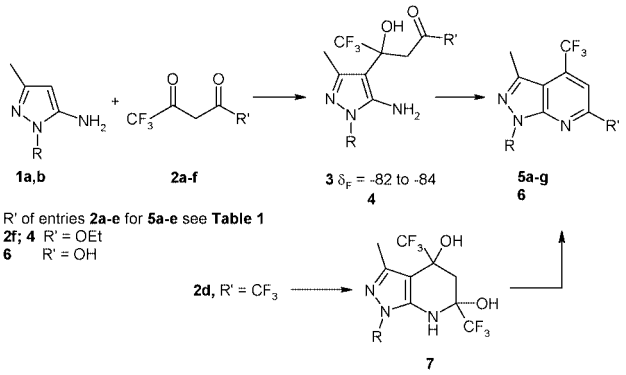
Abstract: The reaction of 4,4,4-trifluoro-3-oxobutanoates with the corresponding electron-rich amino heterocycles was investigated. A simple and flexible general procedure for the regiospecific annulation of the trifluoromethylpyridine ring to electron-rich amino heterocycles was proposed. A set of CF_3-containing fused pyridines in almost quantitative yield was obtained.

Key words: electrophilic aromatic substitutions, annulations, heterocycles, pyridines, fluorine

Since it is known that the furnishing of bioactive molecule with perfluoroalkyl substituents leads to an increase of lipid solubility, and thereby enhances the absorption rate and the transportation in vivo,[1] heterocyclic compounds bearing a trifluoromethyl group are a subject of continuous interest due to their potent pharmacological properties.[1,2] The most widespread method to produce heterocycles with a trifluoromethyl group is assembly from trifluoromethyl-containing building blocks. Recently the most popular trifluoromethyl-containing building blocks have been the following 1,3-electrophilic reagents: 4-triflouromethyl-1,3-diones,[3] β-alkoxyvinyl trifluoromethyl ketones,[4] and β-trifluoromethylsulfones.[5] The character of these approaches is the formation of mixtures of regioisomers in a reaction with non-symmetrical binucleophiles. Hence, the aim of current work within this field is the search for experimental conditions and reagents to increase the regioselectivity of the cyclocondensation.

The objective of recent work has been the continuation of our research into an electrophilic substitution of electron-rich amino heterocycles and their derivatives.[6,7] Here we focused on the reaction of 4,4,4-trifluoro-1-(het)aryl-1,3-butanediones with a set of electron-rich amino heterocycles. The procedure allows the obtainment of various fused pyridines, such as isooxazolo-, furo-, pyrazolo-, thienopyridines, and pyrido[2,3-*d*]pyrimidines, which have been of great interest in recent years because of the wide variety of their biological and pharmacological properties.[2c,8]

Earlier, the regioselective interaction of 5-aminopyrazoles **1** with 4,4,4-trifluoro-3-oxobutirates **2f** forming 4-CF_3 pyrazolo[3,4-*b*]pyridones **6** (Scheme 1) has been described.[9]



Scheme 1

However, the regiospecific trifluoromethylpyridine ring annulation to an amino heterocycle has been considered as a feature only of aminopyrazoles. Nevertheless, it was established that beside 5-aminopyrazole, other electron-rich amino heterocyles, namely 5-aminoisooxazole **8**, 6-aminouraciles **9**, 5-amino-2-carboethoxyfuran **10** and 5-amino-2-carbomethoxythiophene **11**, undergo regioselective reaction with 4,4,4-trifluoro-3-oxobutanoates affording CF_3-containing fused pyridines and pyridones **12**–**18** in high yield (Schemes 1, 2) (Tables 1, 2).

The structure elucidation of γ-CF_3 fused pyridines was based on data from ^1H, ^{13}C and ^{19}F NMR spectroscopy. The most convincing evidence of the formation of the γ-CF_3 isomer is the chemical shift of a CF_3-group ($\delta^{19}F$ –60) and a chemical shift of C(4) ($\delta^{13}C$ 130) with a coupling constant $^2J_{CF}$ ca. 35 Hz, otherwise we would expect a chemical shift of the α-CF_3-group at ($\delta^{19}F$ –67) and a chemical shift of C(2) at ($\delta^{13}C$ 145) (Tables 4, 5).[10,4a] In addition, the distant spin–spin interaction between fluorine atoms of a CF_3-group and hydrogen atoms of a C(5)–CH_3-group with a coupling constant $^6J_{HF}$ ca. 1 Hz is an interesting spectral feature of pyridines **4** and **12** (Table 1).[11]

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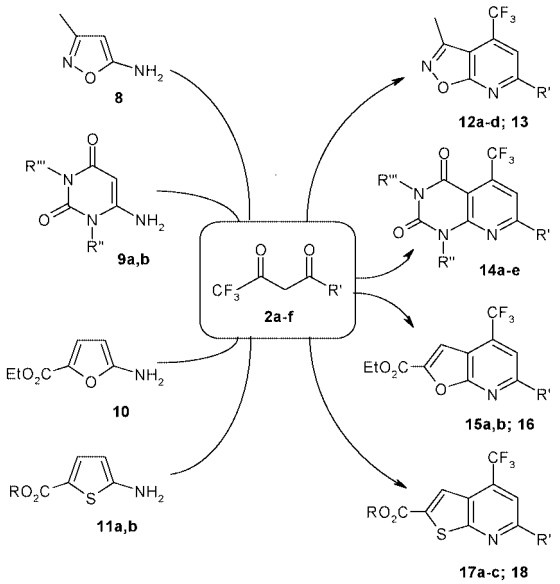
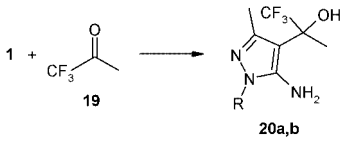


Scheme 2

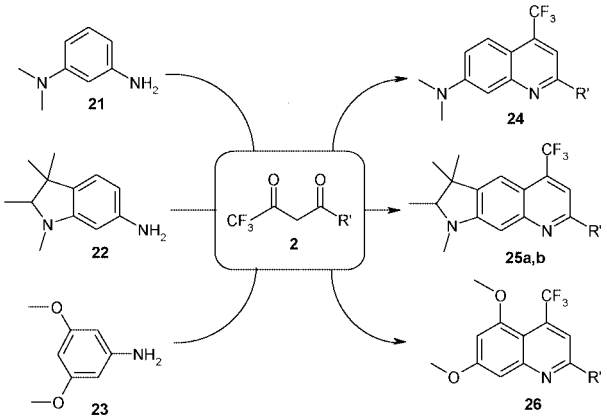
The synthesis of fused pyridines via cyclocondensation of amino heterocycles with 1,3-dicarbonyl compounds is a well-known process. However, it needs sufficiently harsh reaction conditions. Under these conditions for non-symmetrical β-diketones, regioselectivity has not been observed.[12] Nevertheless, the reaction of 4,4,4-trifluoro-3-oxobutanoates with electron-rich amino heterocycles proceeded regiospecifically under mild conditions, refluxing in acetic acid. The selectivity of the reaction with these amino heterocycles can be rationalized by the strong alternation of double bonds in the heterocycle ring and so the amino group–double bond of the ring is almost fully enamine-like. Therefore the initial attack of the active CF_3-carbonyl group occurs at the *C*-nucleophilic carbon atom of the heterocycle nucleus. In the case of 5-aminopyrazoles, the intermediates **3** or **4** were formed, which were detected by ^{19}F NMR spectroscopy. The intermediates **4** have been successfully isolated only when 4,4,4-trifluoro-3-oxobutirates **2f** were used,[9] whereas the intermediates **3** from other diones transform spontaneously into the dihydrate of pyrazolopyridine **7** or into the final products **5** (Scheme 1). However, to prove our hypothesis, the reaction of 5-aminopyrazole with the monoelectrophilic analogue of **2** – 1,1,1-triflouroacetone (**19**) – has been carried



Scheme 3

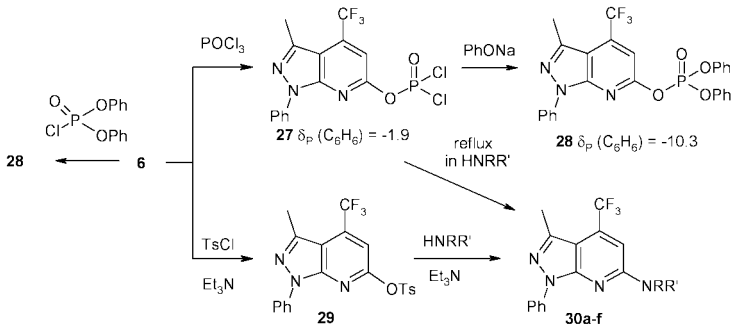
out. As a result, similarly to izatins,[9] the corresponding tertiary alcohols **20** were obtained (Scheme 3).

