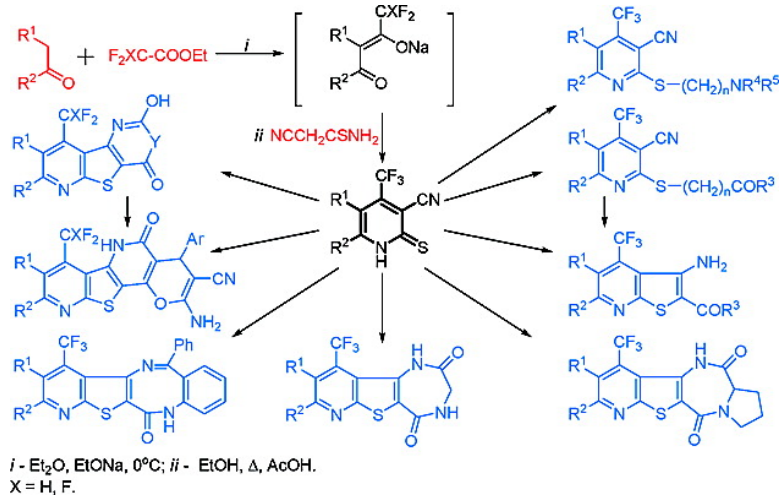
JOURNAL OF combinatorial CHEMISTRY

Article

One-Pot Synthesis of Diverse 4-Di(tri)fluoromethyl-3-cyanopyridine-2(1*H*)-thiones and Their Utilities in the Cascade Synthesis of Annulated Heterocycles

Lyudmila A. Rodinovskaya, Anatoliy M. Shestopalov, Anna V. Gromova, and Alexander A. Shestopalov

J. Comb. Chem., **2008**, 10 (2), 313-322• DOI: 10.1021/cc7001793 • Publication Date (Web): 13 February 2008



More About This Article

Additional resources and features associated with this article are available within the HTML version:

- Supporting Information
- Access to high resolution figures
- Links to articles and content related to this article
- Copyright permission to reproduce figures and/or text from this article

View the Full Text HTML

One-Pot Synthesis of Diverse 4-Di(tri)fluoromethyl-3-cyanopyridine-2(1*H*)-thiones and Their Utilities in the Cascade Synthesis of Annulated Heterocycles

Lyudmila A. Rodinovskaya,* Anatoliy M. Shestopalov, Anna V. Gromova, and Alexander A. Shestopalov

N. D. Zelinsky Institute of Organic Chemistry, RAS, Moscow, Russia, 119991

Received November 7, 2007

Diverse substituted 4-di(tri)fluoromethyl-3-cyanopyridine-2(1*H*)-thiones were synthesized via the Claisen condensation of α-methyl(methylene)ketones with di(tri)fluoroacetate, followed by the immediate Thorpe−Guareschi reaction of the preformed di(tri)fluoromethyl-1,3-diketones with cyanothioacetamide. The procedure allows facile synthesis of the di(tri)flouromethylated pyridine-2(1*H*)-thiones in 50–95% yields, without the need for isolation and purification of intermediates. Resultant 4-di(tri)fluoromethyl-3-cyanopyridine-2(1*H*)-thiones were subsequently utilized in domino reactions to produce first various substituted thieno[2,3-*b*]pyridines and, then, thienopyridines polyannulated with pyridine, pyrimidine, benzodiazocine, diazepine, and pyran rings.

Introduction

The introduction of the di(tri)fluoromethyl group into a structure of an organic molecule often causes significant changes in its chemical, physical, and physiological properties;[1,2] consequently, many fluoromethyl-substituted compounds attract significant attention as possible agrochemicals[3] and drug candidates.[4–9] Likewise, 3-cyanopyridine-2(1*H*)-thiones have been shown to exhibit several potent biological activities such as selective binding to the 5-HT1A, the dopamine D4, and the adenosine receptors, as well as inhibition of nitric oxide synthase.[10–17] Fluoromethylpyridines themselves were identified as potential herbicides[3,18–20] and medically important compounds.[5,6,10,15,21] Apart from the useful biological properties, 6-methyl-4-trifluoromethyl-3-cyanopyridine-2(1*H*)-thiones and 4-methyl-6-trifluoromethyl-3-cyanopyridine-(1*H*)-thiones have been effectively utilized in the past as versatile building blocks suitable for preparation of diverse libraries of annulated and nonannulated heterocycles.[20] These reasons motivated us to develop a new efficient method to synthesize diverse 3-cyanopyridine-2(1*H*)-thiones, containing the di(tri)fluoromethyl group, and to demonstrate these compounds as effective building blocks suitable for fast derivatization.

In most cases, fluoromethylated 3-cyanopyridine-2(1*H*)-thiones are obtained by the reaction of fluoromethylated 1,3-diketones with cyanothioacetamide.[17,20,22–25] Unfortunately, synthesis, isolation, and purification of the fluoromethylated 1,3-diketone starting materials often involve laborious multistep procedures, resulting in poor yields.[7–9,26] Hence, the diversity of the accessible fluoromethylated 3-cyanopyridine-2(1*H*)-thiones was usually determined by the commercial availability of the corresponding fluoromethylated 1,3-diketones,[20,22–25] the majority of which stem from aroyltrifluoroacetones. Here, we report a new regioselective method to synthesize 4-difluoro(trifluoro)methyl-3-cyanopyridine-2(1*H*)-thiones, which excludes the isolation and the purification of the fluoromethylated 1,3-diketone intermediates and allows facile preparation of fluoromethylated 3-canopyridine-2(1*H*)-thione products containing both aromatic and aliphatic substituents in the fifth and sixth positions.

Results and Discussion

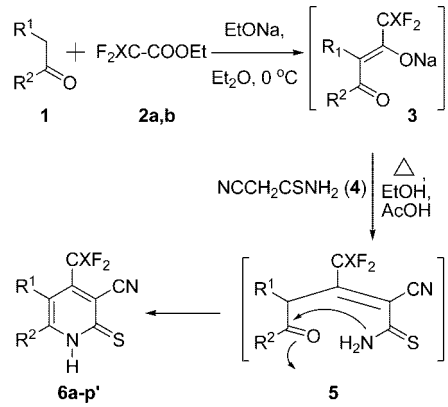
The developed method allows the entire synthesis of the final pyridine-2(1*H*)-thiones to be carried out in a single reaction vessel, without isolation or transfer of the fluoromethylated intermediates. First, the Claisen condensation between corresponding methyl(methylene)ketone **1** and ethyl difluro(trifluoro)acetate **2a**,**b** is conducted in ether in the presence of sodium ethoxide to produce corresponding sodium salt **3**; then, after evaporation of ether, the reaction mixture is reacted with cyanothioacetamide at 50–60 °C in ethanol, quenched with acetic acid, and refluxed for a short period of time to produce final pyridine **6**, which precipitates at 5–10 °C within several hours (Scheme 1). The yields of prepared 4-di(tri)fluoromethyl-3-cyanopyridine-2(1*H*)-thiones **6** vary from 50% to 98% and strongly depend on other substituents present in the pyridine ring (see Supporting Information Tables 2 and 3). Nevertheless, they are comparable with the yields of pyridinethiones obtained straight from the fluoromethylated 1,3-diketones,[17] which, considering unavoidable losses during isolation of the 1,3-diketones, only add to advantages of the developed technique.

The described procedure not only permits synthesis of diverse 4-di(tri)fluoromethyl-3-cyanopyridine-2(1*H*)-thiones with virtually any possible aryl- or heteroaryl-substituents in the sixth position but also allows preparation of various

* Corresponding author. E-mail: lar@ioc.ac.ru.

10.1021/cc7001793 CCC: $40.75
Published on Web 02/13/2008

Scheme 1. Synthesis of 4-Di(tri)fluoromethyl-3-cyanopyridine-2(1*H*)-thiones



6	R^1	R^2	X
a	H	4-CH_3-C_6H_4	F
b	H	4-Br-C_6H_4	F
c	H	2-Cl-C_6H_4	F
d	H	3,4-Cl_2-C_6H_3	F
e	H	2-C_4H_3O	F
f	H	2-(5-CH_3-C_4H_2O)	F
g	H	3-CH_3O-C_6H_4	F
h	H	4-CH_3O-C_6H_4	F
i	H	4-C_2H_5O-C_6H_4	F
j	H	2,5-$(CH_3O)_2$-C_6H_3	F
k	H	3,4-$(CH_3O)_2$-C_6H_3	F
l	H	3,4-OCH_2CH_2O-C_6H_3	F
m	H	3,4-OCH_2O-C_6H_3	F
n	H	3-C_5H_4N	F
o	H	4-C_5H_4N	F
p	H	CH_2-C_6H_5	F
q	H	3,4-$(CH_3O)_2$-C_6H_3-CH_2	F
r	H	*i*-C_3H_7	F
s	H	$C(CH_3)_3$	F
t	H	*c*-C_3H_5	F
u	H	Ad[1]	F

