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Preparation of Trifluoromethylpyridine Libraries

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S-Alkylation followed by heterocyclization of trifluoromethyl-3-cyano-2(1*H*)-pyridinethiones was used for preparation of libraries of S-alkyl trifluoromethylpyridines and thieno[2,3-*b*]pyridines. The S-alkylation (in water−DMF mixtures) was successful for all 18 alkylating agents employed (yields typically >50%). S-Alkyl derivatives were further converted to corresponding thieno[2,3-*b*]pyridines via heterocyclization in base conditions (yields >65%). Structures of new compounds were elucidated by a combination of IR and ^{1}H NMR spectroscopy and elemental analysis and were confirmed by means of single-crystal X-ray diffraction analysis.

Introduction

We have previously reported a facile synthesis of 6-methyl-4-trifluoromethyl-3-cyano-2(1*H*)-pyridinethione (**1**) and isomeric 4-methyl-6-trifluoromethyl-3-cyano-2(1*H*)-pyridinethione (**2**) via heterocyclization of trifluoroacetylacetone or its derivatives and thiocyanoacetamide under base conditions.[1a] Preliminary experiments indicated that these compounds can be easily S-alkylated using appropriate alkylating agents (such as α-bromomethyl carbonyl compounds or alkyl-iodides).[1a] Subsequent heterocyclization of some of these S-alkyl derivatives gave corresponding thieno[2,3-*b*]pyridines in good yield.[1a] These results prompted us to explore chemistry of these heterocyclic scaffolds (**1** and **2**) for synthesis of various substituted trifluoromethyl pyridines and thieno[2,3-*b*]pyridines. The research was driven by our current interest in development of synthetic methods suitable for production of libraries of fluoro-containing heterocycles.

The development of solid- and solution-phase[2−12] combinatorial chemistry progressed rapidly over the last years. This development led to new challenges in the area of high-throughput synthesis, analysis, purification, and robot design.[2,13−22] High-throughput synthesis can substantially improve the productivity of conventional and combinatorial organic chemistry.[2] However, as with any new tool, it requires compatible chemical methods and standardization of reaction conditions. Our previous experience indicates that the chemistry of the above-mentioned trifluoromethylpyridines (**1** and **2**) can meet the requirements of high-throughput parallel synthesis. In addition, libraries of trifluoromethylpyridines (and related thieno[2,3-*b*]pyridines) could be useful in development of new herbicides and other biologically active compounds. A current list of known herbicides includes the following substituted trifluoromethylpyridines: DITHIOPYR (*S*,*S*-dimethyl-2-(difluoromethyl)-4-(2-methylpropyl)-6-(trifluoromethyl)-3,5-pyridinedicarbothiolate), FLUAZIFOP (2-(4-((5-(trifluoromethyl)-2-pyridinyl)oxy)phenoxy)-propanoic acid), FLUPYRSULFURON (2-(((4,6-dimethoxy-2-pyrimidinyl)amino)sulfonyl)-6-(trifluoromethyl)-3-pyridinecarboxylic acid), THIAZOPYR (methyl 2-(difluoromethyl)-5-(4,5-dihydro-2-thiazolyl)-4-(2-methylpropyl)-6-(trifluoromethyl)-3-pyridinecarboxylate), and others. In addition, 4-trifluoromethylpyridine libraries were reported to display activity against Xa factor.[1b]

Results and Discussion

We have reported previously[1a] that both trifluoromethylpyridines **1** and **2** can be easily prepared by regioselective heterocyclization of trifluoroacetylacetone or its O-Me derivative with cyanothioacetamide. The direction of heterocyclization is determined by the order of the reagents addition. Slow addition of trifluoroacetylacetone to an ethanol solution of the sodium salt of cyanothioacetamide gave 4-methyl-6-trifluoromethyl-3-cyano-2(1*H*)-pyridinethione (**1**). The same reaction conducted in a different manner (addition of cyanothioacetamide to the solution of KOH and trifluoroacetylacetone in EtOH) resulted in the formation of isomeric 6-methyl-4-trifluoromethyl-3-cyano-2(1*H*)-pyridinethione (**2**). Compound **2** can also be prepared by direct reaction of trifluoroacetylacetone and cyanothioacetamide in the presence of catalytic amounts of triethylamine.[1a]

