Fluorine-containing heterocycles: Part I. Synthesis of new 7-(2-thienyl)-9-trifluoromethylpyrido[3',2':4,5]thieno[3,2-*d*]pyrimidines and related fused tetracyclic systems

Etify A. Bakhite, Abdu E. Abdel-Rahman* and Elham A. Al-Taifi

Chemistry Department, Faculty of Science, Assiut University, Assiut 71516, Egypt

3-amino-6-(2-thienyl)-4-trifluoromethylthieno[2,3-*b*]pyridine-2-carboxamide (**3**) and 2-carbonitrile analogue **5** were prepared by reaction of 3-cyano-6-(2-thienyl)-4-trifluoromethylpyridine-2(1*H*)-thione **(1)** with chloroacetamide or chloroacetonitrile respectively. Heating compound **3** with triethyl orthoformate led to the formation of pyridothienopyrimidinone derivative **6**. Reaction of **6** with phosphorus oxychloride produced 4-chloropyrimidine derivative **7** which underwent some nucleophilic displacements upon treatment with thiourea, piperidine, morpholine or hydrazine hydrate to give the target 4-substituted pyridothienopyrimidines **8, 10a, 10b** and **11** respectively. Reaction of compound **8** with methyl iodide or ethyl chloroacetate gave compounds **9a,b**. The condensation of 3-amino-6-(2-thienyl)-4-trifluoromethyl-thieno[2,3-*b*]pyridine-2-carbonitrile (**5**) with triethyl orthoformate led to the formation of methanimidate derivative **21** which upon treatment with hydrazine hydrate gave the target 3-amino-3,4-dihydro-4-imino-7-(2-thienyl)-9-trifluoromethylpyrido[3',2':4,5] thieno[3,2-*d*]pyrimidine (**22**). The reactions of compounds **11** and **22** with some reagents namely; triethyl orthoformate, acetic anhydride, formic acid, acetic acid, acetylacetone benzaldehyde and/or diethyl malonate were carried out and their products were identified, in most cases as [1,2,4]triazolopyridothienopyrimidines *via* Dimroth rearrangement.

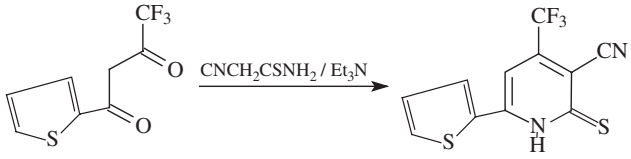
Keywords: thienopyridines, thienopyrimidines, pyridothienopyrimidines, fluorine-containing compounds

Organofluorine compounds, particularly heterocyclic ones, are very attractive targets both from a theoretical and synthetic point of view. They have attracted much attention especially in the last decade in biological and medicinal chemistry.[1] This is due to the unique features of fluorine compounds and foremost their high physiological activity.[2,3] The introduction of fluorine into organic compounds often permits dramatic modification of their chemical and pharmaceutical properties.[4] On the other hand, many of pyridothienopyrimidine derivatives have been the subject of chemical and biological studies on account of their pharmacological properties. Such derivatives have found applications as antimalarial,[5] anticancer,[6] antibacterial[7,8] and as metabolite agents.[9] In view of the above observations and as a continuation of our earlier work on the synthesis of pyridothienopyrimidines,[10-13] we report herein the synthesis of the title compounds which are considered to be active compounds owing to incorporating of different pharmacophores, in addition to the trifluoromethyl group, into their structures.

Results and discussion

The starting compound, 3-cyano-6-(2-thienyl)-4-trifluoromethylpyridine-2(1*H*)-thione (**1**) was prepared by cyclocondensation of 1,1,1-trifluoromethyl-3-(2-thenoyl)acetone with cyanothioacetamide following the reported method.[14]

Refluxing compound **1** with chloroacetamide or chloroacetonitrile in ethanol containing excess amounts of sodium acetate



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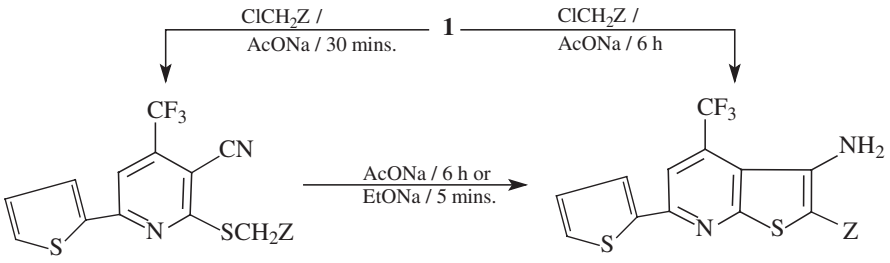
for 6 hours gave 2-functionalised 3-amino-6-(2-thienyl)-4-trifluoromethylthieno[2,3-*b*]pyridines (**3** or **5**). The related intermediates **2** and **4** were only obtained when equimolar amount of sodium acetate was used and the reaction time was reduced to 30 mins. Cyclisation of compounds **2** or **4** into the corresponding thieno[2,3-*b*]pyridines **3** or **5** was affected by heating in ethanol containing catalytic amounts of sodium acetate for 6 hours. The latter cyclisation was also carried out by heating of **2** or **4** in ethanol containing a catalytic amount of sodium ethoxide for 5 min (Scheme 1).