6	R^1	R^2	X
v	CH_3	CH_2CH_3	F
w		-$(CH_2)_3$-	F
x		-$(CH_2)_4$-	F
y		-$(CH_2)_5$-	F
z		-$(CH_2)_6$-	F
a'		$CH_2CH(CH_3)CH_2CH_2$	F
b'		$CH_2CH(CH_2CH_3)CH_2CH_2$	F
c'		$CH_2CH(C(CH_3)_3)CH_2CH_2$	F
d'		$CH_2CH(C_6H_5)CH_2CH_2$	F
e'		$CH_2N(COCH_3)CH_2CH_2$	F
f'	H	4-Cl-C_6H_4	H
g'	H	4-F-C_6H_4	H
h'	H	3-CH_3O-C_6H_4	H
i'	H	4-CH_3O-C_6H_4	H
j'	H	3-C_5H_4N	H
k'	H	2-C_4H_3S	H
l'	H	3,4-$(CH_3O)_2$-C_6H_3	H
m'	H	3,4-OCH_2O-C_6H_3	H
n'	H	Ad[1]	H
o'	H	CH_2-C_6H_5	H
p'		-$(CH_2)_4$-	H

6-alkyl substituted pyridines, including sterically hindered and constrained adamantil- and cyclopropyl-substitutions. Moreover, the same method can be used to obtain 5,6-dialkyl- and 5,6-cycloalkylpyridine-2(1*H*)-thiones or even pyridinethiones annulated with other heterocycles (e.g., *N*-acetylnaphthyridinethione **6e′**). The regioselectivity of the reaction was confirmed by synthesis of 6-methyl-4-trifluromethyl-3-cyanopyridine-2(1*H*)-thione, which was previously studied by X-ray analysis.[24,25]

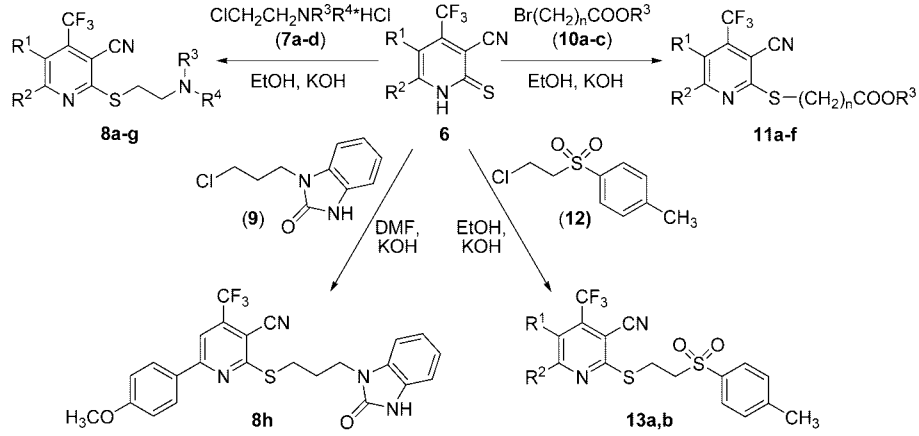
The structures of pyridinethiones **6** were supported by IR, ^{1}H NMR, ^{19}F NMR, and elemental analyses (see Supporting Information Table 1). The IR spectra of **6** show a characteristic adsorption band of the CN group in the 2216–2244 cm^{-1} region. The ^{1}H NMR spectra of **6** with an unsubstituted fifth position contain signals of the 5-H proton at 6.60–8.06 ppm. The NH signals of **6** appear as characteristic singlets in the 13.90–14.89 ppm area.[17,22–25] Difluoromethylpyridine-2(1*H*)-thiones **6c′**−**m′** display CHF_2 signals in their ^{1}H NMR spectra at 7.06–7.15 ppm as triplets with $^2J_{H,F}$ = 52.0–54.5 Hz.[9,27,28] The ^{19}F NMR spectra of trifluoromethyl-substituted **6k**,**p**,**u**,**x** contain singlets of fluorine peaks at −57.67 to −63.23 ppm, whereas fluorine signals of difluoromethyl-substituted pyridines **6g′**,**l′**,**n′**,**o′**,**p′** appear as doublets at −115.62 to −117.72 ppm with $^2J_{H,F}$ = 49.9–55.5 Hz, which correlate well with the literature.[9,27,28]

Our method has also opened new synthetic approaches toward various di(tri)fluoromethylated heterocycles, which frequently attract practical attention.[10]

We have demonstrated that obtained pyridinethiones **6** undergo facile alkylation reaction with alkyl halogenides **7a**−**d** and **9** containing various amino-moieties. Derivatized pyridines **8a**−**h** were obtained in high yields under refluxing conditions in a 10% ethanolic solution of KOH. Similarly, pyridinethiones **6** were reacted with alkyl halogenides **10a**−**c** or **12** to produce polymethylene carboxylic acids and esters **11a**−**f**, and sulfonylarenes **13a**,**b** (Scheme 2).

Using a similar approach, we have prepared several carboxylic acids and esters **15a**−**g**, whose structures have been previously implicated as possible anti-inflammatory drug candidates (Schemes 3 and 4).[15] We have demonstrated that compounds **15** with R^4 = H readily undergo Thorpe−Ziegler cyclization into 3-aminothieno[2,3-*b*]pyridines **16**, which were also prepared directly from pyridinethiones **6** and alkane halogenides **14a**,**c**, without isolating **15**. As such, 3-aminothieno[2,3-*b*]pyridinecarboxyilic acids **16a**−**c** were synthesized by refluxing corresponding pyridinethiones **6** and monochloroacetic acid **14a** in ethanol in the presence of three equivalents of sodium ethoxide. After completion of the reaction (TLC control), free carboxylic acids were precipitated from the reaction mixture with HCl. An analogous approach was utilized to prepare several pyridine derivatives **18a**−**e** and **19a**−**d** containing a carbonyl group. Similar to carboxylic acids **16**, thienopyridines **19** were also prepared directly from **6** and **17**, without isolating **18**. In addition, several 2-(arylthio)pyridines **21a**−**f**, which analogues have previously shown antianginal, antineoplastic, anti-inflam-

Scheme 2. Alkylation Reaction of 4-Di(tri)fluoromethyl-3-cyanopyridine-2(1*H*)-thiones



7: R^3–R^4 = -$CH_2CH_2OCH_2CH_2$- (**a**); -$(CH_2)_5$- (**b**); -$(CH_2)_6$- (**c**); -$(CH_2)_4$- (**d**).
10: n = 2, R^3 = H (**a**); n = 2, R^3 = Et (**b**); n = 3, R^3 = Et (**c**).
13: R^1 = H, R^2 = 4-CH_3O-C_6H_4 (**a**); R^1 = H, R^2 = *c*-C_3H_5 (**b**)

	R^1	R^2	R^3R^4
8a	H	3-CH_3O-C_6H_4	$CH_2CH_2OCH_2CH_2$
8b	H	3,4-Cl_2-C_6H_3	$CH_2CH_2OCH_2CH_2$
8c	H	*c*-C_3H_5	$(CH_2)_5$
8d	H	3,4-OCH_2O-C_6H_3	$(CH_2)_5$
8e	H	4-C_5H_4N	$(CH_2)_6$
8f	H	3,4-$(CH_3O)_2$-C_6H_3	$(CH_2)_4$
8g	$CH_2CH(C_6H_5)CH_2CH_2$		$(CH_2)_4$

	R^1	R^2	R^3	n
11a	H	*c*-C_3H_5	H	2
11b	H	Ad[1]	H	2
11c	H	$C(CH_3)_3$	C_2H_5	2
11d		-$(CH_2)_5$-	C_2H_5	2
11e	H	2-(5-CH_3-C_4H_2O)	C_2H_5	3
11f	$CH_2CH(CH_3)CH_2CH_2$		C_2H_5	3

matory, and vasodilator activities,[11–14,16] have been prepared from **6** and **10** via standard alkylation conditions.

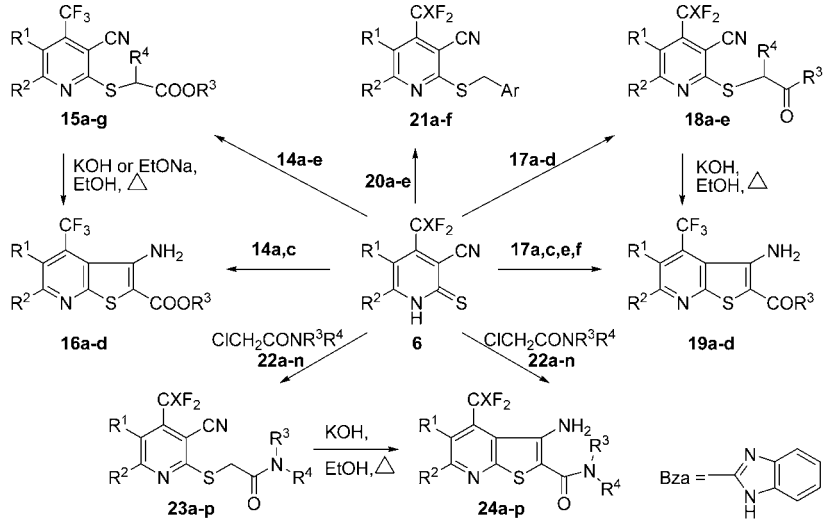
By alkylation of di(tri)fluoromethylated pyridinethiones **6** with α-chloroacetic acid amides **22** we have prepared pyridylthioacetic acid amides **23a**−**p**, which are commonly used as precursors for a subsequent cyclization into polyannulated heterocyclic systems. The alkylation reactions were carried out in DMF in the presence of an equimolar amount of 10% aq KOH. Amides **23** were isolated in 62–96% yields (see Supporting Information Table 7) as colorless high melting point powders, which were generally insoluble even in such polar organic solvents as ethanol. The subsequent cyclization of amides **23** into thienopyridines **24** was accomplished under refluxing conditions in ethanol over a period of 5–7 min in the presence of an equimolar amount of 10% aq KOH. The yields of the thienopyridines **24a**−**p**, obtained by the cyclization of amides **23**, were 60–98% (method A, Supporting Information Table 8). The same thienopyridines **24a**−**p** were also obtained in comparable overall yields (58–92%) directly from pyridinethiones **6** and amides **22** by refluxing the starting material in ethanol over a period of 5–10 min in the presence of two equivalents of 10% aq KOH (method B, Supporting Information Table 8).