In an attempt to broaden the set of available heterocyclic scaffolds (trifluoromethyl-3-cyano-2(1*H*)-pyridinethiones) for further transformations, we investigated heterocyclization of hexafluoroacetylacetone with cyanothioacetamide. This reaction was performed under the same conditions as the trifluoroacetylacetone case. However, the expected product, 4,6-bis(trifluoromethyl)-3-cyano-2(1*H*)-pyridinethione, was

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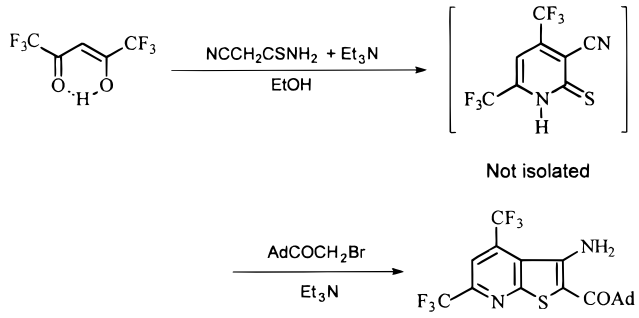
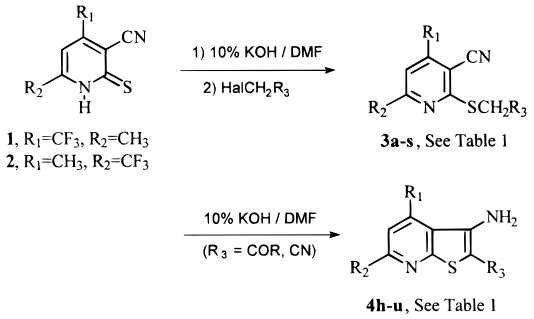
Scheme 1. Synthesis of 2-(1-Adamantylcarbonyl)-3-amino-4,6-bis(trifluoromethyl)thieno[2,3-*b*]pyridine



Scheme 2. Synthesis of 3-Cyano-2-alkylthiopyridines and 3-Aminothieno[2,3-*b*]pyridines



not isolated from the reaction mixture due to its high solubility in water. Its formation was subsequently proved by in situ reaction with α-bromacetyl-adamantane (Scheme 1, 60% yield).

The salts of **1** and **2** react smoothly with a diverse set of alkylating agents such as alkyl iodides, benzylbromides, and α-bromomethyl ketones in water−DMF to give the corresponding S-derivatives **3a**−**s** as major products (Scheme 2 and Table 1). This reaction is regioselective: corresponding N-alkyl derivatives were not detected. In the presence of an excess of KOH, S-derivatives **3a**−**s** undergo self-condensation with the formation of 3-aminothieno[2,3-*b*]pyridines **4h**−**u** in high yields (Table 1).

The spectral characteristics of compounds **3a**−**s** and **4h**−**u** shown in Table 1 are in agreement with the proposed structures. Thus, the strong absorption band for the −CN group (2213−2225 cm^{-1}) was observed in all IR spectra of **3a**−**s**. This peak is absent in IR spectra of compounds **4h**−**u**. Instead, the typical absorptions of the NH_2 group (stretching and deformation modes) were observed. Structures of **3a**−**s** and **4h**−**u** were also confirmed by means of ^1H NMR spectroscopy and X-ray crystallography (**3d**, **4j**).

The results of X-ray diffraction analysis of **3d** and **4j** are in agreement with the proposed regioselectivity of alkylation of **1** and **2**.[23,24] The structural parameters of **3d** and **4j** are typical of these types of compounds.[25,26] X-ray studies of **3d** also showed substantial divergence of the ethyl group out of the plane of the heterocyclic ring. This conformation is probably affected by intramolecular nonvalence contacts between the nitrogen atom in the pyridine ring and an α-hydrogen or carbon atoms of the CH_3CH_2S− group. The thienopyridine fragment in **4j** is planar (the torsion angle between the planes of the fused heterocycles is less than 1°). In addition, the PhNHCO− group is also in-plane with the thienopyridine system. Such flattening of the molecule is favored by the intramolecular hydrogen bonding. Full details of the X-ray analysis of **3d** and **4j** were presented elsewhere.[23,24]

Our experiments demonstrated that both S-alkyl derivatives **3a**−**s** and 3-aminothieno[2,3-*b*]pyridines **4h**−**u** can be produced in satisfactory yields using uniform conditions (see Experimental Section and Table 1). However, the best results can be achieved at optimal reaction times. Thus, cyclization of **3** to **4** requires only 15−20 min at 25 °C when R_3 is COAr, COAd, or CN and more than 4 h in cases of COOEt and CONHR. We also note that the corresponding 3-aminothieno[2,3-*b*]pyridine could not be prepared from S-ethyl derivative **3d** (R_3 = Me), showing some limitation of the proposed method (R_3 should be an electron-withdrawing group).