We were interested to apply the described procedure to anilines for the assembly of γ-CF_3 quinolines, known to be androgen receptor modulators,[13] in a similar way. It was found that only electron-rich anilines such as **21**, **22** and **23**[14] could react in the same way as amino heterocycles, giving γ-CF_3 quinolines **24**, **25** and **26**. The reaction of cyclocondensation with less *C*-nucleophilic anilines, such as 3,4,5-trimethoxyaniline or 2,3-dihydro-1,4-benzodioxin-6-amine, does not occur under analogous conditions (Scheme 4) (Table 3).

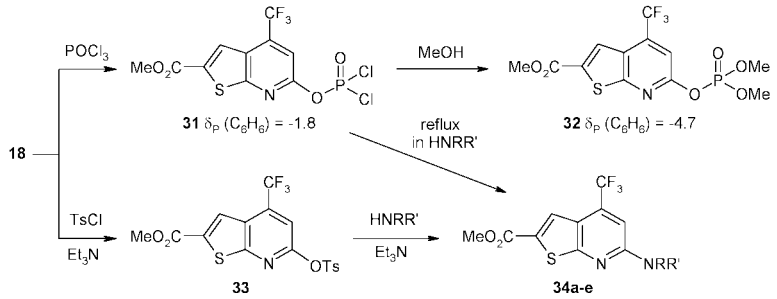


Scheme 4

In order to study pyridones as entry compounds for subsequent functionalizations, we attempted to transform pyridones **6**, **13**, **16** and **18** into corresponding α-chloropyridines. However, it was found that the treatment of 4-trifluoromethyl-1*H*-pyrazolo[3,4-*b*]pyridin-6-one (**6a**) and 4-trifluoromethyl-6,7-dihydrothieno[2,3-*b*]pyridin-6-one (**18**) with $POCl_3$ did not allow the obtainment of chloro derivatives.[15] In our case, corresponding dichloro-



Scheme 5



Scheme 6

phosphates of 4-trifluoromethyl-1*H*-pyrazolo[3,4-*b*]pyridin-6-oxyl **27** and 4-(trifluoromethyl)thieno[2,3-*b*]pyridin-6-oxyl **31**, respectively, (Schemes 5, 6) were isolated in very high yield. These dichlorophosphates were easily transformed into derivative phosphates **28** and **32**. It was expected these phosphates could easily undergo nucleophilic displacement, as a residue of phosphorus acid is a good leaving group. Alas it was not achieved. The target products were prepared in a low yield by boiling dichlorophosphates **27** and **31** in secondary amine, e.g. morpholine.[16] Further we found that pyridones **6** and **18** could be selectively *O*-tosylated giving tosylates **29** and **33**, respectively. Tosylates **29** and **33** underwent nucleophilic displacement under mild conditions with aliphatic amines[17] yielding amino derivatives **30** and **34**, respectively (Schemes 5, 6), the structural analogues of serotonin re-uptake inhibitors.[8a]

In summary, we propose a useful and convenient procedure for the synthesis of CF_3-containing fused pyridines in high yield with a vast variety of combinatorial modifications of fragments in the final structures.

Table 1 Yields, Melting Points and ^{1}H NMR Data of Compounds **3**, **4**, **6**, **11**, **13**, **14**, **18** and **19**[f]

N	R	R′	Yield (%)[a]	Mp, (°C)[b]	^{1}H NMR, δ (ppm), *J* (Hz)
5a[c]	Ph	Ph	85	144	2.73 (3 H, s, CH_3), 7.34 (1 H, t, $^3J_{HH}$ = 7.5, CH), 7.50–7.58 (5 H, m, CH), 7.91 (1 H, s, CH), 8.16 (2 H, d, $^3J_{HH}$ = 6.6, CH), 8.32 (2 H, d, $^3J_{HH}$ = 7.8, CH)
5b[c]	Ph		92	151–152	2.69 (3 H, q, $^6J_{HF}$ = 1.2, CH_3), 7.14 (1 H, dd, $^3J_{HH}$ = 4.8, $^3J_{HH}$ = 3.9, CH), 7.31 (1 H, t, $^3J_{HH}$ = 7.5, CH), 7.47–7.56 (3 H, m, CH), 7.75 (2 H, s, CH), 8.32 (2 H, d, $^3J_{HH}$ = 7.8, CH)
5c[d]	Ph		94	142–143	2.60 (3 H, s, CH_3), 7.37 (1 H, m, CH), 7.58 (3 H, br s, CH), 8.21 (3 H, br s, CH), 8.58 (1 H, d, $^3J_{HH}$ = 4.8, CH), 8.71 (1 H, s, CH), 9.40 (1 H, s, CH)
5d[c]	Ph	CF_3	91	74–75	2.77 (3 H, s, CH_3), 7.36 (1 H, t, $^3J_{HH}$ = 8.1, CH), 7.54 (2 H, t, $^3J_{HH}$ = 8.1, CH), 7.80 (1 H, s, CH), 8.23 (2 H, d, $^3J_{HH}$ = 8.1, CH)
5e[c]	Ph	Me	88	58–59	2.69 (3 H, q, $^6J_{HF}$ = 1.2, CH_3), 2.76 (3 H, s, CH_3), 7.27–7.31 (2 H, m, CH), 7.51 (1 H, t, $^3J_{HH}$ = 8.1, CH), 8.22 (2 H, d, $^3J_{HH}$ = 8.1, CH)
5f[c]	Me		74	119–120	2.61 (3 H, q, $^6J_{HF}$ = 1.0, CH_3), 4.13 (3 H, s, NCH_3), 7.16 (1 H, t, $^3J_{HH}$ = 4.8, CH), 7.49 (1 H, d, $^3J_{HH}$ = 4.8, CH), 7.68 (1 H, s, CH), 7.75 (1 H, d, $^3J_{HH}$ = 3.9, CH)
5g[c]	Me	CF_3	77	Oil	2.68 (3 H, q, $^6J_{HF}$ = 1.1, CH_3), 4.19 (3 H, s, NCH_3), 7.70 (1 H, s, CH)
6[d]	Ph	OH	86	179–181	2.50 (3 H, s, CH_3), 6.95 (1 H, s, CH), 7.34 (1 H, t, $^3J_{HH}$ = 7.6, CH), 7.53 (2 H, t, $^3J_{HH}$ = 7.6, CH), 8.10 (2 H, d, $^3J_{HH}$ = 7.6, CH), 12.26 (1 H, br s, NH)
7[e]	Ph	CF_3	36	214	2.26 (3 H, q, $^6J_{HF}$ = 2.4, CH_3), 2.40 (1 H, d, $^2J_{HH}$ = 14.1, CH_2), 2.56 (1 H, d, $^2J_{HH}$ = 14.1, CH_2), 5.78 (1 H, br s, NH_2), 6.13 (1 H, br s, OH), 6.52 (1 H, br s, OH), 7.36 (1 H, t, $^3J_{HH}$ = 7.5, CH), 7.47–7.57 (4 H, m, CH)
12a[d]	–	Ph	78	117–119	2.60 (3H, q, $^6J_{HF}$ = 0.9, CH_3), 7.58–7.60 (3 H, m, CH), 8.29–8.32 (2 H, m, CH), 8.38 (1 H, s, CH)
12b[d]	–		86	143	2.56 (3 H, q, $^6J_{HF}$ = 1.2, CH_3), 7.28 (1 H, dd, $^3J_{HH}$ = 5.1, $^3J_{HH}$ = 3.9, CH), 7.91 (1 H, dd, $^3J_{HH}$ = 5.1, $^3J_{HH}$ = 0.6, CH), 8.31 (1 H, dd, $^3J_{HH}$ = 3.9, $^3J_{HH}$ = 0.6, CH), 8.36 (1 H, s, CH)
12c[c]	–	CF_3	93	43–44	2.73 (3H, q, $^6J_{HF}$ = 1.2, CH_3), 7.96 (1 H, s, CH)