The structures of compounds **15**, **16**, **18**, **19**, **21**, **23**, and **24** were supported by IR, NMR, and elemental analyses. The IR spectra of all acyclic pyridinethiones **15**, **18**, **21**, and **23** contain a characteristic absorption band of the CN group in the 2224–2232 cm^{-1} region (Supporting Information Tables 4, 6, and 8). Contrarily, all cyclized 3-aminothieno[2,3-*b*]pyridines **16**, **19**, and **24** lack this band in their IR spectra but instead display distinctive deformational (1576–1624 cm^{-1}) and valence (3240–3536 cm^{-1}) vibrations of the NH_2 group (Supporting Information Tables 5 and 8). Presumably, compound **24l** contains an intramolecular hydrogen bond between the CN group and the NH_2 group, which is in part supported by the merge of the IR absorption bands of these two groups into the one broadened band at 1612 cm^{-1} and by the presence of the third valence absorption band of the NH_2 group. The IR spectra of carboxylic acids **15a**−**d** and **16a**−**c**, in addition to other characteristic bands, contain the absorption peak of the OH group at 3440–3536 cm^{-1}. The ^1H NMR spectra of **15** and **18**, containing the thiomethylene group, display the SCH_2 protons at 3.33–5.06 ppm, whereas the ^1H NMR spectra of compounds **21** and **23** have the thiomethylene protons at 4.59–4.97 and 4.04–4.52 ppm, respectively (Supporting Information Tables 4, 6, and 8). 3-Aminothieno[2,3-*b*]pyridines **16**, **19**, and **24** contain signals of the NH_2 group at 3.18–7.67 ppm, depending on the substituent in the second position.

In the past, several examples of thieno[2,3-*b*]pyridines annulated with pyridine,[29–33] pyrimidine,[30–32] and benzodiazepine rings,[34] synthesized via cascade reactions, were reported in the literature. However, no examples of thieno[2,3-*b*]pyridines annulated with eight-membered rings were reported until now.

We have envisioned the formation of the eight-membered diazocine ring system from thienopyridine **24t**, which, having the amino- and keto groups separated by six other atoms, can potentially close to a new polyannulated six-, five-, or eight-membered heterocyclic system. Accordingly, thieno[2,3-*b*]pyridine **25** annulated with the benzodiazocine ring was isolated in 65% yield after refluxing 3-aminothieno[2,3-*b*]pyridine **24t** for 3 h in ethanol in the presence of KOH. The IR spectrum of **25** contains absorption bands of the CONH group at 1652 and 3440 cm^{-1}. In the ^1H NMR spectrum of **25**, a signal of the NH group appears at 12.21 ppm and lacks entirely the NH_2 protons.

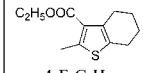
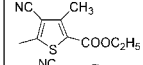
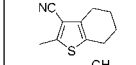
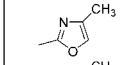
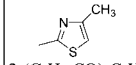
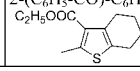
Scheme 3. Synthesis of Di(tri)fluoromethylated 3-Aminothieno[2,3-*b*]pyridines



14: $ClCH_2COOH$ (**a**); $BrCH(C_6H_5)COOH$ (**b**); $ClCH_2COOC_2H_5$ (**c**); $BrCH_2COOCH_2C_6H_5$ (**d**); $BrCH(CH_3)COOC_2H_5$ (**e**).
17: $ClCH_2COCH_3$ (**a**); $ClCH(CH_3)COCH_3$ (**b**); 3,4-(OCH_2O)-C_6H_3-$COCH_2Br$ (**c**); 3,4-$(OH)_2$-C_6H_3-$COCH_2Br$ (**d**); 3,4-(OCH_2CH_2O)-C_6H_3-$COCH_2Br$ (**e**); 3,4-$(OCH_3)_2$-C_6H_3-$COCH_2Br$ (**f**).
20: HOOC-C_6H_4-CH_2-Br (**a**); 2-C_5H_4N-CH_2-Cl.HCl (**b**); $ClCH_2$-Bza (**c**); 5-CH_3-Bza-CH_2-Cl (**d**), 3-(6-Cl-C_5H_3N)-CH_2-Cl.HCl (**e**)

	X	R^1	R^2	R^3	R^4
15a	F	H	3,4-$(CH_3O)_2$-C_6H_3	H	H
15b	F	H	Ad[1]	H	H
15c	F	H	2-C_4H_3O	H	C_6H_5
15d	F	H	4-Br-C_6H_4	H	C_6H_5
15e	F	H	Ad[1]	C_2H_5	H
15f	F	H	2-C_4H_3O	$CH_2C_6H_5$	H
15g	F	H	$CH_2C_6H_5$	C_2H_5	CH_3
18a	F	H	3,4-(OCH_2O)-C_6H_3	CH_3	H
18b	F	H	3,4-(OCH_2CH_2O)-C_6H_3	CH_3	CH_3
18c	F	H	4-C_5H_4N	3,4-(OCH_2O)-C_6H_3	H
18d	F	H	3,4-$(CH_3O)_2$-C_6H_3	3,4-$(OH)_2$-C_6H_3	H
18e	H	H	3,4-$(CH_3O)_2$-C_6H_3	CH_3	H

	R^1	R^2	R^3
16a	H	Ad[1]	H
16b	H	$C(CH_3)_3$	H
16c	H	*c*-C_3H_5	H
16d	H	Ad[1]	C_2H_5
19a	H	3,4-(OCH_2O)-C_6H_3	CH_3
19b	H	4-OCH_3-C_6H_4	3,4-$(OCH_3)_2$-C_6H_3
19c	H	2-(5-CH_3-C_4H_2O)	3,4-(OCH_2O)-C_6H_3
19d	H	4-C_5H_4N	3,4-(OCH_2CH_2O)-C_6H_3

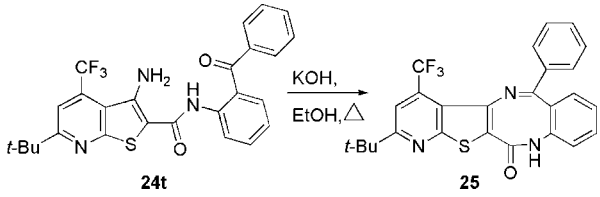
			X	R^1	R^2	R^3	R^4
22a	**23a**	**24a**	F	H	Ad[1]	C_2H_5	C_2H_5
22b	**23b**	**24b**	F	H	Ad[1]	$CH(CH_3)_2$	H
22c	**23c**	**24c**	F	H	4-CH_3-C_6H_4	C_3H_5	H
22d	**23d**	**24d**	F	H	4-CH_3O-C_6H_4	Ad[1]	H
22e	**23e**	**24e**	F	H	*c*-C_3H_5		H
22f	**23f**	**24f**	F		$(CH_2)_6$	4-F-C_6H_4	H
22g	**23g**	**24g**	F		$(CH_2)_4$	4-Cl-2-CH_3-C_6H_3	H
22h	**23h**	**24h**	F		$CH_2N(COCH_3)CH_2CH_2$	3-CN-C_6H_4	H
22i	**23i**	**24i**	F	H	$C(CH_3)_3$		H
22j	**23j**	**24j**	F		$CH_2CH(CH_3)CH_2CH_2$		H
22k	**23k**	**24k**	F	H	4-C_5H_4N		H
22l	**23l**	**24l**	F		$(CH_2)_3$		H
22m	**23m**	**24m**	F	H	$C(CH_3)_3$	2-(C_6H_5-CO)-C_6H_4	H
22n	**23n**	**24n**	H	H	CH_2-C_5H_6	2-F-C_6H_4	H
22m	**23o**	**24o**	H	H	3,4 $(CH_3O)_2$-C_6H_3	2-(C_6H_5-CO)-C_6H_4	H
22e	**23p**	**24p**	H	H	4-CH_3O-C_6H_4		H

	X	R^1	R^2	Ar
21a	F	H	CH_2-C_6H_5	4-COOH-C_6H_4
21b	F	H	3,4-$O(CH_2)_2$-O-C_6H_3	2-C_5H_4N
21c	F	H	4-C_5H_4N	Bza
21d	F	CH_3	C_2H_5	Bza
21e	F	H	2-C_4H_3O	5-CH_3-Bza
21f	H	H	4-OCH_3-C_6H_4	3-(6-Cl-C_5H_3N)

Several natural derivatives of benzopyrrolodiazepinediones **26** (see Figure 1) were previously accounted as potent anticancer agents.[35] We have utilized prepared 4-trifluoro-3-cyanopyridine-2(1*H*)-thiones **6v**,**y** as initial building blocks in the development of synthetic methods leading to new diazepinediones and pyrrolodiazepinediones polyannulated with heterocycles.