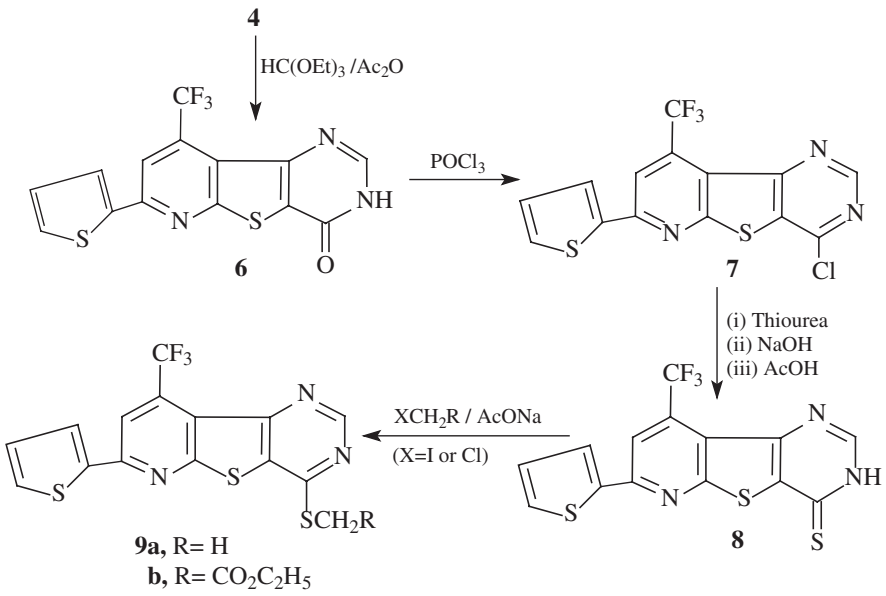
Heating *o*-aminoamide **3** with triethyl orthoformate in the presence of acetic anhydride gave 7-(2-thienyl)-9-trifluoromethylpyrido[3',2':4,5]thieno[3,2-*d*]pyrimi-dine-4(3*H*)-one (**6**). Treatment of **6** with phosphorus oxychloride led to the formation of 4-chloro-7-(2-thienyl)-9-trifluoromethylpyrido [3',2':4,5]thieno[3,2-*d*]pyrimidine (**7**) in nearly quantitative yield. Reaction of the latter compound with thiourea, followed by treatment of the resulting adduct with sodium hydroxide solution and then acidification with acetic acid furnished 7-(2-thienyl)-9-trifluoromethylpyrido [3',2':4,5]thieno[3,2-*d*]



2, Z= $CONH_2$
4, Z=CN

3, Z= $CONH_2$
5, Z=CN

* Correspondent. E-mail: abduelsayed@yahoo.com



Scheme 2

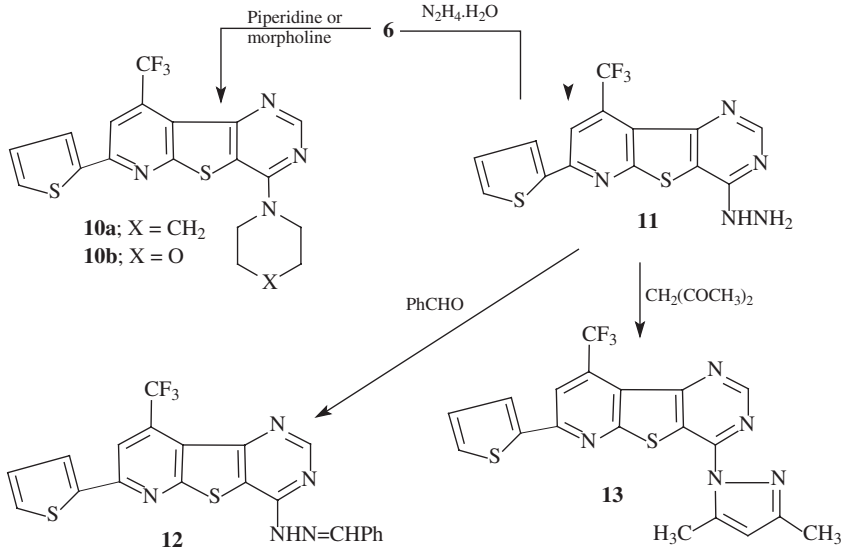
pyrimidine-4(3*H*)-thione (**8**). Upon treatment of compound **8** with methyl iodide or ethyl chloroacetate in the presence of sodium acetate, the corresponding *S*-alkylated-thiopyrido-thienopyrimidine derivatives **9a,b** were obtained (Scheme 2).

The chloropyrimidine derivative **7** underwent other nucleophilic displacements upon treatment with piperidine, morpholine and/or hydrazine hydrate to afford 4-substituted 7-(2-thienyl)-9-trifluoromethylpyrido[3',2':4,5]thieno[3,2-*d*] pyrimidines (**10a, 10b** and **11** respectively). The hydrazino compound **11** was served as a facile point to departure to other pyridothienopyrimidine derivatives. Thus, its condensation with benzaldehyde gave 4-benzylidenehydrazinopyrido-thienopyrimidine derivative **12**. The cyclocondensation of compound **11** with acetylacetone furnished 4-(3,5-dimethyl-1-pyrazolyl)-7-(2-thienyl)-9-trifluoromethylpyrido[3',2':4,5] thieno[3,2-*d*]pyrimidine (**13**) (Scheme 3).

