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Synthesis and reactions of 4-trifluoromethyl-3-cyano pyridine-2(*1H*)-thione/one derivatives

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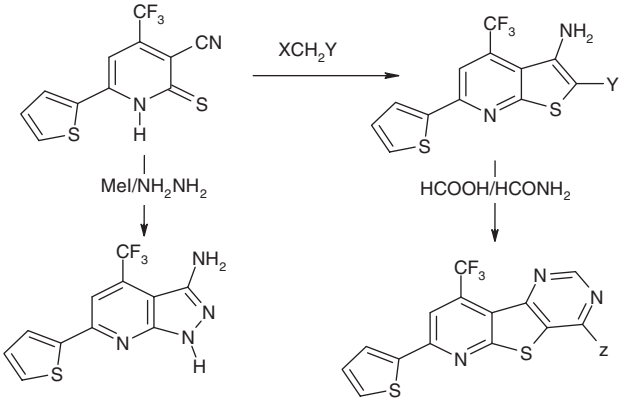
4,4,4-Trifluoro-1-(thiophen-2-yl)butane-1,3-dione was reacted by grinding with cyanothioacetamide and cyanoacetamide under solvent-free conditions at 25 °C to give pyridine-2(1H)thione/one derivatives in excellent yields. These compounds were further reacted by grinding with different halogenated reagents to give 2-*S*/*O*-alkyl pyridine derivatives. The latter compounds were utilized for the synthesis of thieno[2,3-b]pyridine, pyrazolopyridine, pyridothienopyrimidine and pyridothienooxazinone derivatives.



Keywords: Green synthesis; grinding; 3-cyanopyridine-2(*1H*)thione/one; thieno[2,3-b]pyridine; pyridothienopyrimidine; pyrazolopyridine; pyridothienooxazinone

1. Introduction

At present, developing green chemical protocols is one of the most important efforts in organic synthesis. Moreover, improving the efficiency of organic synthesis, lowering the consumption of chemicals, and obtaining polycyclic molecules from simple starting materials are fundamental

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goals in organic synthesis. Grinding the reactants together constitutes the simplest green chemistry protocol. It has proven to be an efficient, economical and environmentally benign process (*1–5*). On the other hand, interest in the development of synthetic approaches for preparation of 3-cyano-2(*1H*)-pyridinethiones is related to their use as versatile precursors in the preparation of dyes, herbicides, bactericides, and other biologically active compounds (*6–9*). Moreover, pyridine-3-carbonitriles were used as cardiotonic (*10, 11*) and antiviral agents (*12*). Also, *S*-alkyl pyridines possess neurotropic activity (*13*) and they are used as adenosine receptor ligands (*14, 15*) and also have cardiovascular activity (*16*). Moreover, thieno[2,3-b]pyridines are of special importance due to their reported biological activities such as antibacterial (*17–20*), antihypertensive (*21*), and anti-inflammatory (*22*). Furthermore, pyridothienopyrimidines were reported to have antiallergic (*23*), antiprotozoals (*24*), antianaphylatic (*25, 26*), and antimicrobial (*21, 27*) properties. Thus, in continuation of previous work together with our interest in developing a green protocol for the synthesis of organic compounds (*1, 28*) we report herein a convenient synthesis of 4-trifluoromethyl-3-cyano-2(*1H*)pyridinethione/one compounds.

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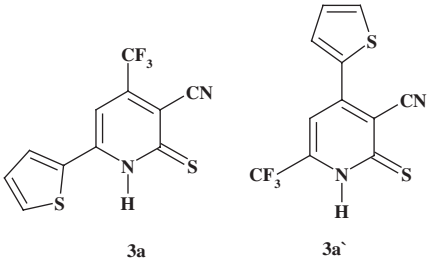
2. Results and discussion

Reaction of 4,4,4-trifluoro-1-thiophen-2-yl-butane-1,3-dione (**1**) with 2-cyanothioacetamide (**2a**) was investigated under different basic conditions. Thus, pyridinethione **3a** was prepared in excellent yield (95%) by grinding equivalent amounts of **1** and **2a** in the presence of solid potassium hydroxide in a porcelain mortar under solvent-free conditions. Grinding for about 1–5 min led to a colored solid mass that proved to be the target pyridinethione **3a** (m.p. according to the literature (*29*)). When the same reaction was carried out in ethanolic triethylamine solution under reflux, compound **3a** was also obtained (m.p., mixed m.p. and TLC) (*29*). On the other hand, when the reaction was carried out in ethoxide solution, it gave a mixture of two compounds as revealed by TLC. These compounds were separated by crystallization from different solvents. One of these two compounds was found to be identical with compound **3a** (m.p., mixed m.p., TLC).

Examination of ^{19}F NMR spectra of the two compounds showed signals at different positions for the trifluoromethyl groups. The ^{19}F NMR δ, ppm (DMSO-d_6) spectra of **3a** showed a signal at 69.87 while its isomer **3a**′ (m.p. $>300\,^{\circ}$C) showed a signal at 64.23.