In summary, we have developed a practical approach for preparation of libraries of trifluoromethylpyridines (**3**) and aminothieno[2,3-*b*]pyridines (**4**) amenable for high-throughput parallel synthesis.

Experimental Section

General Procedures. Melting points are not corrected. All reagents and solvents were used as received. IR spectra were recorded on a Perkin-Elmer-457 spectrometer for samples in potassium bromide pellets. ^1H NMR spectra were run at 250 MHz (Bruker WM-250) in DMSO-d_6 using TMS as internal standard. All chemical shifts are quoted in ppm with coupling constants *J* expressed in hertz (Hz). The yields of compounds **3a**−**s** and **4h**−**u**, together with their melting points and spectral and microanalytical data, are compiled in Tables 1 and 2. Synthesis of **3d** and **4j** was reported previously.[23,24]

3-Cyano-2-alkylthiopyridines (3a−s). General Procedure. A suspension of cyanopyridinethiones (**1** or **2**) (2.2 g, 10 mmol) in DMF (15 mL) was stirred at 20 °C for 10−30 min, during which time the corresponding alkyl iodide (10 mmol) (**3a**−**g**) or α-bromomethyl compound (10 mmol) (**3h**−**s**) and 10% KOH solution in water (5.6 g, 10 mmol of KOH) were added dropwise. The reaction mixture was stirred at 20 °C for an additional 30 min and then diluted with water (10−15 mL). The precipitate was collected by filtration and recrystallized from EtOH (Table 1).

3-Amino-2-thieno[2,3-*b*]pyridines (4h−u). General Procedure. A 10% aqueous solution of KOH (3.0 g, 5.3 mmol of KOH) was added to a suspension of pyridines (**3h**−**s**) (10 mmol) in DMF (15 mL). The reaction mixture was stirred at 20 °C for an additional 3 h and then diluted with water (10 mL). The precipitate was collected by filtration and recrystallized from EtOH (Table 1).

2-(1-Adamantanecarbonyl)-3-amino-4,6-bis(trifluoromethyl)thieno[2,3-*b*]pyridine. A solution of cyanothioacetamide (1.0 g, 10 mmol) and Et_3N (1.4 mL, 10 mmol) in EtOH (30 mL) was stirred at 20 °C for 20 min, during which time hexafluoroacetylacetone (2.1 g, 10 mmol) was added dropwise. After the addition was complete, the reaction mixture was stirred at 20 °C for an additional 3 h. Then 1-bromoacetyladamantane (2.6 g, 10 mmol) and triethyl-

Table 1. Yields, Melting Points, and ^{1}H NMR and IR Spectral Data for the Compounds **3a**−**s** and **4h**−**u**