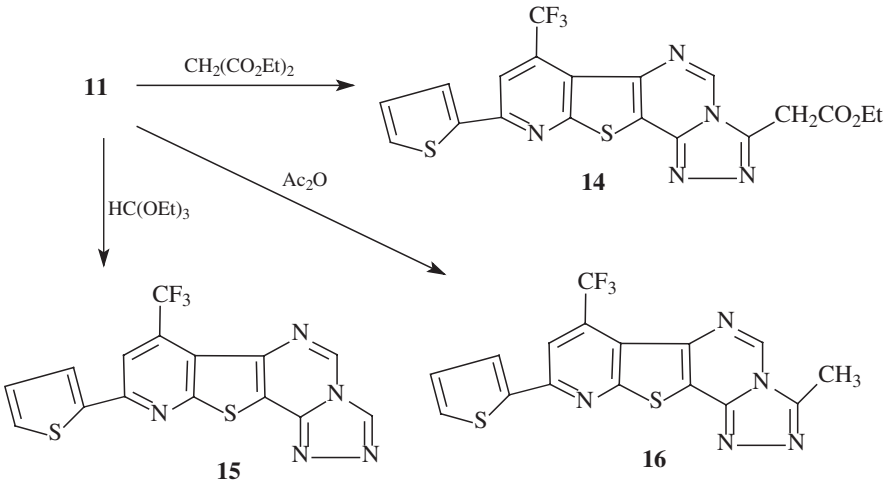
When compound **11** was heated with neat diethyl malonate, the ethyl (9-(2-thienyl)-7-trifluoromethyl-[1,2,4]triazolo[4",3"-*c*]pyrido[3',2':4,5]thieno[2,3-*e*]pyrimi-dine-3-acetate (**14**) was obtained. Also, the cyclocondensation of **11** with triethyl orthoformate under neat condition led to the formation of [1,2,4]triazolopyrido-thienopyrimidine derivative **15**. Moreover, the related 3-methyl analogue **16** was prepared by reaction of compound **11** with acetic anhydride (Scheme 4).

Heating hydrazino compound **11** with formic acid at reflux temperature led to the formation of *s*-triazolo derivative **19** rather than the expecting isomer **15**. In the same manner, the reaction of **11** with acetic acid produced methyl-*s*-triazole **20** rather than related isomer **16**. From thermodynamic point of view,[15] the compounds **19** and **20** seem to be more stable than the corresponding isomers **15** and **16**. The pathway of the latter reactions may be involved firstly the usual formation of compounds **15** and **16** *via* the intermedicay of acid hydrazides **17** and **18** respectively. Under the applied reaction conditions,[15] compounds **15** and **16** underwent spontaneously Dimroth rearrangement *in situ* to give the most stable isomers **19** and **20** (Scheme 5).

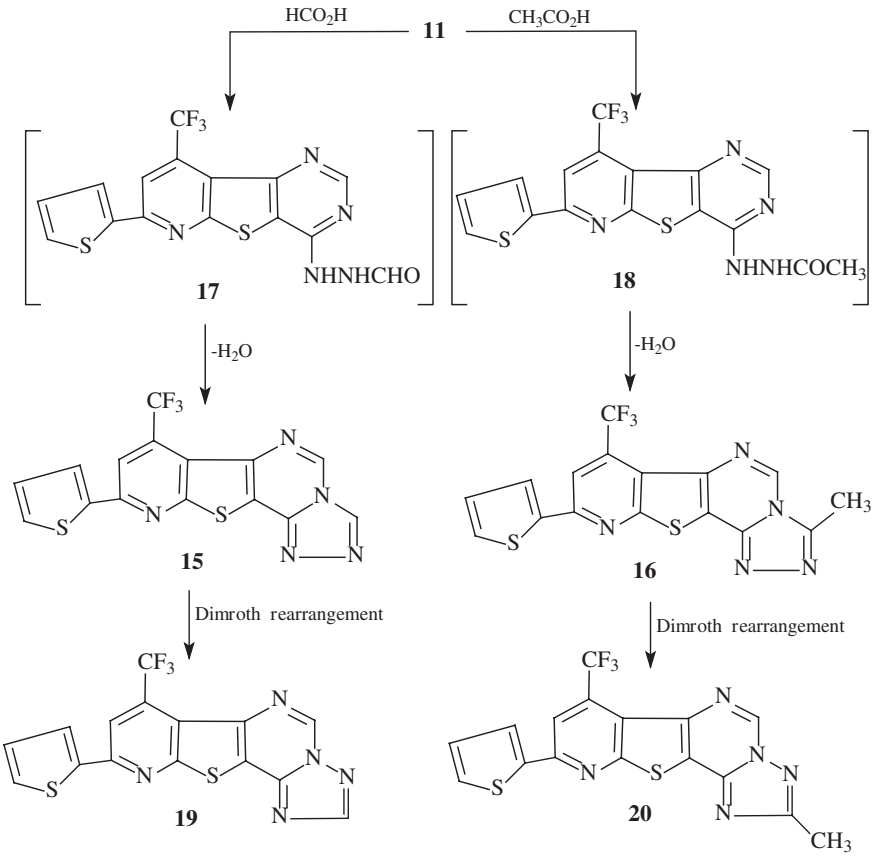
The mechanism of Dimroth rearrangement under investigation is given in Scheme 6.[16] The rearrangement is promoted here by aqueous acids (formic acid 85 % or acetic acid 96 %). It involves initially covalent hydration of **15** or **16**. The hydroxy group enters position 5, then the pyrimidine ring