First, an ethanolic reaction of pyridine-2(1*H*)-thiones **6v**,**y** with *N*-chloroacetyl amino acids **22a′**,**b′** regioselectively gave *S*-substituted pyridines **27** and **30** (glycine and proline

Scheme 4. Synthesis of 2-*tert*-Butyl-6-phenyl-4-(trifluoromethyl)pyrido[3′,2′:4,5]thieno[2,3-*c*][1,5]benzodiazocin-12(11*H*)-one (**25**)



derivatives) at 25 °C in the presence of two equivalents of KOH. Next, after a concise heating in ethanol in the presence of two equivalents of KOH compound **27** underwent the Thorpe−Ziegler cyclization with the formation of substituted thieno[2,3-*b*]pyridine **28** (method A). Compound **28** was also isolated after refluxing pyridine **6y** and acid **22a′** in ethanol with excess KOH (method B). Finally, compound **28** was thermally cyclized (at the melting point temperature) into annulated diazepinedione **29** (Scheme 5). On the contrary, uncyclized pyridine **30** produced pollyannulated pyrrolodiazepinedione **31** directly after ethanolic reflux with the excess of KOH (the maximum yield of **31** was achieved after 3 h of reflux).

In addition to thienopyridines annulated with eight-membered diazocines and seven-membered diazepinediones, prepared 4-di(tri)fluoromethyl-3-cyanopyridine-2(1*H*)-thiones **6** can also be used as precursors in synthesis of thieno[2,3-*b*]pyridines annulated with six-membered pyridine or pyrimidine rings. An interest in such compounds is exemplified by the important biological properties of their analogues, hydroxy(oxo)(pyridines)pyrimidines.[17,33]

A reaction of 4-trifluoromethyl-3-cyano-2(1*H*)-thiones **6** with alkylhalogenides **32a**,**b** in DMF or ethanol in the presence of equimolar amount of KOH gave corresponding thio-substituted pyridines **33a**−**f** (Scheme 6, Supporting Information Table 9). Subsequently, in alkaline conditions (KOH or EtONa), compounds **33a**,**c**,**f** were transformed into 4-hydroxy-1*H*-thieno[2,3-*b*:4,5-*b′*]dipyridine-2-ones **34 h**,**r** (Y = CH) and pyrido[3′,3′:4,5]thieno[3,2-*d*]pyrimidine-2,4-diole **35c** (Y = NH) via two consecutive intramolecular Thorpe−Ziegler and Guareschi−Thorpe condensations.[29–33] Alternatively, more than thirty examples of various compounds (**34** and **35**) were obtained in high yields directly from pyridinethiones **6** and alkylhalogenides **32** via cascade heterocyclization in one technological step without isolation of any intermediates.

Prepared thienopyridinones **34k**,**o**,**s** were used as outstanding precursors for the synthesis of polyannulated pyrans **38a**−**c**. Being strong CH acids,[31,33] they were readily reacting with arylmethylenemalononitriles **36** in DMF in the presence of triethylamine yielding tetra- and penta-annulated 2-amino-4-aryl-5-oxo-3-cyano-5,6-dihydro-4*H*-pyrano[2,3-*d*]pyrido[3′,2′:4,5]thieno[3,2-*b*]pyridines **38**. Compounds **38** were isolated as stable high melting microcrystals poorly soluble in most organic solvents with the exception of DMSO and DMF.

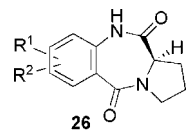


Figure 1. 2,3-Dihydro-1*H*-benzo[*e*]pyrrolo[1,2-*a*][1,4]diazepine-5,11(10*H*,11*H*)-diones.

The structures of compounds **34** and **35** were confirmed by IR, NMR, and elemental analyses. Comparing the ^{1}H NMR spectra of **34** (X = CH) with the spectra of substituted pyridine-2(1*H*)-thiones,[17] we assumed that thieno[2,3-*b*;4,5-*b′*]dipyridines exist in the pyridine-2(1*H*)-thione tautomeric form **A** (Scheme 6). An NMR signal of the C^{3}H proton in **34** is shielded by C^2═O and C^4—OH groups and thus shifted into the strong field at 5.04–6.44 ppm. A signal of the NH group is broad and shifted to the characteristic for pyridine-2(1*H*)-thiones area at 9.21–11.98 ppm.[17] The IR spectra of compounds **34** (X = CH) contain characteristic absorption bands of the NH(CO) and OH groups at 1600–1672 and 3070–3468 cm^{-1}, respectively (Supporting Information Table 10). The IR spectra of **35** (X = N) show absorption bands of the CONH and OH groups (Supporting Information Table 11). The ^{1}H NMR spectra of compounds **35** contain signals of the pyridine ring protons, together with the signals of the ring substituents, and NH and OH groups.

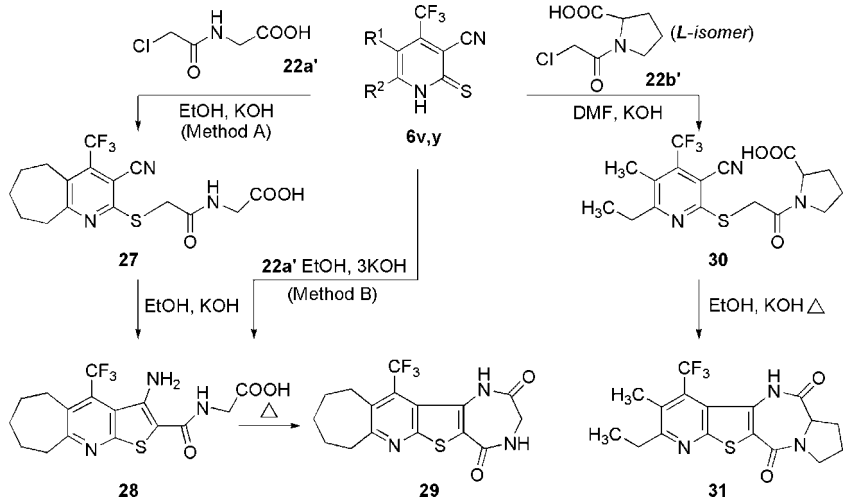
The ^{1}H NMR spectra of compounds **38a**−**c** contain signals of aliphatic and aromatic protons, and singlets of 4H protons of the pyran ring at 4.60–4.67 ppm. Protons of the NH_2 and NH groups appear at 7.23–7.37 and 11.25–11.64 ppm, respectively. The IR spectra of **38a**−**c** contain a valent absorption band of the CN group at 2200–2204 cm^{-1} and characteristic NH_2 and NH groups' valent and deformation bands at 3184–3448 and 1624–1676 cm^{-1}. Analogous IR spectra were previously recorded for other annulated 2-amino-4-aryl-3-cyano-4*H*-pyrans.[36,37]

In conclusion, we developed a novel and simple method of synthesis of diverse 4-di(tri)fluoromethyl-3-cyano-2(1*H*)-thiones **6** and demonstrated that these compounds readily undergo typical transformations for pyridinethiones, which in most cases can be conducted in ethanol (as opposed to DMSO and DMF) due to the higher solubility of fluorinated pyridines. The key feature of this method is the ability to synthesize almost any substituted 4-di(tri)fluoromethyl-3-cyano-2(1*H*)-thiones in one pot directly from readily available starting materials without isolating and purifying any reaction intermediates.

Experimental Details

All reagents were purchased from Sigma-Aldrich and Acros and used as supplied. IR spectra were recorded on the Perkin-Elmer-57 and the Second M80 spectrometers in KBr pellets at a 0.01 M concentration. ^{1}H NMR spectra were collected on the Bruker AC-300 (300 MHz), Bruker AM-300 (300 MHz), and Bruker WM-250 (250 MHz) spectrometers in DMSO-d_6. ^{13}C NMR spectra were recorded on the Bruker AC-200 (50.32 MHz) in DMSO-d_6. ^{19}F NMR spectra were recorded on the Bruker AC-200 (188.31 MHz) in DMSO-d_6. Mass spectra were obtained on the Varian MAT-CH-6 spectrometer with direct sample injection at an ionization voltage of 70 eV. Elemental analysis was performed on the Perkin-Elmer C,H,N-analyzer. Completion of the reactions and purity of the obtained products were

Scheme 5. Synthesis of Diazepinediones and Pyrrolodiazepinediones Polyannulated with Heterocycles



monitored by thin-layer chromatography (TLC) on the Silufol UV-254 plates using a hexane−acetone mixture (5:3) as an eluent and iodine vapors as a stain.

4-Di(tri)fluoromethyl-3-cyanopyridine-2(1*H*)-thiones (6a−p′). A solution of corresponding ketone **1** (0.1 mol) and ethyl difluoroacetate **2a** (0.15 mol) or trifluoroacetate **2b** (0.15 mol) in anhydrous ethyl ether (70 mL) was slowly added (1 h period) to a stirring suspension of sodium ethoxide (6.8 g, 0.1 mol) in anhydrous ethyl ether (150 mL) at 0 °C. The reaction mixture was then stirred at 0 °C for 1 h and at room temperature for 3 h. The solvent was subsequently evaporated under reduced pressure, and the crude material was dissolved in ethanol (100 mL). Cyanothioacetamide (11 g, 0.11 mol) was added to the resulting solution; the reaction mixture was heated at 50–60 °C for 1–2 min and then added with glacial acetic acid (9 mL). Lastly, the reaction mixture was heated to reflux, cooled to room temperature, and left at 5 °C overnight. The resulting precipitate was collected, washed with ethanol (3 × 5 mL) and hexanes (3 × 5 mL), and recrystallized from ethanol to afford analytically pure pyridine-2(1*H*)-thiones **6a−p′**. Yields and physical properties of compounds **6a−p′** are given in Supporting Information Table 1.