Table 1 Yields, Melting Points and ^{1}H NMR Data of Compounds **3**, **4**, **6**, **11**, **13**, **14**, **18** and **19**[f] (continued)

N	R	R′	Yield (%)[a]	Mp, (°C)[b]	^{1}H NMR, δ (ppm), *J* (Hz)
13[d]	–	OH	88	148–150[g]	2.46 (3 H, q, $^6J_{HF}$ = 0.9, CH_3), 7.05 (1 H, s, CH)
15a[d]	–	Ph	56	237–238	1.39 (3 H, t, $^3J_{HH}$ = 7.2, CH_3), 4.42 (2 H, q, $^3J_{HH}$ = 7.2, CH_2), 7.55– 7.58 (3 H, m, CH), 7.75 (1H, q, $^5J_{HF}$ = 1.2, CH), 8.23–8.26 (2 H, m, CH), 8.37 (1 H, s, CH)
15b[d]	-		74	172–173	1.42 (3 H, t, $^3J_{HH}$ = 7.2, CH_3), 4.45 (2 H, q, $^3J_{HH}$ = 7.2, CH_2), 7.26 (1 H, dd, $^3J_{HH}$ = 5.0, $^3J_{HH}$ = 3.8, CH), 7.76 (1 H, s, CH), 7.85 (1 H, d, $^3J_{HH}$ = 5.0, CH), 8.20 (1 H, d, $^3J_{HH}$ = 3.8, CH), 8.38 (1 H, s, CH)
16[d]	-	OH	81	158-160[g]	1.35 (3 H, t, $^3J_{HH}$ = 7.2, CH_3), 4.36 (2 H, q, $^3J_{HH}$ = 7.2, OCH_2), 7.11 (1 H, s, CH), 7.64 (1 H, q, $^5J_{HF}$ = 1.2, CH)
17a[d]	Me	Ph	73	155–156	3.95 (3 H, s, OCH_3), 7.57 (3 H, m, CH), 8.01 (1 H, s, CH), 8.27 (2 H, m, CH), 8.40 (1 H, s, CH)
17b[d]	Me		78	159-160	3.94 (3 H, s, OCH_3), 7.26 (1 H, dd, $^3J_{HH}$ = 4.8, $^3J_{HH}$ = 3.9, CH), 7.85 (1 H, d, $^3J_{HH}$ = 4.8, CH), 7.98 (1 H, s, CH), 8.21 (1 H, d, $^3J_{HH}$ = 3.9, CH), 8.40 (1 H, s, CH)
17c[c]	Et	CF_3	63	72–73	1.47 (3 H, t, $^3J_{HH}$ = 7.2, CH_3), 4.50 (2 H, q, $^3J_{HH}$ = 7.2, CH_2), 7.96 (1 H, s, CH), 8.24 (1 H, s, CH)
18[d]	Me	OH	84	210[g]	3.88 (3 H, s, OCH_3), 7.03 (1 H, s, CH), 7.80 (1 H, q, $^5J_{HF}$ ca. 1, CH)
20a[d]	Ph	–	98	173–175[g]	1.70 (3 H, s, CH_3), 2.14 (3 H, s, CH_3), 5.07 (2 H, br s, NH_2), 6.57 (1 H, s, OH), 7.25 (1 H, t, $^3J_{HH}$ = 7.5, CH), 7.40–7.61 (4 H, m, CH)
20b[c]	Me	–	99	84–86	1.76 (3 H, s, CH_3), 2.19 (3 H, s, CH_3), 3.55 (3 H, s, NCH_3), 4.15 (3 H, br s, NH_2 and OH)
24[d]	–	Ph	43	107	3.12 [6 H, s, $N(CH_3)_2$], 7.19 (1 H, d, $^4J_{HH}$ = 2.6, CH), 7.45 (1 H, dd, $^3J_{HH}$ = 9.6, $^4J_{HH}$ = 2.6, CH), 7.53–7.57 (3 H, m, CH), 7.89 (1H, dq, $^3J_{HH}$ = 9.6, $^5J_{HF}$ = 1.2, CH), 8.01 (1 H, s, CH), 8.28 (2 H, m, CH)
25a[c]	–		63	114–115	1.17 (3 H, s, CH_3), 1.22 (3 H, d, $^3J_{HH}$ = 6.6, CH_3), 1.39 (3 H, s, CH_3), 2.88 (3 H, s, NCH_3), 3.25 (1 H, q, $^3J_{HH}$ = 6.6, CH), 6.92 (1 H, s, CH), 7.15 (1 H, dd, $^3J_{HH}$ = 5.1, $^3J_{HH}$ = 3.3, CH), 7.45 (1 H, d, $^3J_{HH}$ = 5.1, CH), 7.53 (1 H, q, $^5J_{HF}$ = 1.2, CH), 7.69 (1 H, d, $^3J_{HH}$ = 3.3, CH), 7.72 (1 H, s, CH)
25b[c]	–	CF_3	60	46–49	1.20 (3 H, s, CH_3), 1.24 (3 H, d, $^3J_{HH}$ = 6.6, CH_3), 1.41 (3 H, s, CH_3), 2.90 (3 H, s, NCH_3), 3.34 (3 H, q, $^3J_{HH}$ = 6.6, CH), 6.98 (1 H, s, CH), 7.62 (2 H, m, CH)
26[c]	–		31	132	3.96 (3 H, s, OCH_3), 3.97 (3 H, s, OCH_3), 6.61 (1 H, d, $^4J_{HH}$ = 2.4, CH), 7.13 (1 H, d, $^4J_{HH}$ = 2.4, CH), 7.17 (1 H, dd, $^3J_{HH}$ = 5.1, $^3J_{HH}$ = 3.9, CH), 7.49 (1 H, dd, $^3J_{HH}$ = 5.1, $^4J_{HH}$ = 1.9, CH), 7.75 (1 H, dd, $^3J_{HH}$ = 3.9, $^4J_{HH}$ = 1.9, CH), 7.96 (1 H, s, CH)

[a] Yields refer to pure isolated products.
[b] Melting points are uncorrected.
[c] $CDCl_3$.
[d] DMSO-d_6.
[e] Acetone-d_6.
[f] Satisfactory microanalysis data were obtained: C ± 0.33; H ± 0.45; N ± 0.25.
[g] Sublimation.

Table 2 Yields, Melting Points and ^{1}H NMR Data[c] of Compounds **14**[d]

N	R″	R‴	R′	Yield (%)[a]	Mp (°C)[b]	^{1}H NMR, δ (ppm), *J* (Hz)
14a	Bn	H	Ph	92	239	5.52 (2 H, s, NCH_2), 7.21 (1 H, t, $^3J_{HH}$ = 7.5, CH), 7.28 (2 H, t, $^3J_{HH}$ = 7.5, CH), 7.40 (2 H, d, $^3J_{HH}$ = 7.5, CH), 7.49–7.54 (3 H, m, CH), 8.04 (1 H, s, CH), 8.11 (2 H, d, $^3J_{HH}$ = 6.3, CH), 11.98 (1 H, s, NH)
14b	Bn	H		91	253	5.42 (2 H, s, NCH_2), 7.17–7.31 (4 H, m, CH), 7.46 (2 H, d, $^3J_{HH}$ = 7.5, CH), 7.82 (1 H, d, $^3J_{HH}$ = 4.8, CH), 8.02 (1 H, s, CH), 8.17 (1 H, d, $^3J_{HH}$ = 3.6, CH), 11.91 (1 H, s, NH)
14c	Bn	H	CF_3	95	156–158	5.37 (2 H, s, NCH_2), 7.20–7.29 (3 H, m, CH), 7.42 (2 H, d, $^3J_{HH}$ = 7.5, CH), 7.84 (1 H, s, CH), 12.19 (1 H, br s, NH)

Table 2 Yields, Melting Points and ^{1}H NMR Data[c] of Compounds **14**[d] (continued)

N	R″	R‴	R′	Yield (%)[a]	Mp (°C)[b]	^{1}H NMR, δ (ppm), *J* (Hz)
14d	Bn	H	Me	73	200–202	2.63 (3 H, s, CH_3), 5.34 (2 H, NCH_2), 7.25–7.28 (3 H, m, CH), 7.37 (2 H, d, $^3J_{HH}$ = 6.6, CH), 7.52 (1 H, s, CH), 11.88 (1 H, s, NH)
14e	Me	Me		90	180–183	3.30 (3 H, s, NCH_3), 3.62 (3 H, s, NCH_3), 7.26 (1 H, dd, $^3J_{HH}$ = 5.4, $^3J_{HH}$ = 3.3, CH), 7.89 (1 H, d, $^3J_{HH}$ = 5.4, CH), 8.01 (1 H, s, CH), 8.19 (1 H, d, $^3J_{HH}$ = 3.3, CH)

[a] Yields refer to pure isolated products.
[b] Melting points are uncorrected.
[c] DMSO-d_6.
[d] Satisfactory microanalysis data were obtained: C ± 0.28; H ± 0.45; N ± 0.18.