Thus, compound **3a** was assigned as 4-(trifluoromethyl)-1,2-dihydro-6-(thiophen-2yl)-2-thioxopyridine-3-carbonitrile (**3a**) (*29*) while its isomer was assigned as 6-(trifluoromethyl)-1,2-dihydro-4-(thiophen-2-yl)-2-thioxopyridine-3-carbonitrile (**3a**′). These data are in agreement with those of the earlier work which reported stereoselective synthesis of 6-methyl-1,2-dihydro-4-(trifluoromethyl)-2-thioxopyridine-3-carbonitrile and 4-methyl-1,2-dihydro-6-(trifluoromethyl)-2-thioxopyridine-3-carbonitrile (*30, 31*).

Similarly, a mixture of 4,4,4-trifluoro-1-thiophen-2-yl-butane-1,3-dione (**1**) was ground with 2-cyanoacetamide (**2b**) under solvent-free condition to afford 4-trifluoromethyl-1,2-dihydro-2-oxo-6-(thiophen-2-yl)pyridine-3-carbonitrile (**3b**) (96%). This method of preparation of

Table 1. Yield comparison between solvent-free preparation of compounds **3–7a** and **b** and the classical conditions.

	Yield (%)	
Compound	Method A	Method B
3a	95	80
3b	96	92
4a	96	93
4b	75	53
5a	89	85
5b	80	65
6a	92	80
6b	85	75
7a	93	89
7b	79	56

Notes: A: Grinding; B: Classical conditions.

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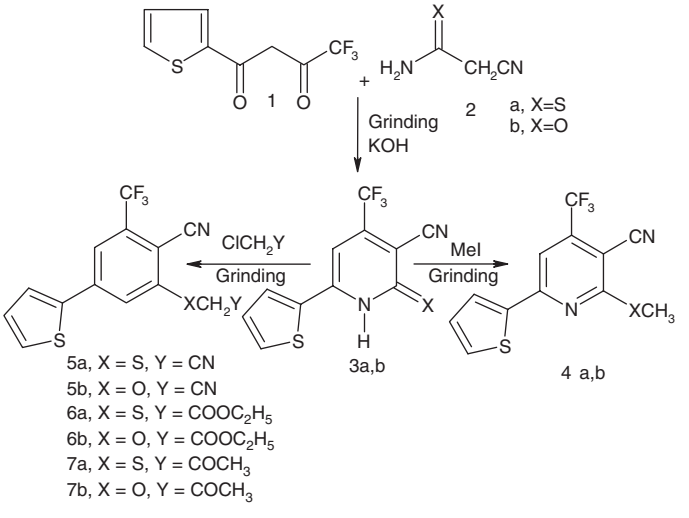
pyridinethionones is simple and effective in terms of short reaction time and excellent yields compared with the classical methods of preparations (*29, 32, 33*) (Table 1).

Structure **3b** was supported by its elemental analysis and spectral data. The IR spectrum of **3b** revealed absorption bands at 2221, 3097, and 1665 cm^{-1} for cyano, NH, and CO groups, respectively. Its ^1H NMR spectrum showed signals at $\delta = 7.29$ (dd, 1H, 4-H of thienyl), 7.66 (s, 1H, 5-H of pyridinyl), 7.93 (d, 1H, 3-H of thienyl), 8.20 (d, 1H, 5-H of thienyl), 13.89 (s, 1H, NH) and its mass spectrum showed a peak corresponding to the molecular ion at *m/z* 270. Compounds **3a** and **b** were reacted with methyliodide, chloroacetonitrile, ethyl bromoacetate, and chloroacetone by grinding in the presence of KOH, in a porcelain mortar; under solvent-free conditions, to give **4a** and **b**, **5a** and **b**, **6a** and **b**, and**7a** and **b** derivatives, respectively, which can be also obtained by the reaction of compounds **3a** and **b** with the same alkylating agents in DMF/KOH (Scheme 1).



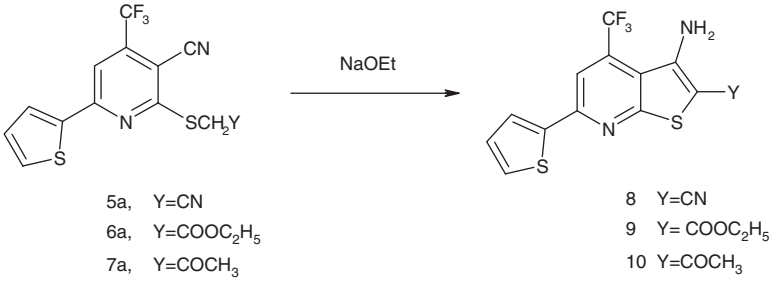
Scheme 1. Reaction of **3a** and **b** with different alkylating agents.

The IR spectrum of **4b** revealed absorption band at 2223 cm^{-1} for the cyano group. Its ^1H NMR spectrum showed a signal at $\delta = 4.18$ (s, 3H, CH_3), 7.27 (dd, 1H, 4-H of thienyl), 7.50 (s, 1H, 5-H of pyridinyl), 7.60 (d, 1H, 3-H of thienyl), and 7.79 (d, 1H, 5-H of thienyl).

The IR spectrum of **5b** revealed the presence of two absorption bands at 2227 and 2268 cm^{-1} for the two cyano groups. Its ^1H NMR spectrum showed signals at $\delta = 5.20$ (s, 2H, CH_2), 7.24 (dd, 1H, 4-H of thienyl), 7.27 (s, 1H, 5-H of pyridinyl), 7.67 (d, 1H, 3-H of thienyl), and 7.86 (d, 1H, 5-H of thienyl).