R_1	R_2	R_3	compd	yield, %	mp, °C	IR, cm^{-1} in KBr	^{1}H NMR, δ, ppm in DMSO-d_6
CH_3	CF_3	CH_3	**3a**	32	27−28	2240 C≡N	1.45t (3H, CH_3CH_2); 2.6s (3H, CH_3); 3.3q (2H, CH_2S); 7.3s (1H, C^5H)
CH_3	CF_3	Ph	**3b**	51	32−35	2228 C≡N	2.6s (3H, CH_3); 4.5s (2H, CH_2S); 7.25−7.5m (6H, C_6H_5, C^5H)
CH_3	CF_3	3-BrC_6H_4	**3c**	77	76−77	2226 C≡N	2.6s (3H, CH_3); 4.45s (2H, CH_2S); 7.1−7.6m (5H, C^5H, C_6H_4)
CF_3	CH_3	CH_3	**3d**	45	50−51	2240 C≡N	1.41t (3H, CH_3CH_2); 2.7s (3H, CH_3); 3.3q (2H, CH_2S); 7.15s (1H, C^5H)
CF_3	CH_3	Pr	**3e**	17	27−29	2232 C≡N	1.0t (3H, CH_3); 1.5−1.75m (4H, CH_2CH_2); 2.7s (3H); 3.3s (2H, CH_2S); 7.1s (1H, C^5H)
CF_3	CH_3	Ph	**3f**	63	45−47	2230 C≡N	2.7s (3H, CH_3); 4.5s (2H, CH_2S); 7.2s (1H, C^5H); 7.25−7.5m (5H, C_6H_5)
CF_3	CH_3	3-BrC_6H_4	**3g**	84	83−84	2228 C≡N	2.6s (3H, CH_3); 4.3s (2H, CH_2S); 7.0−7.5m (5H, C^5H, C_6H_4)
CF_3	CH_3	3-BuO-C_6H_4NHCO	**3h**	73	110−111	1662 δ_{CONH}; 2232 C≡N; 3320, 3340 NH	0.9t (3H, CH_3); 1.35−1.85m (4H, CH_2CH_2); 2.6s (3H, CH_3); 3.9t (2H, CH_2O); 4.1s (2H, CH_2S); 6.65−7.3m (5H, C_6H_4 C^5H); 10.25s (1H, NH)
CF_3	CH_3	$PhCH_2NHCO$	**3i**	65	143−145	1664 δ_{CONH}; 2230 C≡N; 3318, 3336 NH	2.6s (3H, CH_3); 4.1s (2H, CH_2S); 4.3s (2H, CH_2N); 7.25m (5H, C_6H_5); 7.65s (1H, C^5H); 9.5s (1H, NH)
CF_3	CH_3	PhNHCO	**3j**	80	156−157	1550, 1600; 1660 δ_{CONH}; 2240 C≡N; 3300−3330 NH	2.7s (3H, CH_3); 4.2s (2H, CH_2S); 7.0−7.5m (6H, C_6H_5, C^5H); 10.3s (1H, NH)
CF_3	CH_3	2,4-diMe-C_6H_3NHCO	**3k**	78	166−168	1658 δ_{CONH}; 2228 C≡N; 3322, 3336 NH	2.1s (3H,$CH_3C_6H_3$); 2.25s (3H, $CH_3C_6H_3$); 2.7s (3H, CH_3); 4.3s (2H, CH_2S); 7.0−7.6m (4H, C_6H_3, C^5H); 9.5s (1H, NH)
CF_3	CH_3	4-MeO-C_6H_4NHCO	**3l**	85	192−193	1654 δ_{CONH}; 2226 C≡N; 3328, 3342 NH	2.6s (3H, CH_3); 3.7s (3H, CH_3O); 4.2s (2H, CH_2S); 6.8−7.5m (5H, C_6H_4, C^5H); 10.2c (1H, NH)
CF_3	CH_3	4-Me-C_6H_4NHCO	**3m**	91	171−172	1652 δ_{CONH}; 2228 C≡N; 3318, 3336 NH	2.3s (3H, $CH_3C_6H_4$); 2.75s (3H, CH_3); 4.05s (2H, CH_2S); 7.2d + 7.4d (4H, C_6H_4, ^3J = 7.1 Hz); 7.62s (1H, C^5H); 8.4s (1H, NH)