Table 3 Yields, Melting Points and ^{1}H NMR Data of Compounds **27**–**30** and **32**–**34**[g]

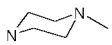
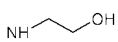
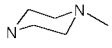
N	NRR′	Yield (%)[a]	Mp (°C)[b]	^{1}H NMR, δ (ppm), *J* (Hz)
27[e]	–	87	110	2.43 (3 H, q, $^6J_{HF}$ = 1.5, CH_3), 6.73 (1 H, s, CH), 7.02 (1 H, t, $^3J_{HH}$ = 8.1, CH), 7.29 (2 H, t, $^3J_{HH}$ = 8.1, CH), 8.38 (2 H, d, $^3J_{HH}$ = 8.1, CH)
28[f]	–	86	68–70	2.65 (3 H, q, $^6J_{HF}$ = 1.5, CH_3), 7.27–7.46 (14 H, m, CH), 8.11 (2 H, d, $^3J_{HH}$ = 7.2, CH)
29[d]	–	84	151–153	2.44 (3 H, s, CH_3), 2.61 (3 H, s, CH_3), 7.35–7.51 (6 H, m, CH), 7.77 (2 H, d, $^3J_{HH}$ = 7.8, CH), 7.89 (2 H, d, $^3J_{HH}$ = 8.1, CH)
30a[c]		68	126	1.71 (6 H, m, CH_2), 2.58 (3 H, q, $^6J_{HF}$ = 1.2, CH_3), 3.72 (4 H, m, NCH_2), 6.87 (1 H, s, CH), 7.25 (1 H, t, $^3J_{HH}$ = 7.5, CH), 7.48 (2 H, t, $^3J_{HH}$ = 7.5, CH), 8.19 (2 H, d, $^3J_{HH}$ = 7.5, CH)
30b[c]		72	137–139	2.61 (3 H, s, CH_3), 3.70 (4 H, t, $^3J_{HH}$ = 5.1, NCH_2), 3.86 (4 H, t, $^3J_{HH}$ = 5.1, OCH_2), 6.86 (1 H, s, CH), 7.26 (1 H, t, $^3J_{HH}$ = 7.5, CH), 7.49 (2 H, t, $^3J_{HH}$ = 7.5, CH), 8.16 (2 H, d, $^3J_{HH}$ = 7.5, CH)
30c[c]		53	87	2.37 (3 H, s, NCH_3), 2.53–2.60 (7 H, m, NCH_2 and CH_3), 3.76 (4 H, t, $^3J_{HH}$ = 4.5, NCH_2), 6.85 (1 H, s, CH), 7.27 (1 H, t, $^3J_{HH}$ = 7.5, CH), 7.47 (2 H, t, $^3J_{HH}$ = 7.5, CH), 8.18 (2 H, d, $^3J_{HH}$ = 7.5, CH)
30d[c]		62	112	1.27 (3 H, t, $^3J_{HH}$ = 6.6, CH_3), 1.83 (2 H, m, CH_2), 2.04 (2 H, m, CH_2), 2.59 (4 H, br s, CH_3 and CH), 3.19 (2 H, t, J_{HH} = 12.3, NCH_2), 4.16 (2 H, q, $^3J_{HH}$ = 6.6, OCH_2), 4.37 (2 H, d, $^2J_{HH}$ = 12.3, NCH_2), 6.87 (1 H, s, CH), 7.26 (1 H, t, $^3J_{HH}$ = 7.5, CH), 7.48 (2 H, t, $^3J_{HH}$ = 7.5, CH), 8.18 (2 H, d, $^3J_{HH}$ = 7.5, CH)
30e[c]		63	109	1.21–1.39 (2 H, m, CH_2), 1.60–1.59 (5 H, m, CH_2, CH and $PhCH_2$), 2.58 (3 H, s, CH_3), 2.95 (2 H, t, J_{HH} = 13.5, NCH_2), 4.46 (2 H, d, $^2J_{HH}$ = 13.5, NCH_2), 6.86 (1 H, s, CH), 7.15–7.36 (6 H, m, CH), 7.46 (2 H, t, $^3J_{HH}$ = 7.5, CH), 8.18 (2 H, d, $^3J_{HH}$ = 7.5, CH)
30f[d]		43	174–176	2.46 (3 H, s, CH_3), 3.50 (2 H, br m, NCH_2), 3.63 (2 H, br m, OCH_2), 4.67 (1 H, br s, OH), 6.89 (1 H, s, CH), 7.24 (1 H, t, $^3J_{HH}$ = 7.2, CH), 7.46 (2 H, t, $^3J_{HH}$ = 7.2, CH), 7.70 (1 H, br s, NH), 8.23 (2 H, d, $^3J_{HH}$ = 7.2, CH)
32[e]	–	59	107–108	3.35 (3 H, s, OCH_3), 3.56 [6 H, d, $^3J_{HP}$ = 12.0, $P(OCH_3)_2$], 6.87 (1 H, s, CH), 8.01 (1 H, q, $^5J_{HF}$ = 1.5, CH)
33[d]	–	73	98–99	2.47 (3 H, s, CH_3), 3.95 (3 H, s, OCH_3), 7.50 (2 H, d, $^3J_{HH}$ = 7.8), 7.68 (1 H, s, CH), 7.94 (2 H, d, $^3J_{HH}$ = 7.8, CH), 8.04 (1 H, s, CH)
34a[c]		72	115–116	1.76 (6 H, m, CH_2), 3.73 (4 H, m, NCH_2), 3.93 (3 H, s, OCH_3), 6.97 (1 H, s, CH), 7.93 (1 H, q, $^5J_{HF}$ ca. 1, CH)
34b		52	156–157	1.30 (6 H, d, $^3J_{HH}$ = 6.6, CH_3), 2.71 (2 H, t, J_{HH} = 11.7, NCH_2), 3.72 (2 H, m, OCH), 3.94 (3 H, s, OCH_3), 4.26 (2 H, d, $^2J_{HH}$ = 11.7), 6.95 (1 H, s, CH), 7.97 (1 H, s, CH)
34c		64	120–121	2.37 (3 H, s, NCH_3), 2.55 (4 H, t, $^3J_{HH}$ = 5.1, NCH_2), 3.77 (4 H, t, $^3J_{HH}$ = 5.1, NCH_2), 3.94 (3 H, s, OCH_3), 6.96 (1 H, s, CH), 7.96 (1 H, q, $^5J_{HF}$ = 1.8)

Table 3 Yields, Melting Points and ^{1}H NMR Data of Compounds **27**–**30** and **32**–**34**[g] (continued)

N	NRR′	Yield (%)[a]	Mp (°C)[b]	^{1}H NMR, δ (ppm), *J* (Hz)
34d[c]		75	160–161	2.07 (4 H, m, CH_2), 3.59 (4 H, m, NCH_2), 3.93 (3 H, s, OCH_3), 6.71 (1 H, s, CH), 7.96 (1 H, q, $^5J_{HF}$ = 1.5, CH)
34e[e]		71	116–117	1.13 (4 H, m, CH_2), 1.31 (4 H, m, CH_2), 3.12 (4 H, br m, NCH_2), 3.40 (3 H, s, OCH_3), 6.52 (1 H, s, CH), 8.26 (1 H, s, CH)

[a] Yields refer to pure isolated products.
[b] Melting points are uncorrected.
[c] $CDCl_3$.
[d] DMSO-d_6.
[e] C_6D_6.
[f] CD_3CN.
[g] Satisfactory microanalysis data were obtained: C ± 0.40; H ± 0.45; N ± 0.34; except for: **27** and **28**: H ± 0.80; N ± 0.95.