The structures of compounds **4a**,**5a**, **6a** and **b**, and **7a** and **b** were also confirmed based on elemental analysis and spectral data.

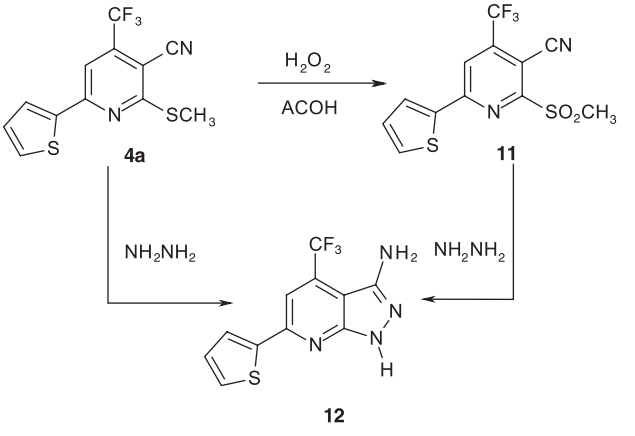
Compounds **5a**, **6a**, and **7a** were converted to the corresponding thienopyridine derivatives by refluxing in sodium ethoxide solution to give **8**, **9**, and **10**, respectively (Scheme 2). The reaction proceeded via intramolecular cyclocondensation to give the substituted thieno[2,3-b] pyridine derivatives in good yield.



Scheme 2. Conversion of *S*-alkyl derivative to thienopyridines.

The absence of cyano group absorption in the IR spectrum of compounds **8**–**10** and the appearance of absorption bands in the region 3050–3400 cm^{-1} for the amino group confirmed the proposed structures. Furthermore, the ^1H NMR spectrum of **10** showed signals at $\delta = 2.52$ (s, 3H, CH_3), 7.17 (dd, 1H, 4-H of thienyl), 7.27 (s, 1H, 5-H of pyridinyl), 7.55 (d, 1H, 3-H of thienyl), 7.78 (d, 1H, 5-H of thienyl), and 14.00 (b, 2H, NH_2) and the disappearance of the signal at δ 4.01 (s, 2H, CH_2). Based on these facts, the structure of compound **10** was assigned as 1-(3-amino-4-(trifluoromethyl)-6-(thiophen-2-yl)thieno[2,3-b]pyridine-2-yl)ethanone.

On the other hand, treatment of **4a** with hydrazine hydrate under reflux for 12 h gave compound **12** in almost quantitative yield (Scheme 3), which was also prepared by the reaction of **11** with hydrazine hydrate under the same conditions. The IR spectrum of compound **12** revealed



Scheme 3. Preparation of pyrazolopyridine derivative.

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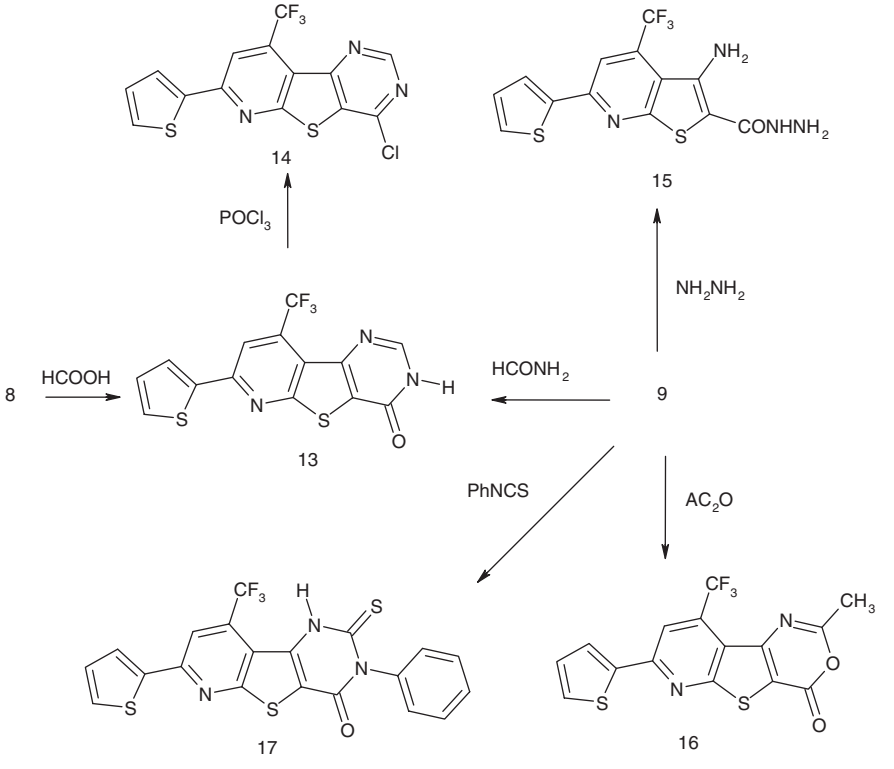
absorption bands at 3330 and 3225 cm^{-1} for the amino group and no absorption was detected for the cyano group.