CH_3	CF_3	C_2H_5OCO	**3n**	68		1740 C═O; 2226 C≡N	1.3t (3H, CH_3CH_2, ^3J = 7.4 Hz); 2.61s (3H, CH); 4.0s (2H, CH_2S); 4.2q (2H, CH_3CH_2, ^3J = 7.4 Hz); 7.31s (1H, C^5H)
CH_3	CF_3	PhCO	**3o**	88	94−95	1680 C═O; 2228 C≡N	2.6s (3H, CH_3); 4.72s (2H, CH_2S); 7.30s (1H, C^5H); 7.50−8.10m (5H, C_6H_5)
CH_3	CF_3	4-ClC_6H_4CO	**3p**	91	150−151	1682 C═O; 2224 C≡N	2.6s (3H, CH_3); 4.7s (2H, CH_2S); 7.3s (1H, C^5H); 7.52d + 8.0d (4H, C_6H_4, ^3J = 7.6 Hz)
CH_3	CF_3	4-Br-C_6H_4CO	**3q**	93	162−163	1682 C═O; 2226 C≡N	2.6s (3H, CH_3); 4.67s (2H, CH_2S); 7.31s (1H, C^5H); 7.68d + 7.92d (4H, C_6H_4, ^3J = 7.8 Hz)
CH_3	CF_3	H_2NCO	**3r**	88	171−172	1668 δ_{CONH}; 2226 C≡N; 3185, 3226, 3343 NH_2	2.6s (3H, CH_3); 4.0s (2H, CH_2S); 7.3s (1H, NH); 7.7s (1H, NH); 7.8s (1H, C^5H)
CH_3	CF_3	4-Me-C_6H_4NHCO	**3s**	63	175−178	1662 δ_{CONH}; 2230 C≡N; 3326, 3310 NH	2.4s (3H, $CH_3C_6H_4$); 2.7s (3H, CH_3); 4.1s (2H, CH_2S); 7.1d + 7.4d (4H, C_6H_4, ^3J = 7.1 Hz); 7.52s (1H, C^5H); 8.3s (1H, NH)
CF_3	CH_3	3-BuO-C_6H_4NHCO	**4h**	68	121−124	1632 δ_{NH_2}; 1648 δ_{CONH}; 3285, 3326, 3400 NH_2 + NH	0.9t (3H, CH_3CH_2); 1.35−1.85m (4H, CH_2CH_2); 2.65s (1H, CH_3); 3.95t (2H, CH_2O); 6.6s (2H, NH_2); 6.65−7.3m (5H, C_6H_4, C^5H); 9.6s (1H, NH)
CF_3	CH_3	$PhCH_2NHCO$	**4i**[24]	85	110−112	1600, 1630 δ_{NH+NH_2}; 3280, 3340, 3500 NH + NH_2	2.75s (3H, CH_3); 6.75s (2H, NH_2); 7.1−7.9m (6H, C_6H_5, C^5H); 9.7s (1H, NH)
CF_3	CH_3	PhNHCO	**4j**	85	122−123	1600, 1630 δ_{NH+NH_2}; 3280, 3340, 3500 NH + NH_2	2.6s (3H, CH_3); 4.15s (2H, CH_2N); 6.6s (2H, NH_2); 7.25m (5H, C_6H_5); 7.5s (1H, C^5H); 9.5s (1H, NH)
CF_3	CH_3	2,4-diMe-C_6H_3NHCO	**4k**	67	145−146	1625 δ_{NH_2}; 1640 δ_{CONH}; 3370, 3386, 3476 NH + NH_2	2.2s (3H, $CH_3C_6H_3$); 2.3s (3H, $CH_3C_6H_3$); 2.7s (3H, CH_3); 6.6s (2H, NH_2); 7.0−7.8m (4H, C_6H_3, C^5H); 9.4s (1H, NH)
CF_3	CH_3	4-MeO-C_6H_4NHCO	**4l**	71	195−198	1628 δNH_2; 1643 δ_{CONH}; 3358, 3387, 3453 NH + NH_2	2.75s (3H, CH_3); 3.8s (3H, CH_3O); 6.64s (2H, NH_2); 6.8−7.5m (6H, C_6H_4, C^5H, NH)