Table 4 ^{19}F and ^{13}C NMR Data of Pyrozolopyridines (X = NPh or NMe) and Isoxazolopyridines (X=O) obtained.

N	^{19}F NMR δ (ppm)	^{13}C NMR, δ (ppm), *J* (Hz)									
		Me at C(3)	C(3)	C(3a)	C(4)	C(5)	C(6)	C(7a)	CF_3	R at C(2)	R at C(6)
5c[a]	–62.1	13.3 (1.5)	140.0	109.3 (1.5)	131.3 (33.6)	109.7 (4.3)	153.3	151.5	121.6 (273.6)	120.2, 125.2, 128.0, 137.8	122.8 132.3, 133.8, 147.7, 150.0
5d[b]	–62.1	14.5	140.5	108.6 (1.5)	130.3 (33.4)	114.8 (4.3)	151.8	151.5	123.2 (273.0)	121.4, 126.6, 129.6, 139.0	25.1
5f[b]	–62.5	14.3 (1.7)	143.3	107.1	130.8 (34.4)	109.4 (2.3)	151.8	151.6	123.2 (272.6)	34.0	129.1, 129.3, 131.0, 138.4
5g[a]	–61.8, –68.0	14.1 (2.9)	139.8	111.1	133.2 (34.9)	108.6	146.7 (36.0)	151.2	122.2 (274.0)	34.1	121.1 (274.7)
6[b]	–60.7	13.9	150.4	104.7	132.5 (33.6)	103.9 (4.3)	163.4	140.3	125.0 (273.7)	121.1, 126.0, 129.0, 138.5	–
7[c]	–77.3, -83.6	14.1	143.3 (4.6)	97.7	70.5 (31.1)	35.2	83.2 (29.5)	146.3	126.0 (285.0)	123.2, 127.5, 129.9, 138.9	124.1 (283.3)
12a[b]	–61.2	12.5	159.4	107.2	133.5 (39.5)	114.0 (4.4)	154.6	170.7	122.4 (274.5)	–	128.3, 129.6, 131.7, 136.3
12c[b]	–60.8, –67.0	12.6	155.3	107.2	135.4 (36.0)	114.3	148.2 (36.0)	169.5	121.8 (274.3)	–	121.0 (276.1)
13[b]	–61.9	12.1	154.1 (11.3)	100.3	134.4 (34.8)	106.6	166.1	170.6	122.2 (273.2)	–	–
30a[b]	–62.3	14.6	140.8	102.3	131.8 (31.1)	101.6	157.8	152.0	123.4 (272.8)	120.5, 125.7, 129.5, 139.6	24.6, 25.6, 46.6

[a] $CDCl_3$.
[b] DMSO-d_6.
[c] Acetone-d_6.

Table 5 ^{19}F and ^{13}C NMR Data of Furopyridines and Thienopyridines Obtained

N	^{19}F NMR, δ (ppm)	^{13}C NMR, δ (ppm), *J* (Hz)									
		C(2)	C(3)	C(3a)	C(4)	C(5)	C(6)	C(7a)	CF_3	R at C(6)	R at C(6)
15b[a]	–61.9	146.3	113.3	113.6	133.4 (34.9)	111.2	152.0	161.8	122.3 (274.5)	14.5, 62.4, 158.3	129.3, 129.5, 131.6, 142.7
16[a]	–62.5	143.6	111.7	107.1	134.9 (34.5)	106.1	158.5	161.6	122.8 (273.4)	14.6, 62.0, 164.5	–
17b[a]	–63.8	134.6	125.3	125.1	133.5 (33.8)	113.8	153.0	163.6	121.6 (273.6)	53.6, 161.9	129.5, 129.8, 132.0, 142.7
17c[a]	–64.0, –68.2	140.3	124.5	129.8	134.8 (35.8)	114.9	146.7 (36.0)	163.0	122.7 (273.5)	14.5, 63.2, 161.1	121.3 (275.1)
18[a]	–63.3	135.3	126.0	121.4	133.8 (36.3)	124.1	163.2 (3.9)	135.7	124.9 (273.7)	53.3, 162.2	–
34a[a]	–64.9	126.4	126.0	116.8	133.9 (32.6)	104.4 (5.0)	157.5	165.1	123.5 (274.4)	53.1, 162.6	24.6, 25.8, 46.3

[a] DMSO-d_6.

^1H, ^{31}P and ^{19}F NMR spectra were recorded on a Varian VXR-300 spectrometer and ^{13}C NMR spectra were recorded on a Varian Mercury-400 spectrometer. ^1H and ^{13}C (300 and 100 MHz, respectively) with TMS as an internal standard; ^{31}P (121 MHz) with 85% H_3PO_4 as an external standard; ^{19}F (282.2 MHz) with $CFCl_3$ as an internal standard. Mass-spectra were obtained on a Hewlett–Packard HP GC/MS 5890/5972 instrument (EI, 70 eV). Column chromatography was performed on silica gel (63–200 mesh, Merck). Silica gel Merck $60F_{254}$ plates were used for TLC. Analytical data are given in Tables 1–5.

Commercially unavailable starting amino heterocycles (5-aminopyrazoles **1**,[17] 5-aminoisooxazoles **8**,[18] 5-aminouracyles **9**,[19] 2-aminofuran **10**,[20] 2-aminothiophenes **11**[21] and 1,2,3,3-tetramethyl-2,3-dihydro-1*H*-6-indolylamine **20**[22]) were prepared according to the literature.

1-R,6-R′-3-Methyl-4-trifluoromethyl-1*H*-pyrazolo[3,4-*b*]pyridines (5); Typical Procedure

A mixture of aminopyrazole **1** (3.00 mmol) and diketone **2** (3.00 mmol) in HOAc (15 mL) was refluxed for 2–4 h [the reaction mixture was monitored by TLC (silica gel; EtOAc)]. HOAc was evaporated in vacuo and the residue was triturated with H_2O and crystallized from 2-propyl alcohol.

Exception: the substance **5g** was purified by column chromatography (silica gel; EtOAc–cyclohexane, 1:1; R_f 0.90).

Compound 5f

MS (EI): *m*/*z* (%) = 297 (M^+, 100), 296 (68), 282 (12), 229 (8.6), 160 (9).

3-Methyl-1-phenyl-4-trifluoromethyl-6,7-dihydro-1*H*-pyrazolo[3,4-*b*]pyridin-6-one (6)

Compound **6** was prepared from aminopyrazole **1a** and ethyl 4,4,4-trifluoro-3-oxobutanoate **2f** using the above procedure for **5**.

MS (EI): *m*/*z* (%) = 293 (M^+, 100), 278 (13), 252 (11), 118 (11), 77 (28), 51 (12).

3-Methyl-1-phenyl-4,6-bis(trifluoromethyl)-4,5,6,7-tetrahydro-1*H*-pyrazolo[3,4-*b*]pyridine-4,6-diol (7)

To a solution of aminopyrazole **1a** (519 mg, 3.00 mmol) in EtOH (5 mL) hexafluoroacetylacetone **2d** (624 mg, 3.00 mmol) and a few crystals of iodine were added and the solution was refluxed for 30 min. After cooling the crystalline precipitate formed was filtered off.

6-R′-3-Methyl-4-trifluoromethylisoxazolo[5,4-*b*]pyridines (12)

Compounds **12** were prepared from aminoisoxazole **8** and diketones **2** using the above procedure for **5**, with exception of **12c**, which was purified by column chromatography (silica gel; EtOAc–cyclohexane, 1:1; R_f 0.89).

Compound 12b

MS (EI): *m*/*z* (%) = 284 (M^+, 100), 256 (15), 241 (29), 215 (16), 197 (11), 146 (25), 69 (10), 45 (9).

3-Methyl-4-trifluoromethyl-6,7-dihydroisoxazolo[5,4-*b*]pyridin-6-one (13)

Compound **13** was prepared from aminoisoxazole **8** and ethyl 4,4,4-trifluoro-3-oxobutanoate **2f** using the above procedure for **5**.

MS (EI): *m*/*z* (%) = 218 (M^+, 100), 199 (11), 190 (18), 176 (22), 149 (13), 121 (17), 106 (31), 70 (20), 63 (16), 42 (26).