Compound **8** as a typical enaminonitrile reacted with formic acid upon heating for several hours to yield 7-thiophen-2-yl-9-trifluoromethyl-3-H-pyrido[3′,2′:4,5]thieno[3,2-d]pyrimidin-4-one (**13**) (Scheme 4). The absence of cyano absorption and the appearance of the NH and carbonyl absorption bands at 3046 and 1668 cm^{-1} in the IR spectrum confirmed the proposed structure **13**. Its mass spectrum showed a peak at m/z 353 (M^+). Compound **13** was alternatively obtained by heating compound **9** in formamide under reflux for 7 h (Scheme 4).



Scheme 4. Synthesis of some new polycyclic compounds.

4-Chloro-7-thiophen-2-yl-9-trifluoromethyl-pyrido[3′,2′:4,5]thieno [3,2-d]pyrimidine (**14**) was obtained by the reaction of **13** with $POCl_3$ under reflux for 1 h. Finally, compound **9** reacted with hydrazine hydrate, acetic anhydride and phenylisothiocyanate to give the corresponding compounds **15**, **16**, and **17**, respectively. Structures of compounds **15**,**16**, and **17** have been determined by their elemental analyses and spectral data.

3. Conclusion

In summary, we developed a new approach for the synthesis and reactions of heterocyclic compounds that has proven to be simple, efficient, environmentally benign, and cost-effective compared with the classical synthetic methods. In the process, we investigated the

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regioselective synthesis of 4-(trifluoromethyl)-1,2-dihydro-6-(thiophen-2-yl)-2-thioxopyridine -3-carbonitrileunder different basic conditions and we isolated the two possible regioisomers, 4- and 6-trifluoromethyl-3-cyano-2(1*H*)-pyridinethiones.

4. Experimental

Melting points were measured on an Electrothermal melting point apparatus and are uncorrected. IR spectra were recorded on a Shimadzu FT-IR 8101 PC infrared spectrophotometer. The ^{1}H NMR spectra were determined in DMSO-d_6 at 300 MHz on a Varian mercury VX 300 NMR spectrometer using TMS as an internal standard. Mass spectra were measured on a GCMS-QP1000 EX spectrometer at 70 eV. Elemental analyses were carried out at the Microanalytical Center of Cairo University.

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4.1. *Synthesis of 3a and b*

Method A. A mixture of **1** (3 mmol), 2-cyanothioacetamide (**2a**) or 2-cyanoacetamide (**2b**) (0.3 g/0.25, 3 mmol), and KOH (4 mmol) was thoroughly ground with a pestle in an open mortar at 25 °C for 3–5 min until the mixture turned into a melt. The initial syrupy reaction mixture solidified within 4–6 min. Grinding continued for 5–15 min and the reaction was monitored by TLC. The solid was washed with water and recrystallized from the proper solvent to give **3a** and **b**, respectively.

Method B. A mixture of **1** (11.1 g, 50 mmol) and 2-cyanothioacetamide or 2-cyanoacetamide **2a** and **b** (5 g, 4.2 g, 50 mmol) was heated under reflux in ethanolic triethylamine solution for 15 min. The reaction mixture was cooled; the so-formed solid was filtered and recrystallized from the proper solvent to give **3a** and **b**, respectively.

4.1.1. *4-(Trifluoromethyl)-1,2-dihydro-2-oxo-6-(thiophen-2-yl) pyridine-3-carbonitrile (**3b**)*

Yellow crystals from ethanol, m.p. 300–302 °C; IR (KBr, cm^{-1}) υ 3197 (NH), υ 2225 (CN), υ 1665 (CO). ^{1}H NMR (DMSO-d_6): $\delta = 7.29$ (dd, 1H, 4-H of thienyl), 7.66 (s, 1H, 5-H of pyridinyl), 7.93 (d, 1H, 3-H of thienyl), 8.20 (d, 1H, 5-H of thienyl), 13.89 (s, 1H, NH). MS (70 eV) $m/z = 270$ (M$^+$). Anal. for $C_{11}H_5F_3N_2OS$: C, 48.89; H, 1.86.; N, 10.37; S, 11.87%. Found: C, 49.00; H, 1.95.; N, 10.35; S, 11.85%.

4.2. *Synthesis of 4a and b, 5a and b, 6a and b, and 7a and b*

Method A. A mixture of **3a** and **b** (3 mmol), methyl iodide, chloroacetonitrile, ethyl bromoacetate, chloroacetone (3 mmol), and KOH (4 mmol) was thoroughly ground with a pestle in an open mortar at 25 °C for 3–5 min until the mixture turned into a melt. The initial syrupy reaction mixture solidified within 4–6 min. Grinding continued for 5–15 min and the reaction was monitored by TLC. The solid was washed with water and recrystallized from the proper solvent to give **4a** and **b,5a** and **b,6a** and **b**, and **7a** and **b**, respectively.

Method B. A mixture of **3a** and**b** (2.86, 2.70, 10 mmol) and potassium hydroxide (0.62, 11 mmol) in *N*,*N*-dimethylformamide (10 ml) was stirred for 2 h at room temperature. Methyl iodide, chloroacetonitrile, ethyl bromoacetate, and chloroacetone (10 mmol each) were then added and stirring was continued for 2 h to give a solid that was collected and recrystallized from the proper solvent to give **4a** and **b**, **5a** and **b**, **6a** and **b**, and **7a,b** respectively.