Scheme 3



Scheme 4

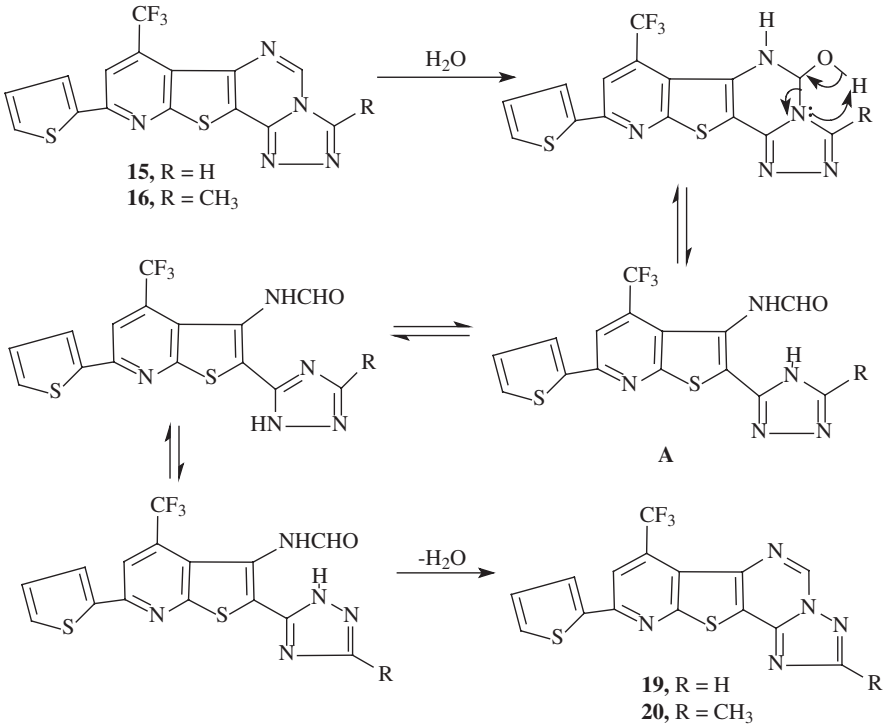


Scheme 5

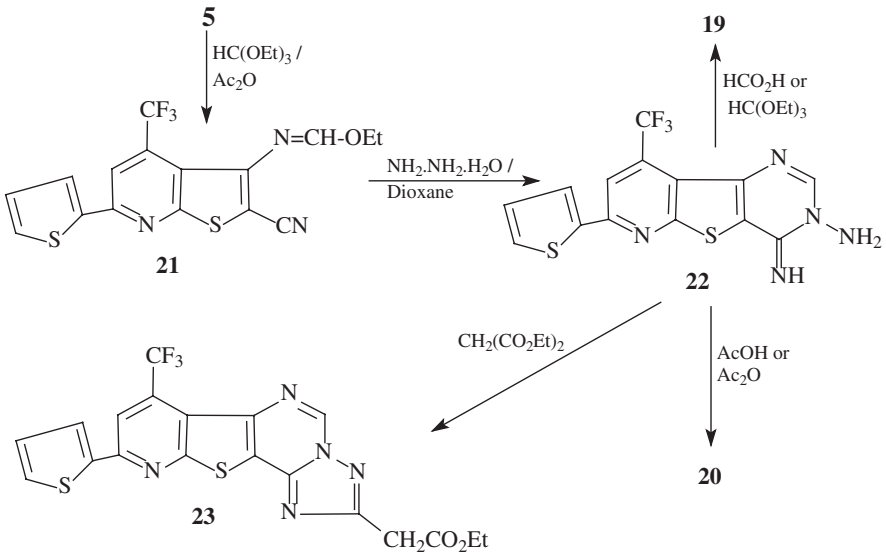
opens and forms the carbonyl intermediates A; the CO group then attacks the more nucleophilic N-2 of the triazole ring and cyclises to the rearranged triazolopyrimidines **19** and **20** respectively.

The structures of compounds **19** and **20** were also confirmed *via* an independent method of preparation as described below. Thus, the condensation of 3-amino-6-(2-thienyl)-4-trifluoromethylthieno[2,3-*b*]pyridine-2-carbonitrile (**5**) with triethyl orthoformate led to the formation of methanimidate derivative **21** which upon treatment with hydrazine hydrate furnished 3-amino-3,4-dihydro-4-imino-7-(2-thienyl)-9-trifluorome thylpyrido[3',2':4,5]thieno[3,2-*d*]pyrimidine (**22**). Heating compound **22** with an excess amount of formic acid or triethyl orthoformate furnished [1,2,4]triazolopyridothienopyrimidine derivative **19**. Compound **20** was also prepared from the reaction of **22** with acetic acid or acetic anhydride. When compound **22** was allowed to react with neat diethyl malonate, ethyl 9-(2-thienyl)-7-trifluoromethyl-[1,2,4]triazolo[2",3"-*c*] pyrido[3',2':4,5]thieno[2,3-e]pyrimidine-2-acetate (**23**) was isolated in high yield (Scheme 7).