Table 1 (Continued)

R_1	R_2	R_3	compd	yield, %	mp, °C	IR, cm^{-1} in KBr	^1H NMR, δ, ppm in DMSO-d_6
CF_3	CH_3	4-Me-C_6H_4NHCO	**4m**	73	210−212	1630 δ_{NH_2}; 1642 δ_{CONH}; 3342, 3376, 3448 NH + NH_2	2.6s (3H, CH_3); 2.7s (3H, $CH_3C_6H_4$); 6.83s (2H, NH_2); 7.2d + 7.7d (4H, C_6H_4, ^3J = 7.2 Hz); 7.5s (1H, C^5H); 9.7s (1H, NH)
CH_3	CF_3	C_2H_5OCO	**4n**	90		1610 δ_{NH_2}; 1670 CO; 3370, 3390, 3490 NH_2	1.4t (3H, CH_3CH_2, ^3J = 7.4 Hz); 2.88s (3H, CH_3); 4.38q (2H, CH_2O, ^3J = 7.4 Hz); 6.2s (2H, NH_2); 7.35s (1H, C^5H)
CH_3	CF_3	PhCO	**4o**	73	147−148	1600 C═O, δ_{NH_2}; 3110, 3486 NH_2	2.95s (3H, CH_3); 7.20s (2H, NH_2); 7.60s (1H, C^5H); 7.30−7.90m (5H, C_6H_5)
CH_3	CF_3	4-ClC_6H_4CO	**4p**	91	144−145	1612 C═O, δ_{NH_2}; 3115, 3486 NH_2	3.0s (3H, CH_3); 7.3s (2H, NH_2); 7.4d + 7.8d (4H, C_6H_4, ^3J = 7.8 Hz); 7.6s (1H, C^5H)
CH_3	CF_3	4-Br-C_6H_4CO	**4q**	95	154−155	1637 C═O, δ_{NH_2}; 3220, 3335 NH_2	2.9s (3H, CH_3); 7.2s (2H, NH_2); 7.4d + 7.6d (4H, BrC_6H_4, ^3J = 7.2 Hz); 7.52s (1H, C^5H)
CH_3	CF_3	H_2NCO	**4r**	85	262−264	1628 δ_{NH_2}; 1650 δ_{CONH_2}; 3185, 3226, 3330 NH_2	2.95s (3H, CH_3); 6.9s (2H, NH_2); 7.4s (2H, $CONH_2$); 7.55s (1H, C^5H)
CH_3	CF_3	4-Me-C_6H_4NHCO	**4s**	72	271−275	1620, 1636 δ_{NH_2} + δ_{CONH}; 3126, 3257, 3338 NH_2	2.8s (3H, CH_3); 7.2s (2H, NH_2); 2.42s (3H, CH_3); 7.3−7.9m (5H, C^5H, C_6H_4); 9.7s (1H, NH)
CH_3	CF_3	CN	**4t**	87		1642 δ_{NH_2}; 2220 C≡N; 3153, 3248, 3367 NH_2	2.92s (3H, CH_3); 6.2s (2H, NH_2); 7.47s (1H, C^5H)
CH_3	CF_3	AdCO	**4u**	83	250−251	1620 δ_{NH_2}; 1668 C═O; 3218, 3316 NH_2	1.7m (6H, Ad); 2.05m (9H, Ad); 2.85s (3H, CH_3); 7.55s (2H, NH_2); 7.48s (1H, C^5H)