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4.2.1. *4-(Trifluoromethyl)-2-(methylthio)-6-(thiophen-2-yl)pyridine-3-carbonitrile (**4a**)*

Light brown crystals from ethanol, m.p. 142–145 °C; IR (KBr, cm^{-1}) υ 2218 (CN). ^{1}H NMR (DMSO-d_6): $\delta = 7.24$ (dd, 1H, 4-H of thienyl), 7.26 (s, 1H, 5-H of pyridinyl), 7.58 (d, 1H, 3-H of thienyl), 7.76 (d, 1H, 5-H of thienyl). MS (70 eV) $m/z = 300$ (M^+). Anal. for $C_{12}H_7F_3N_2S_2$: C, 47.99; H, 2.35; N, 9.33; S, 21.35%. Found: C, 48.00; H, 2.25; N, 9.20; S, 20.99%.

4.2.2. *4-(Trifluoromethyl)-2-(methxoy)-6-(thiophen-2-yl)pyridine-3-carbonitrile (**4b**)*

Yellow crystals from ethanol; m.p. 108–110 °C; IR (KBr, cm^{-1}) υ 2223 (CN). ^{1}H NMR (DMSO-d_6): $\delta = 4.18$ (s, 3H, CH_3), 7.27 (dd, 1H, 4-H of thienyl), 7.50 (s, 1H, 5-H of pyridinyl), 7.60 (d, 1H, 3-H of thienyl), 7.79 (d, 1H, 5-H of thienyl). MS (70 eV) $m/z = 284$ (M^+). Anal. for $C_{12}H_7F_3N_2OS$: C, 50.70; H, 2.48; N, 9.85; S, 11.28%. Found: C, 50.90; H, 2.45; N, 10.00; S, 11.12%.

4.2.3. *2-(Cyanomethylthio)-4-(trifluoromethyl)-6-(thiophen-2-yl)pyridine-3-carbonitrile (**5a**)*

Pale yellow crystals from DMF, m.p. 235 ∘C; IR (KBr, cm^{-1}) υ 2223, 2251 (2 CN). ^{1}H NMR (DMSO-d_6): $\delta = 4.45$ (s, 2H, CH_2), 7.31 (dd, 1H, 4-H of thienyl), 8.01 (d, 1H, 3-H of thienyl), 8.29 (s, 1H, 5-H of pyridinyl), 8.34 (d, 1H, 5-H of thienyl). MS (70 eV) $m/z = 325$ (M^+). Anal. for $C_{13}H_6F_3N_3S_2$: C, 47.99; H, 1.86; N, 12.92; S, 19.71%. Found: C, 48.10; H, 1.80; N, 13.00; S, 19.99%.

4.2.4. *2-(Cyanomethoxy)-4-(trifluoromethyl)-6-(thiophen-2-yl)pyridine-3-carbonitrile (**5b**)*

Yellow crystals from ethanol; m.p. 188–190 °C; IR (KBr, cm^{-1}) υ 2227, 2268 (2 CN). ^{1}H NMR (DMSO-d_6): $\delta = 5.20$ (s, 2H, CH_2), 7.21 (dd, 1H, 4-H of thienyl), 7.27 (s, 1H, 5-H of pyridinyl), 7.67 (d, 1H, 3-H of thienyl), 7.86 (d, 1H, 5-H of thienyl). MS (70 eV) $m/z = 309$ (M^+). Anal. for $C_{13}H_6F_3N_3OS$: C, 50.49; H, 1.96; N, 13.59; S, 10.37. Found: C, 50.10; H, 1.90; N, 13.50; S, 10.35%.

4.2.5. *Ethyl 2- (3-cyano-4-(trifluoromethyl)-6-(thiophen-2-yl)(pyridine-2-ylthio) acetate (**6a**)*

Yellow crystals from acetic acid; m. p. 148–150 °C; IR (KBr, cm^{-1}) υ 2218 (CN), υ 1733 (CO ester). ^{1}H NMR (DMSO-d_6): $\delta = 1.30$ (t, 3H, CH_3, $J = 7$ Hz), 4.01 (s, 2H, CH_2), 4.27 (q, 2H, $\underline{CH_2}CH_3$, $J = 7$ Hz), 7.26 (dd, 1H, 4-H of thienyl), 7.35 (s, 1H, 5-H of pyridinyl), 7.58 (d, 1H, 3-H of thienyl), 7.79 (d, 1H, 5-H of thienyl). MS (70 eV) $m/z = 372$ (M^+). Anal. for $C_{15}H_{11}F_3N_2O_2S_2$: C, 48.38; H, 2.98; N, 7.52; S, 17.22%. Found: C, 48.00; H, 2.95, N, 7.50; S, 17.00%.

4.2.6. *Ethyl 2-(3-cyano-4-(trifluoromethyl)-6-(thiophen-2-yl)pyridine-2-yloxy) acetate (**6b**)*

Yellow crystal from ethanol; m.p. 227–230 °C; IR (KBr, cm^{-1}) υ 2226 (CN), υ 1756 (CO ester). ^{1}H NMR (DMSO-d_6): $\delta = 1.23$ (t, 3H, CH_3, $J = 7$ Hz), 4.22 (q, 2H, $\underline{CH_2}CH_3$, $J = 7$ Hz), 5.14 (s, 2H, CH_2) 7.28 (dd, 1H, 4-H of thienyl), 7.95 (s, 1H, 5-H of pyridinyl) 8.19 (d, 1H, 3-H of thienyl), 8.26 (d, 1H, 5-H of thienyl). MS (70 eV) $m/z = 356$ (M^+). Anal. for $C_{15}H_{11}F_3N_2O_3S$: C, 50.56; H, 3.11; N, 7.86; S, 9.00%. Found: C, 50.45; H, 3.00; N, 7.76; S, 9.00%.