Substituted 2-Aminoethylthio-4-trifluoromethyl-3-cyanopyridines (8a−g). To a suspension of 4-trifluoromethyl-3-cyanopyridine-2(1*H*)-thione **6** (0.005 mol) in ethanol (30 mL) was added a 10% aq KOH solution (5.6 mL, 0.01 mol) and then corresponding alkyl halogenide **7** (0.005 mol). The reaction mixture was refluxed until all starting materials were dissolved and then cooled down to room temperature. Precipitate (if needed water can be added to the reaction mixture to initiate precipitation) was filtered out and washed with water (2 × 10 mL), ethanol (3 × 5 mL), and hexanes (3 × 5 mL) to afford pure alkylated pyridinethiones **8a−g**. Yields and physical properties of compounds **8a−g** are given in Supporting Information Table 2.

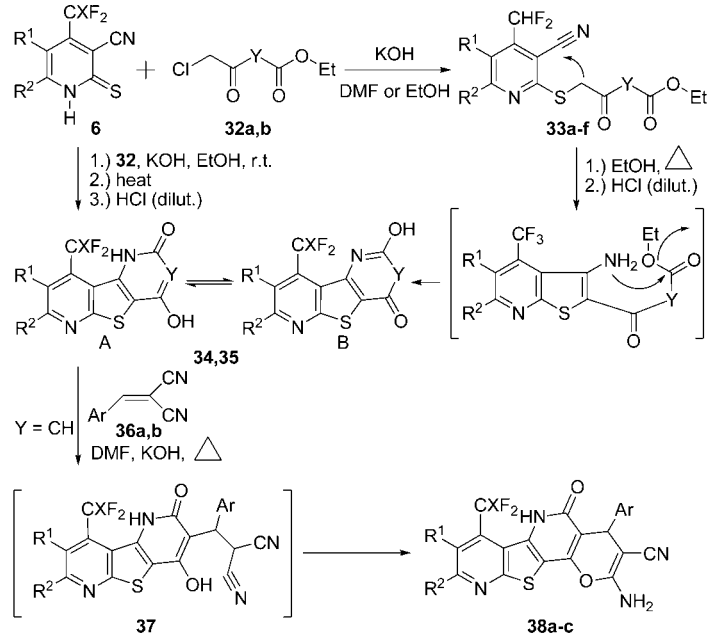
2-Alkylthio-4-trifluoromethyl-3-cyanopyridines (8h, 11a−f, and 13a,b). To a suspension of 4-trifluoromethyl-3-cyanopyridine-2(1*H*)-thione **6** (0.005 mol) in ethanol (30 mL) was added a 10% aq KOH solution (2.8 mL, 0.005 mol) and then corresponding alkyl halogenide **10a−c** and **12** (0.005 mol). The reaction mixture was refluxed until all starting materials were dissolved and then cooled down to room temperature. Resultant precipitate (if needed water can be added to the reaction mixture to initiate precipitation) was filtered out and washed with water (2 × 10 mL), ethanol (3 × 5 mL), and hexanes (3 × 5 mL) to afford pure alkylated pyridinethiones **11a−f** and **13a**,**b**. Compound **8h** was obtained from pyridinethione **6h** and alkyl halogenide **9** following the same protocol and using dimethylformamide as a solvent. Yields and physical properties of compounds **8h**, **11a−f**, and **13a**,**b** are given in Supporting Information Table 3.

S-substituted 4-Di(tri)fluoromethyl-3-cyanopyridines (15, 18, 21, and 23). To a suspension of 4-trifluoromethyl-3-cyanopyridine-2(1*H*)-thione **6** (0.005 mol) in ethanol (30 mL) or DMF (30 mL) was added a 10% aq KOH solution (2.8 mL, 0.005 mol) and then corresponding alkyl halogenide **14a−e**, **17a−d**, **20a−c**, and **22a−y** (0.005 mol). The reaction mixture was refluxed until all starting materials have dissolved and then cooled down to room temperature. Precipitate (if needed water can be added to the reaction mixture to initiate precipitation) was filtered out, washed with water (2 × 10 mL), ethanol (3 × 5 mL), and hexanes (3 × 5 mL) to afford pure alkylated pyridinethiones **15**, **18**, **21**, and **23**. Compound **21b** was obtained following the same protocol, but using 1.2 equiv of KOH. Yields and physical properties of compounds **15**, **18**, **21**, and **23** are given in Supporting Information Tables 4, 6, and 7.

4-Trifluoromethyl-3-aminothieno[2,3-*b*]pyridine carboxylic acids (16a−c). Method A. A reaction mixture comprising compound **15b** (1.19 g, 0.003 mol) and sodium ethoxide (0.06 mol) in ethanol (50 mL) was refluxed for 1 h and cooled down to room temperature. It was then diluted with water (7 mL) and acidified with hydrochloric acid until no more precipitation was observed. After 2 h, the precipitate was filtered out and washed with water (2 × 10 mL), ethanol (3 × 5 mL), and hexanes (3 × 5 mL) yielding pure **16a** (0.74 g, 0.00186 mol, 62% yield).

Method B. Pyridinethione **6** (0.28 g, 0.003 mol), sodium ethoxide (0.61 g, 0.009 mol) and monochloroacetic acid (0.28 g, 0.003 mol) were refluxed in ethanol (50 mL) for 1 h (TLC

Scheme 6. Synthesis of Thieno[2,3-*b*]pyridines Annulated with Pyridine or Pyrimidine Rings



32: Y = CH_2 (**a**), NH (**b**). **36**: Ar = 4-Cl-C_6H_4 (**a**); 4-CH_3O-C_6H_4 (**b**) **38**: X = F, R^1 - R^2 = $(CH_2)_5$, Ar = 4-Cl-C_6H_4 (**a**); X = H, R^1 = H, R^2 = 3,4-OCH_2O-C_6H_3, Ar = 4-Cl-C_6H_4 (**b**); X = H, R^1 = H, R^2 = 4-OCH_3-C_6H_4, Ar = 4-CH_3O-C_6H_4 (**c**).

	X	Y	R^1	R^2
33a	F	CH_2	H	3,4-OCH_2O-C_6H_3
33b	F	CH_2		$CH_2CH(C(CH_3)_3)CH_2CH_2$
33c	H	CH_2	H	3,4-$(CH_3O)_2$-C_6H_3
33d	F	NH	H	$C(CH_3)_3$
33e	F	NH	H	Ad[1]
33f	F	NH	H	3,4-$(CH_3O)_2$-C_6H_3
34a	F	CH	H	Ad[1]
34b	F	CH	H	*c*-C_3H_5
34c	F	CH	H	$CH_2C_6H_5$
34d	F	CH	H	2-Cl-C_6H_4
34e	F	CH	H	4-CH_3-C_6H_4
34f	F	CH	H	4-CH_3O-C_6H_4
34g	F	CH	H	3,4-OCH_2CH_2O-C_6H_3
34h	F	CH	H	3,4-OCH_2O-C_6H_3
34i	F	CH	H	2,5-$(CH_3O)_2$-C_6H_3
34j	F	CH	H	3,4-$(CH_3O)_2$-C_6H_3
34k	F	CH		$(CH_2)_5$
34l	H	CH	H	4-Cl-C_6H_4
34m	H	CH	H	4-F-C_6H_4
34n	H	CH	H	3-CH_3O-C_6H_4
34o	H	CH	H	4-CH_3O-C_6H_4
34p	H	CH	H	3-C_5H_4N
34q	H	CH	H	2-C_4H_3S
34r	H	CH	H	3,4-$(CH_3O)_2$-C_6H_3
34s	H	CH	H	3,4-OCH_2O-C_6H_3
34t	H	CH	H	Ad[1]
34u	H	CH		$(CH_2)_4$
35a	F	N	H	2-Cl-C_6H_4
35b	F	N	H	3,4-OCH_2CH_2O-C_6H_3
35c	F	N	H	3,4-$(CH_3O)_2$-C_6H_3
35d	F	N	H	4-C_5H_4N
35e	F	N	H	3-C_5H_4N
35f	F	N	H	2-C_4H_3S
35g	F	N	H	$CH_2C_6H_5$
35h	F	N	H	*c*-C_3H_5
35i	F	N		$(CH_2)_5$
35j	H	N	H	3-CH_3O-C_6H_4
35k	H	N	H	3-C_5H_4N
35l	H	N	H	Ad[1]
35m	H	N		$(CH_2)_4$

control). The reaction mixture was then cooled down to room temperature, diluted with water (7 mL), and acidified with hydrochloric acid until no more precipitation was observed. After 2 h, the precipitate was filtered out and washed with water (2 × 10 mL), ethanol (3 × 5 mL), and hexanes (3 × 5 mL) to afford pure **16a**−**c**. Yields and physical properties of compounds **16a**−**c** are given in Supporting Information Table 5.