Table 2. Elemental Analysis Data for the Compounds **3a**−**s** and **4h**−**u**

	found				calculated		
compd	C	H	N	formula	C	H	N
3a	48.59	3.66	11.25	$C_{10}H_9F_3N_2S$	48.77	3.68	11.32
3d	48.53	3.67	11.29	$C_{10}H_9F_3N_2S$	48.77	3.68	11.32
3b	58.33	3.59	9.04	$C_{15}H_{11}F_3N_2S$	58.43	3.60	9.09
3f	58.31	3.57	9.08	$C_{15}H_{11}F_3N_2S$	58.43	3.60	9.09
3c	46.31	2.59	7.21	$C_{15}H_{10}BrF_3N_2S$	46.52	2.60	7.24
3g	46.47	2.58	7.19	$C_{15}H_{10}BrF_3N_2S$	46.52	2.60	7.24
3e	52.44	4.74	10.15	$C_{12}H_{24}F_3N_2S$	52.54	4.78	10.21
3h	56.34	4.73	9.87	$C_{20}H_{20}F_3N_3O_2S$	56.73	4.76	9.92
3i	56.36	4.75	9.83	$C_{20}H_{20}F_3N_3O_2S$	56.73	4.76	9.92
3i	55.46	3.84	11.43	$C_{17}H_{14}F_3N_3OS$	55.88	3.86	11.50
4i	56.70	3.85	11.45	$C_{17}H_{14}F_3N_3OS$	55.88	3.86	11.50
3j	54.31	3.42	11.86	$C_{16}H_{12}F_3N_3OS$	54.65	3.44	11.95
3k	56.73	4.21	10.99	$C_{18}H_{16}F_3N_3OS$	56.98	4.25	11.08
4k	56.74	4.24	11.01	$C_{18}H_{16}F_3N_3OS$	56.98	4.25	11.08
3l	53.17	3.67	10.87	$C_{17}H_{14}F_3N_3O_2S$	53.54	3.70	11.02
4l	53.29	3.69	10.98	$C_{17}H_{14}F_3N_3O_2S$	53.54	3.70	11.02
3m	55.67	3.83	11.77	$C_{17}H_{14}F_3N_3OS$	55.88	3.86	11.50
4m	55.63	3.80	11.79	$C_{17}H_{14}F_3N_3OS$	55.88	3.86	11.50
3n	46.00	3.63	9.17	$C_{12}H_{11}F_3N_2O_2S$	47.36	3.64	9.21
4n	47.13	3.61	9.16	$C_{12}H_{11}F_3N_2O_2S$	47.36	3.64	9.21
4t	46.37	2.34	16.27	$C_{10}H_6F_3N_3S$	46.69	2.35	16.34
3o	57.23	3.43	8.54	$C_{16}H_{11}F_3N_2OS$	57.13	3.30	8.33
4o	57.11	3.45	8.37	$C_{16}H_{11}F_3N_2OS$	57.13	3.30	8.33
3p	52.51	2.70	7.52	$C_{16}H_{10}ClF_3N_2OS$	52.91	2.72	7.56
4p	52.53	2.71	7.55	$C_{16}H_{10}ClF_3N_2OS$	52.91	2.72	7.56
3q	45.99	2.43	6.71	$C_{16}H_{10}BrF_3N_2OS$	46.28	2.43	6.75
4q	46.17	2.42	6.71	$C_{16}H_{10}BrF_3N_2OS$	46.28	2.43	6.75
3r	43.29	2.93	15.16	$C_{10}H_8F_3N_3OS$	43.63	2.93	15.27
4r	43.35	2.91	15.25	$C_{10}H_8F_3N_3OS$	43.63	2.93	15.27
3s	54.54	3.84	11.47	$C_{17}H_{14}F_3N_3OS$	55.88	3.86	11.50
4s	54.59	3.84	11.41	$C_{17}H_{14}F_3N_3OS$	55.88	3.86	11.50
4u	60.65	5.34	7.05	$C_{20}H_{21}F_3N_2OS$	60.89	5.37	7.10

amine (1.4 mL, 10 mmol) were added dropwise in sequential manner. The reaction mixture was refluxed for 3 h and then diluted with 20 mL of water. The precipitate was collected by filtration and recrystallized from benzene to yield 2.7 g (60%) of title compound with a mp of 142−144 °C. IR (ν, cm^{-1}, KBr): 1628 (δ NH); 1657 (C═O); 3185, 3276 (NH_2). ^1H NMR (δ, ppm, in DMSO-d_6): 1.32, 1.64, 2.03m (15H, Ad); 6.83s (2H, NH_2); 7.86s (1*H*, C^5H). Anal. Calcd for $C_{20}H_{18}F_6N_2OS$: C, 53.57; H, 4.02; N, 6.28. Found: C, 51.18; H, 3.08; N 5.01.

Note Added in Proof

Since the submission of the manuscript, this method was successfully applied for expansion of the existing library of trifluoromethylpyridines, primarily by diversification of R_1 and R_2 groups (CF_3− and C_6H_5−, C_4H_3S−) and further diversification of R_3 (CH_2═CH−, NH_2C(═NCN)−, *t*-BuNHCO−, CH_3OCO−, $PhCH_2OCO$−, *cyclo*C_3H_5CO−, *cyclo*C_3H_5NHCO−, (*N*-morpholino)CH_2−, (*N*-*cyclo*$C_6H_{12}N$)CH_2−, 2-$ClC_6H_4CH_2$−, 4-$ClC_6H_4CH_2$−, 2,4-diMeC_6H_3CO-, 2-$NO_2C_6H_4CO$-, 3-$NO_2C_6H_4CO$−, 4-$NO_2C_6H_4CO$−, 4-$NO_2C_6H_4NHCO$−, 4-$NH_2COC_6H_4CO$−, 4-MeC_6H_4CO−, 3-$CF_3C_6H_4NHCO$−, 2-Me-4-I−C_6H_3NHCO−, 3,4-di$MeOC_6H_3CO$−, 2-(3,5-diBrC_5H_2N)$NHCO$−, 2-(6-MeC_5H_3N)$NHCO$−, 2-(5-MeC_5H_3N)$NHCO$−, 2-(4-MeC_3HNS)$NHCO$−, 2-(5-EtC_2N_2S)$NHCO$−. Seventy-one new compounds were added to the library.

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