4.2.7. *2-(2-Oxopropylthio)-4-(trifluoromethyl)-6-(thiophen-2-yl)pyridine-3-carbonitrile (**7a**)*

Brown crystals from ethanol/DMF; m.p. 176–181 °C; IR (KBr, cm^{-1}) υ 2221 (CN), υ 1717 (CO). ^{1}H NMR (DMSO-d_6): $\delta = 2.41$ (s, 3H, CH_3), 4.15 (s, 2H, CH_2), 7.21 (dd, 1H, 4-H of thienyl), 7.27 (s, 1H, 5-H of pyridinyl) 7.60 (d, 1H, 3-H of thienyl), 7.75 (d, 1H, 5-H of thienyl). MS (70 eV) $m/z = 342$ (M^+). Anal. for $C_{14}H_9F_3N_2OS_2$: C, 49.12; H, 2.65; N, 8.18; S, 18.73. Found: C, 49.00; H, 2.45; N, 8.00; S, 18.55%.

4.2.8. *2-(2-Oxopropoxy)-4-(trifluoromethyl)-6-(thiophen-2-yl)pyridine-3-carbonitrile (**7b**)*

Yellow crystals from ethanol, m.p. 143–145 °C; IR (KBr, cm^{-1}) υ 2226 (CN), υ 1669 (CO). ^{1}H NMR (DMSO-d_6): $\delta = 2.32$ (s, 3H, CH_3), 5.08 (s, 2H, CH_2), 7.21 (dd, 1H, 4-H of thienyl), 7.27 (s, 1H, 5-H of pyridinyl), 7.60 (d, 1H, 3-H of thienyl), 7.75 (d, 1H, 5-H of thienyl). MS (70 eV) $m/z = 326$ (M^+). Anal. for $C_{14}H_9F_3N_2O_2S$: C, 51.53; H, 2.78; N, 8.59; S, 9.83%. Found: C, 51.25; H, 2.58; N, 8.35; S, 9.75%.

4.3. *Synthesis of 8–10*

General procedure. Compounds **5a** (3.25 g, 10 mmol), **6a** (3.7 g, 10 mmol) and **7a** (3.4 g, 10 mmol) were refluxed in sodium ethoxide solution (0.23 g, 10 ml) for 3 h. The so-formed solid was collected by filtration and recrystallized from the proper solvent to give **8**, **9**, and **10**, respectively.

4.3.1. *3-Amino-4-(trifluoromethyl)-6-(thiophen-2-yl)thieno[2,3-b]pyridine-2-carbonitrile (**8**)*

Orange crystals from ethanol (84%), m.p. 253–255 °C; IR (KBr, cm^{-1}) υ 3460, υ 3313 (NH_2) υ 2206 (CN). ^{1}H NMR (DMSO-d_6): $\delta = 6.67$ (b, 2H, NH_2), 7.47 (dd, 1H, 4-H of thienyl), 7.82 (s, 1H, 5-H of pyridinyl), 8.18 (d, 1H, 3-H of thienyl), 8.26 (d, 1H, 5-H of thienyl). MS (70 eV) $m/z = 325$ (M^+). Anal. for $C_{13}H_6F_3N_3S_2$: C, 47.99; H, 1.86; N, 12.92; S, 19.71%. Found: C, 48.00; H, 1.90; N, 13.00; S, 19.50% (literature 237 °C (*29*)).

4.3.2. *Ethyl 3-amino-4-(trifluoromethyl)-6-(thiophen-2-yl)thieno[2,3-b]pyridine-2-carboxylate (**9**)*

Yellow crystals from ethanol/DMF (86%), m.p. 175–179 °C; IR (KBr, cm^{-1}) υ 3479, 3371 (NH_2), υ 1685 (CO). ^{1}H NMR (DMSO-d_6): $\delta = 1.47$ (t, 3H, CH_3, $J = 7$ Hz), 4.44 (q, 2H, $\underline{CH_2}CH_3$, $J = 7$ Hz), 6.35 (b, 2H, NH_2), 7.21 (dd, 1H, 4-H of thienyl), 7.53 (s, 1H, 5-H of pyridinyl), 7.56 (d, 1H, 3-H of thienyl), 7.90 (d, 1H, 5-H of thienyl). ^{13}C NMR: $\delta = 14.1$ (CH_3), 60.9 (CH_2), 118.8 (CH), 122.0 (C), 125.3 (CH), 125.5 (CH), 125.6 (CH), 125.9 (CH), 128 (C), 134 (C), 140.0 (C), 147.7 (C), 152.4 (C), 156.0 (C), 160.6 (C=O ester). MS (70 eV) $m/z = 372$ (M^+). Anal. for $C_{15}H_{11}F_3N_2O_2S_2$: C, 48.38; H, 2.98; N, 7.52; S, 17.22%. Found: C, 48.38; H, 2.88; N, 7.50; S, 7.50% (literature 182 °C (*29*)).