1-R″-3-R‴-7-Methyl-5-trifluoromethyl-1,2,3,4-tetrahydropyrido[2,3-*d*]pyrimidine-2,4-diones (14)

Compounds **14** were prepared from aminouracyles **9** and diketones **2** using the above procedure for **5**.

Compound 14d

^{13}C NMR (DMSO-d_6): δ = 24.7 (CH_3), 44.5 (NCH_2Ph), 104.9 [*C*(4a)], 116.2 [$^3J_{CF}$ = 6.6, *C*(6)], 121.7 ($^1J_{CF}$ = 273.6, CF_3), 126.9 [*C*(*p*-Ph)], 127.7 [*C*(*o*-Ph)], 128.0 [*C*(*m*-Ph)], 136.9 [*C*(*ipso*-Ph)], 137.6 [$^2J_{CF}$ = 34.3, *C*(5)], 149.8 [*C*(2)], 152.8 [*C*(8a)], 158.0 [*C*(7)], 164.9 [*C*(4)].

^{19}F NMR (DMSO): δ = –60.1.

Compound 14e

MS (EI): *m*/*z* (%) = 341 (M^+, 100), 313 (16), 272 (13), 229 (81), 160 (19).

6-R′-2-Carboethoxy-4-trifluoromethylfuro[2,3-*b*]pyridines (15)
Compounds **15** were prepared from aminofurane **10** and diketones **2** using the above procedure for **5**.

Compound 15b
MS (EI): *m*/*z* (%) = 341 (M^+, 100), 313 (91), 296 (19), 269 (30), 240 (19), 190 (9), 176 (9).

2-Carboethoxy-4-trifluoromethylfuro[2,3-*b*]pyridin-6-one (16)
Compound **24** was prepared from aminofuran **10** and ethyl 4,4,4-trifluoro-3-oxobutanoate **2f** using the above procedure for **5**.

MS (EI): *m*/*z* (%) = 275 (M^+, 93), 247 (98), 230 (100), 203 (92), 147 (45), 155 (23), 146 (33), 126 (27), 69 (19).

6-R′-2-Carboalkoxy-4-trifluoromethylthieno[2,3-*b*]pyridines (17)
Compounds **14** were prepared from aminothiophenes **11** and diketones **2** using the above procedure for **5**, with the exception of **17c**, which was purified by column chromatography (silica gel; EtOAc–cyclohexane, 1: 1; R_f 0.87).

Compound 17b
MS (EI) *m*/*z* (%) = 343 (M^+, 100), 312 (73), 284 (7), 264 (10), 240 (9), 215 (19), 156 (5).

2-Carbomethoxy-4-trifluoromethylthieno[2,3-*b*]pyridin-6-one (18)
Compound **25** was prepared from aminothiophene **11a** and ethyl 4,4,4-trifluoro-3-oxobutanoate **2f** using the above procedure for **5**.

MS (EI): *m*/*z* (%) = 277 (M^+, 58), 246 (100), 190 (15), 163 (33), 119 (8), 94 (7), 69 (11).

2-(5-Amino-1-R,3-methyl-1*H*-4-pyrazolyl)-1,1,1-trifluoro-2-propanols (20); Typical Procedure
To an aminopyrazole **1** (3.00 mmol), trifluoroacetone **19** (2 mL) and a few crystals of iodine were added and the heterogeneous reaction mixture was refluxed 10 min. After cooling the reaction mixture was maintained at r.t. for 1 h. The excess of trifluoroacetone was evaporated in vacuo and the residue was crystallized from toluene (for **20a**) or a mixture toluene–cyclohexane (for **20b**).

Compound 20a
^{13}C NMR (DMSO-d_6): δ = 15.6 (CH_3), 23.2 (CH_3), 72.6 ($^2J_{CF}$ = 27.6, CF_3C), 98.8 [*C*(4)], 123.7 [*C*(*o*-Ph)], 126.9 [*C*(*p*-Ph)], 127.5 ($^1J_{CF}$ = 287.4, CF_3), 129.7 [*C*(*m*-Ph)], 139.3 [*C*(*i*-Ph)], 146.0 [*C*(3)], 146.8 [*C*(5)].

^{19}F NMR (DMSO): δ = –83.0.

Compound 20b.
^{13}C NMR (DMSO-d_6): δ = 15.4 (CH_3), 23.2 (CH_3), 34.2 (NCH_3), 72.4 ($^2J_{CF}$ = 27.9, CF_3C), 97.7 [C(4)], 127.6 ($^1J_{CF}$ = 277.8, CF_3), 143.2 [C(3)], 146.7 [C(5)].

^{19}F NMR (DMSO): δ = –84.2.

7-(*N*,*N*-Dimethylamino)-2-phenyl-4-trifluoromethylquinoline (24)
Compound **24** was prepared from aniline **21** and diketone **2a** using the above procedure for **5** and was purified by column chromatography (silica gel; EtOAc, R_f 0.68).

^{13}C NMR (DMSO-d_6): δ = 40.3 [$N(CH_3)_2$], 107.1 [C(6)], 111.3 [$^3J_{CF}$ = 2.8, C(3)], 113.3 [C(4a)], 118.5 [C(8)], 124.1 [C(5)], 124.3 ($^1J_{CF}$ = 274.5, CF_3), 127.7 [*C*(*m*-Ph)], 129.4 [*C*(*o*-Ph)], 130.4 [*C*(*p*-Ph)], 133.7 [$^2J_{CF}$ = 31.5, C(4)], 138.5 [*C*(*ipso*-Ph)], 150.9 [*C*(8a)], 151.8 [*C*(2)], 156.3 [*C*(7)].

^{19}F NMR (DMSO): δ = –62.7.

MS (EI): *m*/*z* (%) = 316 (M^+, 100), 315 (68).

7-R′-1,2,3,3-Tetramethyl-5-trifluoromethyl-2,3-dihydro-1*H*-pyrrolo[3,2-*g*]quinolines (25)
Compounds **25** were prepared from aniline **22** and diketones **2** using the above procedure for **5** and were purified by column chromatography (silica gel; EtOAc–cyclohexane; 1:1).

Compound 25a
R_f (EtOAc–cyclohexane,1:1) 0.88.

^{13}C NMR (DMSO-d_6): δ = 12.8 [C(2)CH_3], 23.5 [C(3)CH_3], 26.2 [C(3)CH_3], 32.1 [N(1)CH_3], 42.6 [C(3)], 70.7 [C(2)], 101.4 [C(9)], 110.0 [$^3J_{CF}$ = 4.2, C(6)], 115.3 [C(4)], 115.7 [C(4a)], 124.4 ($^1J_{CF}$ = 273.7, CF_3), 127.7 [C(3′-Thio)], 129.1 [*C*(4′-Thio)], 130.2 [*C*(5′-Thio)], 133.3 [$^2J_{CF}$ = 30.5, *C*(5)], 144.8 [*C*(2′-Thio)], 145.3 [*C*(3a)], 150.6 [*C*(7)], 151.4 [*C*(8a)], 154.0 [*C*(9a)].

^{19}F NMR (DMSO): δ = –62.5.

MS (EI): *m*/*z* (%) = 376 (M^+, 49), 361 (100), 346 (49), 331 (6), 188 (5), 180 (9), 173 (18).

Compound 25b
R_f (EtOAc–cyclohexane, 1:1) 0.79.

^{13}C NMR (DMSO-d_6): δ = 12.9 [C(2)CH_3], 23.4 [C(3)CH_3], 26.4 [C(3)CH_3], 31.8 [N(1)CH_3], 43.1 [C(3)], 70.5 [C(2)], 100.8 [C(9)], 108.9 [C(6)], 115.2 [C(4)], 118.4 [C(4a)], 121.8 ($^1J_{CF}$ = 275.9, CF_3), 123.7 ($^1J_{CF}$ = 276.4, CF_3), 134.1 [$^2J_{CF}$ = 31.3, C(5)], 145.5 [$^2J_{CF}$ = 31.3, C(7)] 149.2 [C(3a)], 151.3 [C(8a)], 154.4 [C(9a)].

^{19}F NMR (DMSO): δ = –62.4 (3 F), –68.8 (3 F).

MS (EI): *m*/*z* (%) = 362 (M^+, 31), 347 (100), 332 (57), 156 (8), 69 (7).