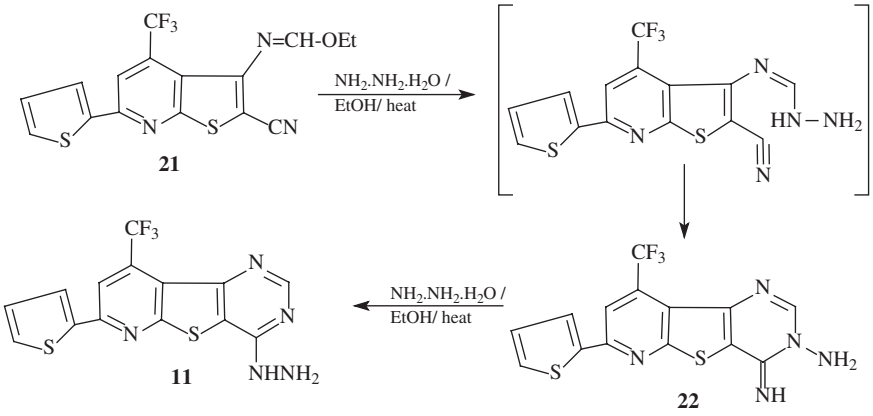
It is interesting to note that the reaction of methanimidate derivative **21** with hydrazine hydrate by refluxing in ethanol led to the formation of hydrazino compound **11**. The pathway of this reaction can be outlined *via* the intermediacy of compound **22** which underwent Dimroth rearrangement under the reaction conditions to give **11**. This fact was supported



Scheme 6



Scheme 7

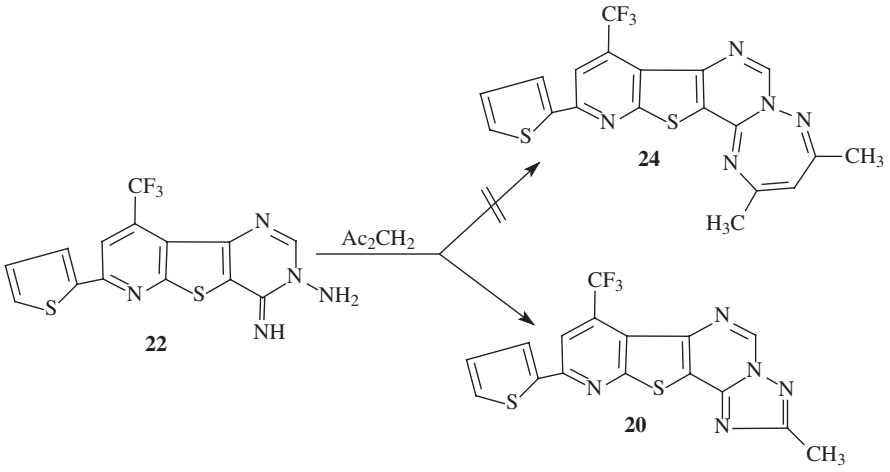


Scheme 8

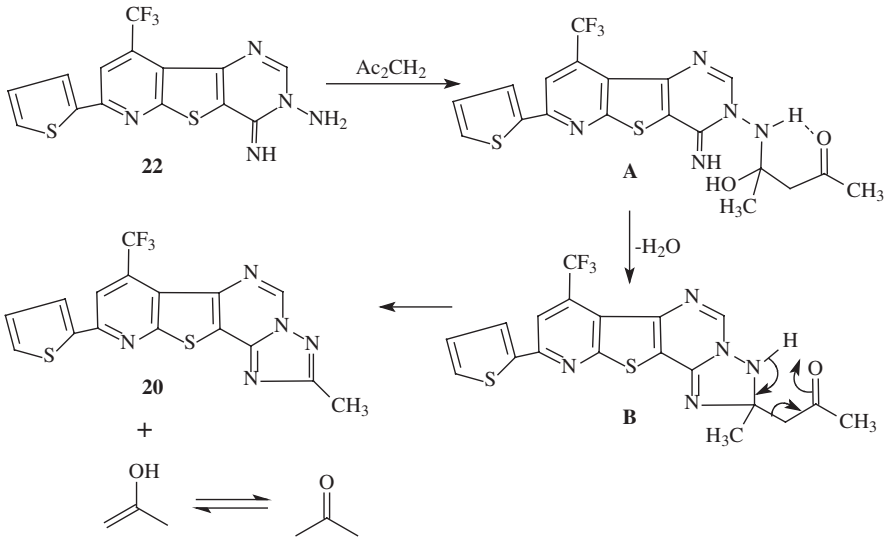
by refluxing compound **22** with hydrazine hydrate in ethanol wherein the compound **11** was also isolated[17] (Scheme 8). The mechanism of this rearrangement is similar to that described for compounds **15** and **16**.

The reaction of compound **22** with acetylacetone under neat conditions did not give the expected triazepine derivative **24** and instead the methyl[1,2,4]triazole derivative **20** was isolated (Scheme 9). This result can be explained by assuming the formation of the addition product **A** as a first step. Subsequent loss of water and acetone leads to **20**[18] (Scheme 10).