4-Di(tri)fluoromethyl-3-aminothieno[2,3-*b*]pyridines (16d, 19a−**d, and 24a**−**r). Method A.** A reaction mixture comprising corresponding *S*-alkylpyridine **15e**, **18a**, **23a**−**p** (0.003 mol), and 10% aq KOH (1.68 mL) in ethanol (50 mL) was refluxed for 5–10 min, cooled down to room temperature, and then diluted with water (10 mL). After 2 h, the formed precipitate was filtered out and washed with water (2 × 10 mL), ethanol (3 × 5 mL) and hexanes (3 × 5 mL) affording pure **16d**, **19a**, and **24a**−**p**.

Method B. A solution of pyridinethione **6** (0.003 mol); corresponding alkylhalogenide **14a**,**c**; **17a**,**c**,**e**,**f**; **22a**−**n** (0.03 mol), and 10% aq KOH (3.36 mL) in ethanol (50 mL) was refluxed for 5–10 min, cooled down to room temperature, and then diluted with water (10 mL). After 2 h, the resulting precipitate was filtered out and washed with water (2 × 10 mL), ethanol (3 × 5 mL), and hexanes (3 × 5 mL) yielding pure **16d**, **19a**−**d**, and **24a**−**p**. Properties of compounds **16**, **19**, and **24** are given in Supporting Information Tables 5 and 8.

2-(*t*-Buthyl)-6-phenyl-4-(trifluoromethyl)pyrido[3′,2′:4,5]-thieno[2,3-*c*][1,5]benzodiazocine-12(11*H*)-one (25). A solution of 3-aminothieno[2,3-*b*]pyridine **24t** (1 g, 0.002 mol) and 10% aq KOH (1.12 mL) in ethanol (30 mL) was refluxed for 3 h (TLC control). The reaction mixture was then cooled down to room temperature, acidified with hydrochloric acid (0.2 mL), and diluted with water (10 mL) yielding thieno[2,3-*c*][1,5]benzodiazocine-12(11*H*)-one **25**, which was subsequently filtered out, washed with water (2 × 10 mL), ethanol (3 × 5 mL), and hexanes (3 × 5 mL) to produce an analytically pure sample. Yield: 0.62 g, 0.0013 mol (65%).

Mp: 244–245 °C (colorless crystals). IR (cm^{-1}): 1652, 3440 (CONH). ^{1}H NMR, δ, (DMSO-d_6, *J*/Hz): 1.16 (s, 9H, $C(CH_3)_3$); 7.01 (d, 1H, Ar, $J = 8.1$); 7.14 (t, 1H, Ar, $J = 8.1$); 7.24 (m, 2H, Ar); 7.50 (m, 4H, C^5H, Ph); 7.59 (m, 2H, Ph); 12.21 (s, 1H, NH). ^{13}C NMR, δ, (DMSO-d_6): 28.58 ($(CH_3)_3$); 112.23, 112.32, 112.41 (C-3); 113.27, 118.74, 124.21 (CF_3); 115.14, 119.37, 121.99, 127.34, 127.86, 128.40, 128.49, 131.56, 136.09, 139.13, 140.34 (Ar); 157.18 (NCS); 158.68 (CO); 163.15 (C-2); 173.88 (C-6); $C(CH_3)_3$ carbon signal is overlapped with DMSO signals. ^{19}F NMR, δ, (DMSO-d_6): −61.97 s. MS (EI, 70 eV): *m*/*z* (%) = 479 (100); 478 (91); 464 (21); 252 (16); 235 (16); 234 (25); 220 (11); 190 (14); 165 (18). Found: C 65.01, H 4.34, N 8.88%. Calculated for $C_{26}H_{20}F_3N_3OS$: C 65.12, H 4.20, N 8.76%.

Synthesis of Substituted 4-Trifluoromethyl-3-cyanopyridines (27 and 30). To a suspension of corresponding 4-trifluoromethyl-3-cyanopyridine-2(1*H*)-thione **6v,y** (0.003 mol) in ethanol (25 mL) was added 10% aq KOH (3.36 mL) and then corresponding *N*-chloroacetyl aminoacid **22a′, b′** (0.003 mol). The reaction mixture was heated on the hot plate to dissolve the starting materials and then was stirred at room temperature for 30 min. The resulting mixture was diluted with water (5 mL) to precipitate corresponding final pyridine **27** or **30**, which was subsequently filtered out and washed with water (2 × 10 mL), ethanol (3 × 5 mL), and hexanes (3 × 5 mL).

27. Yield: 0.89 g, 0.0023 mol (77%). Mp: 202–204 °C colorless crystals (from isopropanol). IR (cm^{-1}): 1628 (CONH), 1764 (COOH), 2232 (CN), 3296 br. (NH). ^{1}H NMR, δ, (DMSO-d_6, *J*/Hz): 1.63 (m, 4H, C^6H_2, C^7H_2); 1.78 (m, 2H, C^8H_2); 2.88 (m, 2H, C^5H_2); 3.15 (m, 2H, C^9H_2); 3.76 (d, 2H, NHCH_2, $J = 5.8$); 4.05 (s, 2H, SCH_2); 8.38 (t, 1H, NH, $J = 5.8$); 12.43 (br s, 1H, OH). Found: C 49.72, H 4.29, N 10.67%. Calculated for $C_{16}H_{16}F_3N_3O_3S$: C 49.61, H 4.16, N 10.85%.

30. Yield: 0.74 g, 0.00186 mol (62%). Mp: 117–118 °C colorless crystals (from isopropanol). IR (cm^{-1}): 1632 (CONH), 1728 (COOH), 2228 (CN), 3508 (OH). ^{1}H NMR, δ, (DMSO-d_6, *J*/Hz): 1.24 (t, 3H, CH_2CH_3, $J = 7.4$); 1.76–2.25 (m, 4H, $C^{3'}H_2$, $C^{4'}H_2$); 2.35 (s, 3H, CH_3); 2.92 (q, 2H, CH_2CH$_3$, $J = 7.4$); 3.41 (t, 1H, $C^{5'}H$, $J = 7.0$); 3.69 (t, 1H, $C^{5'}H$, $J = 6.6$); 3.97–4.73 (m, 1H, $C^{2'}H$), 4.29 (d, 2H, SCH_2, $J = 4.5$); 12.52 (br s, 1H, OH). Found: C 50.98, H 4.41, N 10.55%. Calculated for $C_{17}H_{18}F_3N_3O_3S$: C 50.87, H 4.52, N 10.47%.

***N*-[(3-Amino-6,7,8,9-tetrahydro-4-trifluoromethyl-5*H*-cyclohepta[*b*]thieno[3,2-*e*]pyridin-2-yl)carbonyl]glycine (28). Method A.** A mixture of *S*-alkylpyridine **27** (0.77 g, 0.002 mol) and 10% aq KOH (2.24 mL) in ethanol (30 mL) was refluxed for 5–10 min. Concentrated hydrochloric acid (0.2 mL) was then added to the reaction mixture at room temperature followed by water (10 mL). After 2 h, the formed precipitate was filtered out and washed with water (2 × 5 mL), ethanol (3 × 5 mL), and hexanes (3 × 5 mL) to afford pure **28**.

Method B. A mixture of corresponding pyridinethione **6y** (0.54 g, 0.002 mol), acid **22a′** (0.3 g, 0.02 mol), and 10% aq KOH (3.36 mL) in ethanol (50 mL) was refluxed for 5–10 min. Concentrated hydrochloric acid (0.2 mL) was then added to the room temperature reaction mixture followed by water (10 mL). After 2 h, the formed precipitate was filtered out and washed with water (2 × 5 mL), ethanol (3 × 5 mL), and hexanes (3 × 5 mL) to give pure **28**.

Yield: 0.67 g, 0.00174 mol (87%, method A), 0.57 g, 0.00148 mol (74%, method B). Mp: 223–224 °C yellow crystals (from nitromethane). IR (cm^{-1}): 1644 (CONH), 1740 (COOH), 3548 (OH). ^{1}H NMR, δ, (DMSO-d_6, *J*/Hz): 1.76 (m, 6H, C^6H_2, C^7H_2, C^8H_2); 3.04 (m, 2H, C^5H_2); 3.28 (m, 2H, C^9H_2); 3.87 (d, 2H, $NHCH_2$, $J = 5.4$); 6.74 (s, 2H, NH_2); 8.18 (t, 1H, NH, $J = 5.4$); 12.54 (br s, 1H, OH). Found C 49.42, H 4.40, N 10.63%. Calculated for $C_{16}H_{16}F_3N_3O_3S$: C 49.61, H 4.16, N 10.85%.

13-(Trifluoromethyl)-3,4,9,10,11,12-hexahydrocyclohepta[5′,6′]pyrido[3′,2′:4,5]thieno[3,2-*e*][1,4]diazepine-2,5(1*H*,8*H*)-dione (29). Thienopyridine **28** (0.39 g, 0.001 mol) was heated slightly above melting point (225 + ∼10 °C) for 10 min, cooled down to room temperature, and dissolved in ethanol (25 mL). The resulting reaction mixture was refluxed for 2 min and cooled down to room temperature to give **29**, which was filtered out, washed with ethanol (3 × 3 mL), and hexanes (3 × 5 mL) to afford the pure sample.