4.3.3. *1-(3-Amino-4-(trifluoromethyl)-6-(thiophen-yl)thieno[2,3-b]pyridine-2-yl) ethanone (**10**)*

Orange crystals form ethanol (80%), m.p. 165–167 °C; IR (KBr, cm^{-1}) υ 3527, 3307 (NH_2), υ 1718 (CO). ^{1}H NMR (DMSO-d_6): $\delta = 2.52$ (s, 3H, CH_3), 7.27 (s, 1H, 5-H of pyridinyl) 7.55 (d, 1H, 3-H of thienyl), 7.78 (b, 2H, NH_2), 7.87 (dd, 1H, 4-H of thienyl), 7.90 (d, 1H, 5-H of thienyl). ^{13}C NMR: $\delta = 27.8$ (CH_3), 122.0 (C), 125.3 (CH), 125.5 (CH), 125.6 (CH), 125.9 (CH),

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128 (C), 133 (C), 140.0 (C), 146 (C) 147.7 (C), 152.4 (C), 156.8 (C), 190.5 (C=O). MS (70 eV) $m/z = 342$ (M^+). Anal. for $C_{14}H_9F_3N_2OS_2$: C, 48.38; H, 2.98; N, 8.18; S, 18.73%. Found: C, 48.38; H, 2.88; N, 8.00; S, 18.74%.

4.4. *Synthesis of 11*

To a stirred mixture of **4a** (1.5 g, 5 mmol) in glacial acetic acid (10 ml) was added 30% H_2O_2 solution (15 ml) and the mixture was heated under reflux for 3 h. After cooling, the solid that formed was collected and recrystallized from ethanol to give **11**.

4.4.1. *4-(Trifluoromethyl)-2-(methylsulfonyl)-6-(thiophen-2-yl)pyridine-3-carbonitrile (**11**)*

Green crystals from ethanol (65%), m.p. 208–210 °C; IR (KBr, cm^{-1}) υ 2219 (CN). ^{1}H NMR (DMSO-d_6): $\delta = 3.40$ (s, 3H, CH_3), 7.01 (dd, 1H, 4-H of thienyl), 7.20 (d, 1H, 5-H of thienyl), 7.55 (d, 1H, 3-H of thienyl), 8.00 (s, 1H, 5-H of pyridinyl). MS (70 eV) $m/z = 332$ (M^+). Anal. for $C_{12}H_7F_3N_2O_2S_2$: C, 43.37; H, 2.12; N, 8.43; S, 19.30%. Found: C, 43.43; H, 2.01; N, 8.50; S, 19.72%.

4.5. *Synthesis of 12*

Method A. A mixture of **4a** (1.5 g, 5 mmol) and excess of hydrazine hydrate was refluxed for 6h. The reaction mixture was cooled, and the solid that formed was filtered, dried, and recrystallized from ethanol to give **12**.

Method B. A mixture of **11** (1 g, 3 mmol) and excess of hydrazine hydrate was refluxed for 3h. The reaction mixture was cooled, and the solid that formed was filtered, dried, and recrystallized from ethanol to give **12**.

4.5.1. *4-(Trifluoromethyl)-6-(thiophen-2-yl)-1H-pyrazolo[3,4-b]pyridine-3-amine (**12**)*

Yellow crystals from ethanol (90%), m.p. 229–230 °C; IR (KBr, cm^{-1}) υ 3450, υ 3330, υ 3225 (NH_2, NH). ^{1}H NMR (DMSO-d_6): $\delta = 7.55$ (d, 1H, 3-H of thienyl), 7.60 (s, 1H, 5-H of pyridinyl), 7.78 (b, 2H, NH_2), 7.87 (dd, 1H, 4-H of thienyl), 7.90 (d, 1H, 5-H of thienyl), 13.7 (s, 1H, NH). MS (70 eV) $m/z = 284$ (M^+). Anal. for $C_{11}H_7F_3N_4S$: C, 46.48; H, 2.48; N, 19.71; S, 11.28%. Found: C, 46.43; H, 2.50; N, 19.70; S, 11.30%.

4.6. *Synthesis of 13*

Method A. A mixture of **8** (1.8 g, 5 mmol) and formic acid (20 ml) was heated under reflux for 7 h. After cooling, the reaction mixture was poured on ice and the solid that formed was collected and recrystallized from DMF to give **13**.

Method B. Compound **9** (2 g, 5 mmol) was heated under reflux with formamide (20 ml) for 2 h. After cooling, the reaction mixture was poured on ice and the solid that formed was collected and recrystallized from DMF to give **13**.

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4.6.1. *7-Thiophen-2-yl-9-trifluoromethyl-3H-pyrido[3′ ,2′ :4,5]thieno[3,2-d]pyrimidin-4-one (**13**)*

Dark brown crystals from DMF (75%), m.p. >300 °C; IR (KBr, cm^{-1}) υ 3450 (NH), υ 1668 (CO). ^{1}H NMR (DMSO-d_6): $\delta = 7.24$–7.64 (m, 4H, Ar-H), 7.50 (s, 1H, 2-H of pyrimidinyl), 7.55 (d, 1H, 3-H of thienyl), 7.60 (s, 1H, 5-H of pyridinyl), 7.87 (dd, 1H, 4-H of thienyl), 7.90 (d, 1H, 5-H of thienyl). MS (70 eV) $m/z = 353$ (M^+). Anal. for $C_{14}H_6F_3N_3OS_2$: C, 47.59; H, 1.71; N, 11.89; S, 18.15%. Found: C, 47.50; H, 1.90; N, 12.00; S, 18.35%.