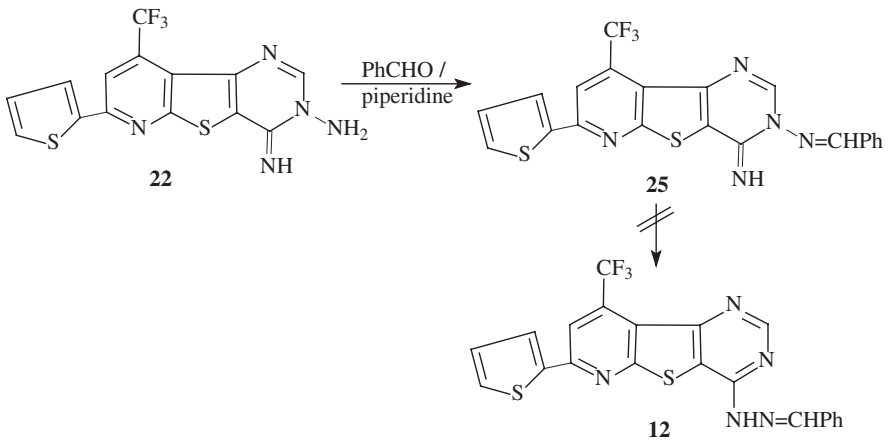
The condensation of compound **22** with benzaldehyde by refluxing in ethanol containing few drops of piperidine gave the expected Schiff's base **25** which did not undergo Dimroth rearrangement under the applied reaction conditions to give its isomeric hydrazone **12** as reported for a similar function[19] (Scheme 11).



Scheme 9



Scheme 10



Scheme 11

It is noteworthy that the trifluoromethyl group did not react with any reactive entity such as sodium ethoxide, thiourea, sodium hydroxide, piperidine, morpholine or hydrazine hydrate during the entire sequence of reactions described in this investigation. This may be the result of high stability of the trifluoromethyl group.[20]

The structures of all newly synthesised compounds were elucidated and confirmed by elemental analyses, IR, ^{1}H NMR and mass spectral data (*cf*. Experimental part).

Experimental

All m.p.'s are uncorrected and measured on a Gallen-Kamp apparatus. IR spectra were recorded on a Shimadzu 470 IR-spectrophotometer (KBr; ν_{max} in cm^{-1}); ^{1}H-NMR spectra on a Varian EM-390, 90 MHz spectrometer with TMS as internal standard (δ in ppm); MS on a Jeol JMS-600 mass spectrometer and elemental analyses on an Elementar Analysen system GmbH VARIOEL V2.3 July 1998 CHNS Mode. The purity of all synthesised compounds was checked by TLC.

3-Cyano-6-(2-thienyl)-4-trifluoromethylpyridine-2(1H)-thione (**1**): The compound was prepared according to the reported method.[14]

3-Cyano-6-(2-thienyl)-4-trifluoromethylpyridin-2-ylthioacetamide (2): To a suspension of compound 1 (5.72 g, 20 mmol) and sodium acetate trihydrate (2.72 g, 20 mmol) in ethanol (50 ml), chloroacetamide (1.9 g, 20 mmol) was added. The resulting mixture was heated under reflux for 30 mins. The precipitate that formed on cooling was collected and recrystallised from an ethanol–chloroform mixture as white needles of 2; yield: 6.1 g, 89 %; m.p.: 237–238°C; Lit.[14] m.p. 237–238 °C.

3-Cyano-6-(2-thienyl)-4-trifluoromethylpyridin-2-ylthioacetonitrile (4): This compound was prepared by reaction of 1 with chloroacetonitrile in analogy to the above procedure. It was recrystallised from an ethanol–chloroform mixture as white crystals; yield: 6.0 g (92 %); m.p.: 235–236°C. Anal. Calcd. for $C_{13}H_6F_3N_3S_2$(325.34): C, 47.99; H, 1.86; N, 12.92; S, 19.71%. Found: C, 48.23; H, 1.70; N, 12.83; S, 20.02 %. IR: ν = 2220, 2200 (2 C≡N) cm^{-1}. ^{1}H NMR (TFA) δ: 8.4 (m, 1H, CH thienyl), 8.3 (s, 1H, CH pyridine), 7.8 (m, 1H, CH thienyl), 7.5 (m, 1H, CH thienyl), 4.4 (s, 2H, SCH_2).

3-Amino-6-(2-thienyl)-4-trifluoromethylthieno[2,3-b]pyridine-2-carboxamide (**3**): *Method* (**A**): To a suspension of compound **1** (5.72 g, 20 mmol) and sodium acetate (5.44 g, 40 mmol) in ethanol (70 ml), chloroacetamide (1.9 g, 20 mmol) was added. The resulting mixture was refluxed for 6 h. The yellow precipitate that formed on hot was collected and recrystallised from an ethanol–chloroform mixture to give compound **3;** yield: 5.2 g (91%); m.p.: 253–254 °C; Lit.[14] m.p. 253–254 °C.

Method (B): A mixture of compound 2 (3.43 g, 10 mmol) and sodium acetate (1.36 g, 10 mmol) in ethanol (40 ml) was refluxed for 6 h. The yellow precipitate that formed on hot was collected and recrystallised from an ethanol–chloroform mixture to give 3; yield: 3.1 g (90%); m.p.: 253–254 °C; m.m.p.: 253–254 °C.

Method (C): Compound 2 (3.43 g, 10 mmol) was suspended in sodium ethoxide solution (0.12 g of sodium in 30 ml of abs. ethanol) and heated under reflux for 5 mins. The yellow precipitate that formed on cooling was collected and recrystallised from an ethanol–chloroform mixture to give 3; yield: 3.2 g (93 %); m.p.: 253–254 °C; m.m.p.: 253–254 °C.