Yield: 0.15 g, 0.00041 mol (41%). Mp: 254–255 °C (colorless crystalls). IR (cm^{-1}): 1648, 1692, 3200, 3236 (CONH). ^{1}H NMR, δ, (DMSO-d_6, *J*/Hz): 1.72 (m, 4H, C^6H_2, C^7H_2); 1.82 (m, 2H, C^8H_2); 3.06 (m, 2H, C^5H_2); 3.27 (m, 2H, C^9H_2); 3.83 (d, 2H, $NHCH_2$, $J = 4.4$); 8.87 (s, 1H, NH); 9.84 (s, 1H, NH). MS (EI, 70 eV): *m*/*z* (%) = 370 (22); 369 (66) (M+); 340 (24); 339 (38); 325 (23); 319 (20); 313 (16); 312 (100); 311 (42); 298 (19); 297 (22); 293 (14); 286 (15); 255 (20); 284 (23); 283 (22); 255 (13); 243 (14); 229 (14); 216 (13); 211 (20); 185 (11); 165 (11); 142 (22); 101 (13); 59 (25); 58 (113); 57 (24). Found: C 52.21, H 3.97, N 11.20%. Calculated for $C_{16}H_{14}F_3N_3O_2S$: C 52.03, H 3.82, N 11.38%.

2-Ethyl-3-methyl-4-(trifluoromethyl)-6,7,8,9-tetrahydro-6*H*-pyrido[3′,2′:4,5]thieno[3,2-*e*]pyrrolo[1,2-*a*][1,4]diazepine-6,11(5*H*)-dione (31). A solution of compound **30** (0.8 g, 0.002 mol) and 10% aq KOH (1.4 mL) in ethanol (25 mL) was refluxed for 3 h, cooled down to room temperature, diluted with water (5 mL), acidified with conc hydrochloric acid (1 mL), and kept at 4 °C for 10 h. The formed precipitate was filtered out and washed with water (2 × 5 mL), ethanol (3 × 5 mL), and hexanes (3 × 5 mL) to give **31**.

Yield: 0.60 g, 0.00156 mol (78%), coloress crystals (from nitromethane). Mp: 245–247 °C. IR (cm^{-1}): 1624, 1696, 3268, 3440 (CONH). ^{1}H NMR, δ, (DMSO-d_6, *J*/Hz): 1.30 (t, 3H, CH_2CH_3, $J = 7.3$); 1.95–2.07 (m, 4H, C^7H_2, C^8H_2); 2.53 (s, 3H, CH_3); 3.03 (q, 2H, CH_2CH_3, $J = 7.3$); 3.57 (m, 2H, C^9H); 4.43 (d, 1H, C^5H, $J = 6.6$), 9.88 (s, 1H, NH). MS (EI, 70 eV): *m*/*z* (%) = 385 (15); 384 (20); 383 (98) (M^+); 355 (12); 354 (44); 334 (16); 327 (39); 313 (17); 286 (33); 285 (13); 270 (14); 269 (24); 267 (32); 259 (26); 258 (66); 257 (95); 243 (16); 70 (86); 59 (16). Found: C 53.07, H 4.38, N 10.74%. Calculated for $C_{17}H_{16}F_3N_3O_2S$: C 53.26, H 4.21, N 10.96%.

4-[6-(1,3-Benzodioxo-5-yl)-3-cyanoo-(4-di(tri)fluoromethyl) pyridin-2-ylthio]acetoacetic Acid Ethyl Esters (33a,b) and 4-(3-Cyanopyridil-2-thio)-acethyluretans (33c−f). To a suspension of pyridine-2(1*H*)-thione **6** (0.01mol) in DMF (25 mL) was added 10% aq KOH (5.6 mL) followed by

corresponding alkyhalogenide **32a**,**b** (0.01 mol). The reaction mixture was stirred at room temperature for 20–30 min and then diluted with water. The formed precipitate was filtered out and washed with water (2 × 5 mL), ethanol (3 × 5 mL), and hexanes (3 × 5 mL). Properties of compounds **33a**−**f** are given in Supporting Information Table 9.

4-Hydroxy-1*H*-thieno[2,3-*b*;4,5-*b*]dipyridine-2-ones (34 a-u) and pyrido[3′,2′:4,5]thieno[3,2-*d*]pyrimidine-2,4-dioles (35a−m). Method A. To a suspension of 4-(3-cyanopyridyl-2-thio)acetoacetic acid ester **33a**,**c** (0.02 mol) or acetylthiourethane **33f** (0.01 mol) in ethanol (50 mL) was added sodium ethoxide (1.36 g, 0.02 mol). The reaction mixture was then refluxed for 30 min, cooled down to room temperature, and acidified with 10% hydrochloric acid (2.5 mL). The formed precipitate was filtered out and washed with water (2 × 5 mL), ethanol (3 × 3 mL), and hexanes (3 × 3 mL).

Method B. To a mixture of corresponding pyridine-2(1*H*)-thione **6** (0.01 mol) and KOH (0.56 g, 0.01 mol) in ethanol (35 mL) was added ethyl ester of 4-chloroacetoacetic acid **32a** (1.65 g, 0.001 mol) or chloroacetylurethane **32b** (1.66 g, 0.001 mol). The reaction mixture was stirred at room temperature for 15 min, after which additional KOH (1.12 g, 0.02 mol) or sodium ethoxide (1.36 g, 0.02 mol) in ethanol (15 mL) was added. The resulting solution was refluxed for 30 min (TLC control), cooled down to room temperature, and acidified with 10% hydrochloric acid (2.5 mL). The formed precipitate was filtered out and washed with water (2 × 5 mL), ethanol (3 × 3 mL), and hexanes (3 × 3 mL). Properties of compounds **34** and **35** are given in Supporting Information Tables 10 and 11.

2-Amino-4-aryl-5,6-dihydro-5-oxo-3-cyano-4*H*-pyrano[2,3-d]pyrido[3′,2′:4,5]thieno[3,2-*b*]pyridines (38a−c). A suspension of compound **34k**,**o**,**s** (0.002 mol) in DMF (30 mL) was added with corresponding arylidenmalononitrile **36a**,**b** (0.002 mol) and thiethylamine (0.05 mL). The reaction mixture was refluxed for 2–3 h (TLC control), cooled down to room temperature, and quenched with concentrated hydrochloric acid (0.2 mL). Formed precipitate was filtered out, washed with water (2 × 5 mL), ethanol (3 × 5 mL), and hexanes (3 × 5 mL) to give pure **38**. Melting points of compounds **38a**−**c** were above 300 °C.

38a. Yield: 0.76 g, 0.0014 mol (70%). IR (cm^{-1}): 2204 (CN); 1624, 1664, 3184, 3270, 3448 (CO, NH, NH_2). ^1H NMR, δ, (DMSO-d_6, *J*/Hz): 1.71 (m, 6H, CH_2, CH_2, CH_2); 3.06 (m, 2H, CH_2); 3.24 (m, 2H, CH_2); 4.66 (s, 1H, C^4H); 7.24 (d, 2H, $C^{3'}H$, $C^{5'}H$, $J = 8.3$); 7.37 (m, 4H, NH_2, $C^{4'}H$, $C^{6'}H$); 11.25 (br s, 1H, NH). MS: 542 (7); 475 (100); 441 (57); 354 (29); 283 (12); 240 (13); 205 (13); 178 (18); 149 (17); 136 (31); 122 (98); 109 (77); 83 (23); 76 (12); 73 (24); 70 (53); 66 (63); 59 (56); 55 (75). Found: C 57.82, H 3.49, N 10.31%. Calculated for $C_{26}H_{18}ClF_3N_4O_2S$: C 57.51, H 3.34, N 10.50%.

38b. Yield: 0.83 g, 0.00144 mol (72%). IR (cm^{-1}): 2200 (CN); 1648, 1676, 3200, 3292, 3328, 3436 (CO, NH, NH_2). ^1H NMR, δ, (DMSO-d_6, *J*/Hz): 4.67 (s, 1H, C^4H); 6.13 (s, 2H, OCH_2O); 7.05 (d, 1H, $C^{6''}H$, $J = 8.3$); 7.24 (d, 2H, $C^{3'}H$, $C^{5'}H$, $J = 8.3$); 7.37 (m, 4H, NH_2, $C^{4'}H$, $C^{6'}H$); 7.82 (m, 2H, C^5H, $C^{2''}H$); 8.19 (m, 1H, $C^{5''}H$); 8.28 (t, 1H, CHF_2, $J = 53.7$); 11.64 (s, 1H, NH). MS: 576 (5); 510 (100); 490 (25); 476 (59); 465 (25); 434 (13); 388 (56); 286 (12); 163 (11); 153 (14); 101 (65); 83 (39); 69 (34); 66 (66); 59 (69). Found: C 58.32, H 2.80, N 9.59%. Calculated for $C_{28}H_{15}ClF_2N_4O_4S$: C 58.29, H 2.62, N 9.71%.

38c. Yield: 0.67 g, 0.0012 mol (60%). IR (cm^{-1}): 2200 (CN); 1648, 1676, 3192, 3324, 3416 (CO, NH, NH_2). ^1H NMR, δ, (DMSO-d_6, *J*/Hz): 3.72 (s, 3H, OCH_3); 3.85 (s, 3H, OCH_3); 4.60 (s, 1H, C^4H); 6.87(d, 2H, 2CH, $J = 8.3$); 7.00–7.20 (m, 5H, Ar, Ar); 7.23 (s, 2H, NH_2); 8.20–8.38 (m, 5H, CHF_2, Ar); 11.50 (s, 1H, NH). MS: 558 (21); 491 (98); 477 (11); 472 (15); 461 (29); 458 (12); 442 (18); 386 (15); 374 (31); 312 (16); 184 (26); 133 (11); 121 (12); 101 (43); 88 (14); 82 (20); 66 (67); 59 (50). Found: C 62.45, H 3.47, N 10.16%. Calculated for $C_{29}H_{20}F_2N_4O_4S$: C 62.36, H 3.61, N 10.03%.