4.7. *Synthesis of 14*

Compound **13** (1.1 g, 3 mmol) reacted with $POCl_3$ (20 ml) under reflux for 1 h. The reaction mixture was poured over ice, and the resulting solid was collected by filtration and recrystallization from DMF to give **14**.

4.7.1. *4-Chloro-7-thiophen-2-yl-9-trifluoromethyl-pyrido[3′, 2′:4,5]thieno[3,2-d] pyrimidine (**14**)*

Dark brown crystals from DMF (75%), m.p. >300 °C; ^{1}H NMR (DMSO-d_6): $\delta = 7.55$ (d, 1H, 3-H of thienyl), 7.60 (s, 1H, 5-H of pyridinyl), 7.87 (dd, 1H, 4-H of thienyl), 7.90 (d, 1H, 5-H of thienyl), 9.46 (s, 1H, 2-H of pyrimidinyl). MS (70 eV) $m/z = 371$ (M^+). Anal. for $C_{14}H_5ClF_3N_3S_2$: C, 45.23; H, 1.36; N, 11.30; S, 17.25%. Found: C, 45.50; H, 1.46; N, 11.00; S, 17.30%.

4.8. *Synthesis of 15*

A mixture of **9** (4.0 g, 10 mmol) and hydrazine hydrate (4 ml, 85% solution, 4 mmol) in absolute ethanol (20 ml) for 24 h was heated under reflux. The reaction mixture was cooled, and the resulting solid was collected and recrystallized from ethanol to give **15**.

4.8.1. *3-Amino-6-thiophen-2-yl-4-trifluoromethyl-thieno[2,3-b]pyridine-2-carboxylic acid hydrazide (**15**)*

Yellow crystals from ethanol/DMF (65%), 294–297 °C; IR (KBr, cm^{-1}) υ 3346, υ 3319 (NH_2, NH), υ 1650, (CO). MS (70 eV) $m/z = 358$ (M^+). Anal. Calcd for $C_{13}H_9F_3N_4OS_2$: C, 43.57; H, 2.53, N, 15.63; S, 17.89%. Found: C, 43.50; H, 2.50; N, 15.50; S, 17.90%.

4.9. *Synthesis of 16*

A mixture of **9** (4.0 g, 10 mmol) and acetic anhydride (10 ml) in was heated under reflux for 5 h. The reaction mixture was cooled, and the resulting solid was collected and recrystallized from acetic acid to give **16**.

4.9.1. *2-Methyl-7-thiophen-2-yl-9-trifluoromethylpyrido[3′, 2′ :4,5]thieno[3,2-d][1,3]oxazin-4-one (**16**)*

Yellow crystals from acetic acid (80%), m.p. 255 °C; IR (KBr, cm^{-1}) υ 1743 (CO). ^{1}H NMR (DMSO-d_6): $\delta = 2.59$ (s, 3H, CH_3), 7.27 (dd, 1H, 4-H of thienyl), 7.85 (d, 1H, 3-H of thienyl), 7.87 (d, 1H, 5-H of thienyl), 8.06 (s, 1H, 5-H of pyridinyl). MS (70 eV) $m/z = 368$ (M^+). Anal.

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for $C_{15}H_7F_3N_2O_2S_2$: C, 48.91; H, 1.92; N, 7.60; S, 17.41%. Found: C, 48.98; H, 1.88; N, 7.70; S, 17.50%.

4.10. *Synthesis of 17*

A mixture of **9** (4.0 g, 10 mmol) and the phenyl isothiocyanate (1.35 g, 10 mmol) in acetonitrile (30 ml) was heated under reflux for 15 h in the presence of anhydrous potassium carbonate (1.4 g). The reaction mixture was cooled, filtered, dilute with water (10 ml), and neutralized with hydrochloric acid (2M). The resulting solid was collected, washed with water, and recrystallized from ethanol to give **17**.

4.10.1. *3-Phenyl-7-thiophen-2-yl-2-thioxo-9-trifluoromethyl-2,3-dihydro-1H-pyrido[3′, 2′ :4,5]thieno[3,2-d]pyrimidine (**17**)*

Yellow crystals from ethanol (75%), m.p. 183–185 °C; IR (KBr, cm^{-1}) υ 3337 (NH), υ 1674 (CO). ^{1}H NMR (DMSO-d_6): $\delta = 7.24$–7.64 (m, 4H, Ar-H), 7.55 (d, 1H, 3-H of thienyl), 7.60 (s, 1H, 5-H of pyridinyl), 7.87 (dd, 1H, 4-H of thienyl), 7.90 (d, 1H, 5-H of thienyl). ^{13}C NMR: $\delta = 121.6$ (2 CH), 124.4 (CH), 125.3 (CH), 125.5 (CH), 125.6 (CH), 125.9 (CH), 129 (2 CH), 129 (2 C), 132.8 (C), 133.4 (C), 140.0 (C), 147.7 (C), 152.4 (C), 156.8 (C), 165.2 (C9O amide), 177.0 (C9S). MS (70 eV) $m/z = 461$ (M^+). Anal. for $C_{20}H_{10}F_3N_3OS_3$: C, 52.05; H, 2.18; N, 9.10; S, 20.84% Found: C, 52.12; H, 2.20; N, 8.99; S, 20.50%.

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