3-Amino-6-(2-thienyl)-4-trifluoromethylthieno[2,3-b]pyridine-2-carbonitrile (**5**): This compound was prepared in analogy to the above procedures by reaction of **1** with chloroacetonitrile (method A; yield: 85 %) or by cyclisation of compound **3** (method B; yield: 91% or method C; yield: 82 %). It recrystallised from an ethanol–chloroform mixture as canary yellow plates; m.p.: 248–249° C. Anal. Calcd. For $C_{13}H_6F_3N_3S_2$(325.34): C, 47.99; H, 1.86; N, 12.92; S, 19.71%. Found: C, 48.08; H, 1.96; N, 12.69; S, 19.45 %. IR: ν = 3450, 3350 (NH_2), 2200 (C=N) cm^{-1}. ^{1}H NMR (DMSO-d_6): δ: 8.3 (m, 1H, CH thienyl), 8.0 (s, 1H, CH pyridine), 7.6 (m, 1H, CH thienyl), 7.3 (m, 1H, CH thienyl), 5.6 (s, 2H, NH_2). MS: *m/z* = 327 (M+2, 61%) 325.32 (M$^+$, 100 %), 307 (M+2-HF, 16%) 306 (M-F, 37 %), 305 (M-HF, 100 %), 285 (M-2HF, 75 %), 69 (CF_3^+, 22 %).

7-(2-Thienyl)-9-trifluoromethylpyrido[3',2':4,5]thieno[3,2-d] pyrimidine-4(3H)-one (**6**): This compound was prepared according to the reported method.[14]

4-Chloro-7-(2-thienyl)-9-trifluoromethylpyrido[3',2':4,5]thieno [3,2-d] pyrimidine (**7**): A suspension of compound **6** (1.77g, 5 mmol) in excess phosphorus oxychloride (30 ml) was heated under reflux for 3 h. The cooled reaction mixture was poured with vigorous stirring into ice-water (150 ml). The precipitated solid was collected and crystallised from an ethanol–chloroform as yellow needles. Yield: 1.7g (91 %); m.p.: 285–286°C. IR: ν = 1600 (C=N) cm^{-1}. ^{1}H NMR (TFA) δ: 9.1 (s, 1H, CH pyrimidine), 8.4 (d, 1H, CH thienyl), 8.3 (s, 1H, CH pyridine), 7.8 (m, 1H, CH thienyl), 7.5 (m, 1H, CH thienyl). MS: *m/z* = 371.36 (M$^+$, 100 %), 335.44 (M$^+$-Cl, 40 %), 69 (CF_3^+, 14 %). Anal. Calcd. For $C_{14}H_5ClF_3N_3S_2$ (371.79): C, 45.23; H, 1.36; N, 11.30; S, 17.25 %. Found: C, 45.58; H, 1.54; N, 11.35; S, 17.38 %.

7-(2-Thienyl)-9-trifluoromethylpyrido[3',2':4,5]thieno[3,2-d] pyrimidine-4(3H)-thione (**8**): A mixture of compound **7** (1.86 g, 5 mmol) and thiourea (0.76 g, 10 mmol) in DMF (20 ml) was heated under reflux for 3 h and then left to cool. The separated solid was collected, dissolved in warm 10% sodium hydroxide solution and filtered off. The clear filtrate was acidified with acetic acid whereby a yellow precipitate separated. It was collected and crystallised from DMF as yellow needles of **8**. Yield: 1.62 g (88 %); m.p.:>300° C. IR: ν = 3330–3120 (NH) cm^{-1}. ^{1}H NMR (TFA) δ: 9.1 (s, 1H, CH pyrimidine), 8.4 (d, 1H, CH thienyl), 8.3 (s, 1H, CH pyridine), 7.8 (m, 1H, CH thienyl), 7.5 (m, 1H, CH thienyl). MS : *m/z* = 369 (M$^+$, 100 %). Anal. Calcd. For $C_{14}H_6F_3N_3S_3$ (369.41): C, 45.52; H, 1.64; N, 11.37; S, 26.04 %. Found: C, 45.70; H, 1.58; N, 11.30; S, 26.25 %.

Reaction of compound 8 with methyl iodide or ethyl chloroacetate; general procedure: To a mixture of **8** (1.48 g, 4 mmol) and sodium acetate trihydrate (1.36 g, 10 mmol) in ethanol (30 ml), methyl iodide or ethyl chloroacetate (4 mmol) was added. The reaction mixture was heated under reflux for 2 h. The precipitated solid was collected and recrystallised from ethanol–chloroform mixture to give pale yellow crystals of **9a** or **9b** respectively.

4-Methylthio-7-(2-thienyl)-9-trifluoromethylpyrido[3',2':4,5]thieno[3,2-d] pyrimidine (**9a**): Obtained using methyl iodide in the above general procedure. Yield: 1.3 g (85 %); m.p.: 280–281° C. IR: ν = 1600 (C=N) cm^{-1}. ^{1}H NMR (TFA) δ: 9.4 (s, 1H, CH pyrimidine), 8.3 (s, 1H, CH pyridine), 8.1 (m, 1H, CH thienyl), 7.9 (m, 1H, CH thienyl), 7.5 (m, 1H, CH thienyl), 3.1 (s, 3H, SCH_3). MS: *m/z* = 383 (M$^+$, 100 %), 336 (M$^+$-SCH_3, 43 %). Anal. Calcd. For $C_{15}H_8F_3N_3S_3$ (383.44): C, 46.99; H, 2.10; N, 10.96; S, 25.08 %. Found: C, 46.73; H, 2.03; N, 10.74; S, 25.15 %.