Acknowledgment. We acknowledge the financial support of the Global IPP program through the Civilian Research and Development Foundation (CRDF) under contract DE-AC01-00NN40184.

Supporting Information Available. Tables with melting points, yields, NMR, IR, and elemental analysis data for all described compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

References and Notes

(1) Sheppard, W. A.; Sharts, C. M. *Organic Fluorine Chemistry*; Frontiers in Chemistry; Benjamin: New York, 1969; p 602.
(2) Chambers, R. D. *Fluorine in Organic Chemistry*; Interscience Monographs in Organic Chemistry; Wiley: New York, 1973; p 624.
(3) Yoshioka, H.; Takayama, C.; Matsuo, N. *Yuki Gosei Kagaku Kyokaishi* **1984**, *42*, 809–821.
(4) Filler, R., Kobayashi, Y., Eds. *Biomedicinal Aspects of Fluorine Chemistry*; Elsevier: Amsterdam, 1982; p 246.
(5) Welch, J. T.; Eswarakrishnan, S. *Fluorine in Bioorganic Chemistry*; Wiley: New York, 1991; p 261.
(6) Filler, R., Kobayashi, Y., Yagupolskii, L. M., Eds. Organofluorine Compounds in Medicinal Chemistry and Biomedical Applications. In *Studies in Organic Chemistry*; Elsevier: Amsterdam, 1993; Vol. 48, p 386.
(7) Singh, S. K.; Saibaba, V.; Rao, K. S.; Reddy, P. G.; Daga, P. R.; Rajjak, S. A.; Misra, P.; Rao, Y. K. *Eur. J. Med. Chem.* **2005**, *40*, 977–990.
(8) Li, J.; DeMello, K. M. L.; Cheng, H.; Sakya, S. M.; Bronk, B. S.; Rafka, R. J.; Jaynes, B. H.; Ziegler, C. B.; Kilroy, C.; Mann, D. W.; Nimz, E. L.; Lynch, M. P.; Haven, M. L.; Kolosko, N. L.; Minich, M. L.; Li, C.; Dutra, J. K.; Rast, B.; Crosson, R. M.; Morton, B. J.; Kirk, G. W.; Callaghan, K. M.; Koss, D. A.; Shavnya, A.; Lund, L. A.; Seibel, S. B.; Petras, C. F.; Silvia, A. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 95–98.
(9) Penning, T. D.; Talley, J. J.; Bertenshaw, S. R.; Carter, J. S.; Collins, P. W.; Docter, S.; Graneto, M. J.; Lee, L. F.; Malecha, J. W.; Miyashiro, J. M.; Rogers, R. S.; Rogier, D. J.; Yu, S. S.; Anderson, G. D.; Burton, E. G.; Cogburn, J. N.; Gregory, S. A.; Koboldt, C. M.; Perkins, W. E.; Seibert, K.; Veenhuizen, A. W.; Zhang, Y. Y.; Isakson, P. C. *J. Med. Chem.* **1997**, *40*, 1347–1365.
(10) Rottlaender, M.; Moltzen, E. K.; Mikkelsen, I.; Ruhland, T.; Andersen, K.; Krog-Jensen, C. Patent Application WO 2002-DK435 (2003002556), 2003; p 40.
(11) Gaeta, F.; Stracker, E. C. Patent Application US 95-539934 (5,767,278), 1998; p 16.

(12) Rosentreter, U.; Kraemer, T.; Vaupel, A.; Huebsch, W.; Diedrichs, N.; Krahn, T.; Dembowsky, K.; Stasch, J.-P. Patent Application WO 2002-EP2121 (2002070485), 2002; p 69.

(13) Rosentreter, U.; Henning, R.; Bauser, M.; Kraemer, T.; Vaupel, A.; Huebsch, W.; Dembowsky, K.; Salcher-Schraufstaetter, O.; Stasch, J.-P.; Krahn, T.; Perzborn, E. Patent Application WO 2000-EP9153 (2001025210), 2001; p 316.

(14) Rosentreter, U.; Kraemer, T.; Shimada, M.; Huebsch, W.; Diedrichs, N.; Krahn, T.; Henninger, K.; Stasch, J.-p. Patent Application WO 2002-EP7324 (2003008384), 2003; p 36.

(15) Birkinshaw, T.; Connolly, S.; Luker, T.; Mete, A.; Millichip, I. Patent Application WO 2002-SE876 (2002090332), 2002; p 123.

(16) Gaeta, F. C. A.; Stracker, E. C. Patent Application US 95-535988 (5,770,613), 1998; p 17.

(17) Litvinov, V. P.; Rodinovskaya, L. A.; Sharanin, Y. A.; Shestopalov, A. M.; Senning, A. *Sulfur Rep.* **1992**, *13*, 1–155.

(18) Yagupol'skii, L. M. *Aromatic and Heterocyclic Compounds with Fluorine-Containing Substituents [in Russian]*; Naukova Dumka: Kiev, 1988; p 319.

(19) Isikava, N., Ed. *Fluorinated compounds: Synthesis and Application [in Russian]*; Mir: Moscow, 1990; p 374.

(20) Shestopalov, A. M.; Kislyi, V. P.; Kruglova, E.; Nikishin, K. G.; Semenov, V. V.; Buchanan, A. C.; Gakh, A. A. *J. Comb. Chem.* **2000**, *2*, 24–28.

(21) Krueger, M.; Petrov, O.; Thierauch, K.-H.; Siemeister, G. Patent Application WO 2002-EP4559 (2002094814), 2002; p 34.

(22) Rodinovskaya, L. A.; Sharanin, Y. A.; Litvinov, V. P.; Shestopalov, A. M.; Promonenkov, V. K.; Zolotarev, B. M.; Mortikov, V. Y. *Z. Org. Khim.* **1985**, *21*, 2439–2444.

(23) Kislyi, V. P.; Nikishin, K. G.; Kruglova, E. Y.; Shestopalov, A. M.; Semenov, V. V.; Gakh, A. A.; Buchanan, A. C., III *Tetrahedron* **1996**, *52*, 10841–10848.

(24) Nikishin, K. G.; Kislyi, V. P.; Nesterov, V. N.; Shestopalov, A. M.; Struchkov, Y. T.; Semenov, V. V. *Russ. Chem. Bull.* **1998**, *47*, 465–468.

(25) Nikishin, K. G.; Nesterov, V. N.; Kislyi, V. P.; Shestopalov, A. M.; Semenov, V. V. *Russ. Chem. Bull.* **1998**, *47*, 679–681.

(26) Katsuyama, I.; Ogawa, S.; Yamaguchi, Y.; Funabiki, K.; Matsui, M.; Muramatsu, H.; Shibata, K. *Synthesis* **1997**, 1321–1324.

(27) Pashkevich, K. I.; Sevenard, D. V.; Khomutov, O. G.; Vorontsov, I. I. *Russ. Chem. Bull.* **2001**, *50*, 669–672.

(28) Pretsch, E.; Buehlmann, P.; Affolter, C. *Structure Determination of Organic Compounds: Tables of Spectral Data*, 3rd completely revised and enlarged ed.; Springer: Berlin, 2000; p 421.

(29) Rodinovskaya, L. A.; Shestopalov, A. M. *Russ. Chem. Bull.* **2000**, *49*, 348–354.

(30) Shestopalov, A. A.; Gromova, A. V.; Rodinovskaya, L. A.; Nikishin, K. G.; Litvinov, V. P.; Shestopalov, A. M. *Russ. Chem. Bull.* **2004**, *53*, 2353–2354.

(31) Rodinovskaya, L. A.; Shestopalov, A. M.; Gromova, A. V. *Russ. Chem. Bull.* **2003**, *52*, 2185–2196.

(32) Shestopalov, A. M.; Nikishin, K. G.; Gromova, A. V.; Rodinovskaya, L. A. *Russ. Chem. Bull.* **2003**, *52*, 2203–2206.

(33) Rodinovskaya, L.; Shestopalov, A.; Gromova, A.; Shestopalov, A. *Synthesis* **2006**, 2357–2370.

(34) Fedorov, A. E.; Shestopalov, A. M.; Belyakov, P. A. *Russ. Chem. Bull.* **2003**, *52*, 2197–2202.

(35) Thurston, D. E. *Mol. Aspects Anticancer Drug−DNA Interact.* **1993**, 54–88.

(36) Shestopalov, A. M.; Emeliyanova, Y. M.; Shestopalov, A. A.; Rodinovskaya, L. A.; Niazimbetova, Z. I.; Evans, D. H. *Org. Lett.* **2002**, *4*, 423–425.

(37) Shestopalov, A. M.; Yakubov, A. P.; Tsyganov, D. V.; Emel'yanova, Y. M.; Nesterov, V. N. *Chem. Heterocycl. Compd.* **2002**, *38*, 1180–1189.

CC7001793