5,7-Dimethoxy-2-(2-thienyl)-4-trifluoromethylquinoline (26)
Compound **26** was prepared from aniline **23** and diketone **2b** using the above procedure for **5** and was purified by column chromatography (silica gel; EtOAc; R_f 0.76).

^{13}C NMR ($CDCl_3$): δ = 56.4 (OCH_3), 56.7 (OCH_3), 101.2 [C(6)], 101.9 [C(6)], 111.0 [C(4a)], 114.2 [$^3J_{CF}$ = 7.8, C(3)], 124.1 ($^1J_{CF}$ = 273.5, CF_3), 127.2 [C(3′-Thio)], 128.9 [C(4′-Thio)], 129.9 [C(5′-Thio)], 134.6 [$^2J_{CF}$ = 33.1, C(4)], 144.8 [C(2′-Thio)], 152.9 [C(2)], 153.0 [C(8a)], 156.2 [C(5)], 162.2 [C(7)].

^{19}F NMR (acetone): δ = –60.7.

MS (EI) *m*/*z* (%) = 339 (M^+, 100), 310 (20), 296 (12), 281 (15), 266 (11), 253 (16), 108 (10).

3-Methyl-1-phenyl-4-trifluoromethyl-1*H*-pyrazolo[3,4-*b*]pyridin-6-yl Phosphoric Acid Dichloroanhydride (27)
To a pyrazolopyridone **6a** (2.92 g, 10 mmol) was added $POCl_3$ (4 mL) and the reaction mixture was refluxed for 3 h. The excess of $POCl_3$ was evaporated in vacuo. The residue was dissolved in a mixture of anhyd toluene (20 mL) and anhyd hexane (10 mL). The solution was filtered under a blanket of anhyd argon to remove the insoluble precipitate, solvents were evaporated in vacuo and the residue was crystallized (anhyd hexane).

3-Methyl-1-phenyl-4-trifluoromethyl-1*H*-pyrazolo[3,4-*b*]pyridin-6-yldiphenylphosphate (28)
Method via Dichloroanhydride 27
To a stirring solution of sodium phenolate (0.566 g, 4.8 mmol) in anhyd dioxane (20 mL) dichloroanhydride **27** (1.00 g, 2.4 mmol) was added. The reaction mixture was maintained at r.t. for 1.5 h and

then was refluxed for 15 min. Dioxane was evaporated in vacuo, the residue was triturated with H_2O and crystallized (2-propyl alcohol).

Method via Phosphorylation of Pyrazolopyridone 6a
Compound **28** was prepared from pyrazolopyridone **6a** and $(PhO)_2POCl$ using the below procedure for **29**.

Yield: 71%.

3-Methyl-6-(4-methylphenylsulfonyloxy)-1-phenyl-4-trifluoromethyl-1*H*-pyrazolo[3,4-*b*]pyridine (29)
To a solution of pyrazolopyridone **6a** (2.92 g, 10 mmol) and Et_3N (1.4 mL, 10 mmol) in dioxane (20 mL), tosyl chloride (1.91 g, 10 mmol) was added. The reaction mixture was refluxed 8 h, then dioxane was evaporated in vacuo, and the residue was triturated with H_2O and washed with MeOH (5 mL).

3-Methyl-6-morpholino-1-phenyl-4-trifluoromethyl-1*H*-pyrazolo[3,4-*b*]pyridine (30b)
Method via Dichloroanhydride 27
To a pyrazolopyridone **6a** (0.5 g, 1.71 mmol) was added $POCl_3$ (2 mL) and reaction mixture was refluxed for 3 h. The excess of $POCl_3$ was evaporated in vacuo. To the residue was added morpholine (3 mL) and the mixture was refluxed for 4 h, then the excess of morpholine was evaporated in vacuo, the residue was triturated with H_2O and crystallized (2-propyl alcohol).

Yield: 0.245 g (39%).

6-(*N*-R,*N*′-R′-Amino)-3-methyl-1-phenyl-4-trifluoromethyl-1*H*-pyrazolo[3,4-*b*]pyridines (30); Typical Procedure
To a solution of tosylate **29** (0.45 g, 1.0 mmol) in dioxane (10 mL), the appropriate amine (2.5 mmol) was added. The reaction mixture was refluxed 2–4 h [the reaction was monitored by TLC (silica gel; EtOAc)]. Dioxane was evaporated in vacuo, and the residue was triturated with H_2O and crystallized from an appropriate solvent: **30 a**,**b**, *i*-PrOH; **30 d**,**f**, MeOH; **30e**, mixture of *i*-PrOH–heptane ca. 10:1.

Exeption: the substunce **30c** was purified by the following procedure. The crude product was placed on a short silica gel column and washed with EtOAc to wash out the by-products and then washed with MeOH to afford the target product.

Compound 30a
MS (EI): *m*/*z* (%) = 360 (M^+, 100), 345 (12), 331 (54), 317 (24), 304 (45), 292 (24), 277 (22), 251 (9), 236 (6), 180 (8), 84 (21), 77 (28).

Compound 30c
MS (EI): *m*/*z* (%) = 375 (M^+, 22), 318 (11), 305 (100), 83 (19), 77 (20), 70 (51), 43 (24).

2-Carbomethoxy-4-trifluoromethylthieno[2,3-*b*]pyridin-6-yl Dimethylphosphate (32)
To a thienopyridone **18** (2.77 g, 10 mmol) was added $POCl_3$ (4 mL) and reaction mixture was refluxed 3 h. The excess of $POCl_3$ was evaporated in vacuo. To the residue anhyd benzene (20 mL) was added. The solution was filtered under anhyd argon to remove the insoluble precipitate. To the stirred filtrate, Et_3N (4 mL, 29 mmol) and anhyd MeOH (1 mL, 31 mmol) were added. The reaction mixture was maintained at r.t. for 1.5 h, and then was refluxed for 15 min. The precipitate of $Et_3N{\cdot}HCl$ formed was filtered off. The filtrate was concentrated in vacuo and the residue was crystallized (MeOH).

2-Carbomethoxy-6-(4-methylphenylsulfonyloxy)-4-trifluoromethylthieno[2,3-*b*]pyridine (33)
To a solution of thienopyridone **18** (2.77 g, 10 mmol) and Et_3N (1.4 mL, 10 mmol) in dioxane (20 mL), tosyl chloride (1.91 g, 10 mmol) was added. The reaction mixture was refluxed 16 h, then the dioxane was evaporated in vacuo, the residue was triturated with H_2O and crystallized (MeOH).

6-(*N*-R,*N*′-R′-Amino)-2-carbomethoxy-4-trifluoromethylthieno[2,3-*b*]pyridine (34); Typical Procedure
To a solution of tosylate **33** (0.43 g, 1.0 mmol) in dioxane (10 mL) an appropriate amine (1.3 mmol) and *i*-Pr_2NEt (0.70 mL, 4 mmol) were added. The reaction mixture was refluxed 4–8 h (the reaction mixture was monitored by TLC (silica gel; EtOAc). Dioxane was evaporated in vacuo, the residue was triturated with H_2O and crystallized from an appropriate solvent: **34 a**,**d**,**e**, *i*-PrOH; **34b**, MeOH; **34c**, mixture of *i*-PrOH–heptane ca. 10:3.

Compound 34a
MS (EI): *m*/*z* (%) = 344 (M^+, 100), 329 (11), 315 (49), 301 (40), 288 (41), 276 (30), 261 (42), 245 (11), 230 (21), 182 (8), 84 (23), 41 (10).

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References

(1) (a) Filler, R. In *Flourine Containing Drugs in Organoflourine Chemicals and Their Industrial Application*, Chap. 6; Pergamon: New York, **1979**. (b) Holland, G. F.; Pereira, J. N. *J. Med. Chem.* **1967**, *10*, 149.
(2) (a) Rempfler, H.; Duerr, D. EP 337944, **1989**; Chem. Abstr. 1990, 112, 139043r. (b) Rempfler, H.; Duerr, D.; Thummel, R. C. EP 337943, **1989**; *Chem. Abstr.* **1990**, *112*, 139044s. (c) Kawasaki, H.; Ozawa, K.; Yamamoto, K. WO 0198301, **2001**; *Chem. Abstr.* **2001**, *136*, 69807. (d) Grutzmann, R.; Muller, U.; Bischoff, H.; Zaiss, S. WO 0197787, **2001**; *Chem. Abstr.* **2001**, *136*, 64132. (e) Strobel, H.; Wohlfart, P.; Safarova, A.; Walser, A.; Suzuki, T.; Dharanipragada, R. M. WO 0264545, **2002**; *Chem. Abstr.* **2002**, *137*, 185515. (f) Yoshimi, K.; Kozuka, M.; Sakai, J.; Iizawa, T.; Shimizu, Y.; Kaneko, I.; Kojima, K.; Iwata, N. *Jpn. J. Pharmacol.* **2002**, *88*, 174; *Chem. Abstr.* **2002**, *137*, 15686.
(3) (a) Denisova, A. B.; Sosnovskikh, V. Ya.; Dehaen, W.; Toppet, S.; Meervelt, L. V.; Bakulev, V. A. *J. Flourine Chem.* **2002**, *115*, 183. (b) Song, L. P.; Zhu, S. Z. *J. Flourine Chem.* **2001**, *111*, 201; and references cited therein. (c) Ohkura, H.; Berbasov, D. O.; Soloshonok, V. A. *Tetrahedron Lett.* **2003**, *44*, 2417.
(4) (a) Bonacorso, H. G.; Duarte, S. H. G.; Zanatta, N.; Martins, M. A. P. *Synthesis* **2002**, 1037. (b) Bonacorso, H. G.; Watowski, A. D.; Muniz, M. N.; Zanatta, N.; Martins, M. A. P. *Synthesis* **2002**, 1079. (c) Martins, M. A. P.; Sinhorin, A. P.; Da Rosa, A.; Flores, A. F. C.; Wastowski, A. D.; Pereira, C. M. P.; Flores, D. S.; Beck, P.; Freitag, R. A.; Brondani, S.; Cunico, W.; Bonacorso, H. G. *Synthesis* **2002**, 2353.
(5) (a) Krasovsky, A. L.; Moiseev, A. M.; Nenajdenko, V. G.; Balenkova, E. S. *Synthesis* **2002**, 901. (b) Krasovsky, A. L.; Hartuluari, A. S.; Nenajdenko, V. G.; Balenkova, E. S. *Synthesis* **2002**, 133.
(6) (a) Pushechnikov, A. O.; Volochnyuk, D. M.; Tolmachev, A. A. *Synlett* **2002**, 1040. (b) Volochnyuk, D. M.; Kostyuk, A. N.; Pinchuk, A. N.; Tolmachev, A. A. *Tetrahedron Lett.* **2003**, *44*, 391.

(7) (a) Volochnyuk, D. M.; Pushechnikov, A. O.; Krotko, D. G.; Koydan, G. N.; Marchenko, A. P.; Chernega, A. N.; Pinchuk, A. M.; Tolmachev, A. A. *Synthesis* **2003**, 906. (b) Tolmachev, A. A.; Dovgopoly, S. I.; Kostyuk, A. N.; Kozlov, E. S.; Pushechnikov, A. O.; Holzer, W. *Heteroat. Chem.* **1999**, *10*, 391. (c) Kovaleva, S. A.; Chubaruk, N. G.; Tolmachev, A. A.; Pinchuk, A. M. *Khim. Geterotsikl. Soed.* **2001**, 1287; *Chem. Abstr.* **2002**, *137*, 47274. (d) Oshovsky, G. V.; Pinchuk, A. M.; Tolmachev, A. A. *Mendeleev Commun.* **1999**, *9*, 161. (e) Kovaleva, S. A.; Ivonin, S. P.; Pinchuk, A. M.; Tolmachev, A. A. *Khim. Geterotsikl. Soed.* **2001**, 1285; *Chem. Abstr*. **2002**, *137*, 47273.

(8) (a) Suzuki, M.; Iwasaki, H.; Fujikawa, Y.; Sakashita, M.; Kitahara, M.; Sakoda, R. *Bioorg. Med. Chem. Lett.* **2001**, *11*, 1285. (b) Bondavalli, F.; Botta, M.; Bruno, O.; Ciacci, A.; Corelli, F.; Fossa, P.; Lucacchini, A.; Manetti, F.; Martini, C.; Menozzi, G.; Mosti, L.; Ranise, A.; Schenone, S.; Tafi, A.; Trincavelli, M. L. *J. Med. Chem.* **2002**, *45*, 4875. (c) Straub, A.; Stasch, J.-P.; Alonso-Alija, C.; Benet-Buchholz, J.; Ducke, B.; Feurer, A.; Fuerstner, C. *Bioorg. Med. Chem. Lett.* **2001**, *11*, 781. (d) Shutske, G. M.; Roehr, J. E. *J. Heterocycl. Chem.* **1997**, *34*, 789.

(9) Balicki, R. *Pol. J. Chem.* **1983**, *57*, 789.

(10) Linderman, R. J.; Kirollos, K. S. *Tetrahedron Lett.* **1990**, *31*, 2689.

(11) For distant spin-spin H–F interaction see: Ionin, B. I.; Yershov, B. A.; Kol'tsov, A. I. *NMR-Spectroscopy in Organic Chemistry*, 2nd ed.; Yershov, B. A., Ed.; Leningrad: Khimiya, **1983**.

(12) (a) Lynch, B. M.; Khan, M. A.; Teo, H. C.; Pedrotti, F. *Can. J. Chem.* **1988**, *66*, 420. (b) Emerson, W. S.; Holly, F. W.; Klemm, L. H. *J. Am. Chem. Soc.* **1941**, *63*, 2569.

(13) (a) Hamann, L. G.; Kong, J.; Edwards, J. P. WO 0116133, **2001**; *Chem. Abstr.* **2001**, *134*, 222698. (b) Kong, J. W.; Hamann, L. G.; Ruppar, D. A.; Edwards, J. P.; Marschke, K. B.; Jones, T. K. *Bioorg. Med. Chem. Lett.* **2000**, *10*, 411. (c) Zhi, L.; Van Oeveren, C. A.; Chen, J.-H.; Higuchi, R. I. WO 0266475, **2002**; *Chem. Abstr.* **2002,** *137*, 201294. (d) Hamann, L. G.; Mani, N. S.; Davis, R. L.; Wang, X.-N.; Marschke, K. B.; Jones, T. K. *J. Med. Chem.* **1999**, *42*, 210.

(14) Pushechnikov, A. O.; Krotko, D. G.; Volochnyuk, D. M.; Tolmachev, A. A. *Synlett* **2001**, *6*, 860.

(15) Chandra Sheker Reddy, A.; Narsian, B.; Venkataratman, R. V. J. *J. Flourine Chem.* **1997**, *86*, 127; and references cited therein.

(16) (a) Arutyunnyan, E. A.; Gunar, V. I.; Gracheva, E. P.; Zav'yalov, S. I. *Izv. Akad. Nauk USSR, Ser. Khim.* **1968**, 445; *Chem. Abstr*. **1968**, *69*, 86943u. (b) Rosowsky, A.; Papathanasopoulos, N. *J. Heterocycl. Chem.* **1972**, *9*, 1235.

(17) (a) Arcadi, A.; Cacchi, S.; Fabrizi, G.; Manna, F.; Pace, P. *Synlett* **1998**, *4*, 446. (b) Cacchi, S.; Carangio, A.; Fabrizi, G.; Moro, L.; Pace, P. *Synlett* **1997**, *12*, 1400. (c) Hinkle, J. S.; Lever, O. W. *Tetrahedron* **1988**, *44*, 3391.

(18) Grandberg, I. I.; Ting, W.-P.; Kost, A. N. *Zh. Obshich. Khim*. **1961**, *31*, 2311; *Chem. Abstr*. **1962**, *56*, 25079.

(19) Abushanab, E.; Lee, D. Y.; Goodman, L. *J. Heterocycl. Chem*. **1973**, *10*, 181.

(20) Traube, W. *Chem. Ber.* **1900**, *33*, 1381.

(21) Dann, O. *Chem. Ber.* **1943**, *76*, 419.

(22) Tolmachev, A. A.; Tolmacheva, V. S.; Shevchuk, L. I.; Kozlov, E. S.; Babichev, F. S. *Khim. Geterotsikl. Soed.* **1989**, 919; *Chem. Abstr*. **1990**, *112*, 35624.