4-Ethoxycarbonylmethylthio-7-(2'-thienyl)-9-trifluoromethylpyrido[3',2': 4,5]thieno[3,2-d]pyrimidine (**9b**): Obtained using ethyl chloroacetate in the above general procedure. Yield:1.53 g (84 %); m.p.: 198–199° C. IR: ν = 1730 (C=O) cm^{-1}. ^{1}H NMR ($CDCl_3$) δ: 8.9 (s, 1H, CH pyrimidine), 8.4 (m, 1H 2CH thienyl), 8.2 (s, 1H, CH pyridine), 7.9 (m, 1H, CH thienyl), 7.3 (m, 1H, CH thienyl), 4.3–4.5 (m, 4H, SCH_2 and OCH_2), 1.3–1.5 (t, 3H, CH_3). Anal. Calcd. For $C_{18}H_{12}F_3N_3O_2S_2$ (455.50): C, 47.46; H, 2.66; N, 9.23; S, 21.12 %. Found: C, 47.28; H, 2.45; N, 9.36; S, 21.01 %.

Reaction of compound **7** *with piperidine or morpholine; general procedure:* A suspension compound **7** (1.86 g, 5 mmol) in piperidine or morpholine (4 ml) was gently heated under reflux for 2 h. The reaction mixture was triturated with ethanol (15 ml) and then left to cool The precipitate that formed was collected and recrystallised from ethanol as pale yellow crystals of **10a,b**.

4-Piperidino-7-(2-thienyl)-9-trifluoromethylpyrido[3',2':4,5] thieno[3,2-d] pyrimidine (**10a**): Obtained using piperidine in the above general procedure. Yield: 1.76 g (83 %); m.p.: 210–11°C. IR: ν = 1600 (C=N) cm^{-1}; MS: *m/z* = 420 (M$^+$, 100 %), 84 ($C_4H_3S^+$, 34 %). Anal. Calcd. For $C_{19}H_{15}F_3N_4S_2$ (420.48): C, 54.27; H, 3.59; N,13.32; S,15.25 %. Found: C, 54.16; H, 3.48; N,13.28; S, 15.20 %.

4-Morpholino-7-(2-thienyl)-9-trifluoromethylpyrido[3',2':4,5] thieno[3,2-d]pyrimidine (**10b**): Obtained using morpholine in the above general procedure. Yield: 1.8 g (85 %); m.p.: 296–297° C. IR: ν = 1600 (C=N) cm^{-1}. ^{1}H NMR (TFA): δ = 9.0 (s, 1H, CH pyrimidine), 8.4 (s, 1H, CH pyridine), 8.2 (m, 1H, CH thienyl), 7.9 (m, 1H, CH thienyl), 7.4 (m, 1H, CH thienyl), 4.6 (t, 4H, two OCH_2), 4.3 (t, 4H, two NCH_2) ppm. Anal. Calcd. For $C_{18}H_{13}F_3N_4OS_2$ (422.45): C, 51.18; H, 3.10; N,13.26; S,15.18 %. Found: C, 51.33; H, 3.16; N,13.28; S,15.26 %.

4-Hydrazino-6-(2-thienyl)-9-trifluoromethylpyrido[3',2':4,5] thieno[3,2-d] pyrimidine (**11**): *Method* (A): A mixture of **7** (1.86 g, 5 mmol) and hydrazine hydrate 99% (1.0 ml, 20 mmol) in ethanol (20 ml) was heated under reflux for 2 h. The product that formed while hot was collected and recrystallised from dioxane to give white needles of 11. Yield: 1.63 g (88 %); m.p.: 345–346° C. IR: ν = 3420, 3380, 3200 ($NHNH_2$) cm^{-1}. MS: *m/z* = 367 (M$^+$, 100 %), 351 (M– NH_2, 46 %), 337 (M–NNH_2, 91 %), 69 (CF_3^+, 16 %). Anal. Calcd. For $C_{14}H_8F_3N_5S_2$ (367.38): C, 45.77; H, 2.19; N,19.09; S,17.46 %. Found: C, 45.78; H, 2.11; N,19.18; S,17.61%.

Method (**B**): A mixture of **21** (1.9 g, 5 mmol) and hydrazine hydrate 99% (2.0 ml, 40 mmol) in ethanol (20 ml) was heated under

reflux for 4 h. The product that formed while hot was collected and recrystallised from dioxane to give **11**.

Method **(C):** A mixture of **22** (1.83 g, 5 mmol) and hydrazine hydrate 99% (1.0 ml, 20 mmol) in ethanol (20 ml) was heated under reflux for 3 h. The product that formed while hot was collected and recrystallised from dioxane to give **11**.

4-Benzylidenehydrazino-7-(2-thienyl)-9-trifluoromethylpyrido [3',2':4,5] thieno[3,2-d]pyrimidine **(12)**: A mixture of hydrazino compound **11** (0.73 g, 2 mmol) and benzaldehyde (0.2 ml, 2 mmol) in ethanol (15 ml) was heated under reflux for 3 h. The precipitated solid was collected and recrystallised from dioxane to give pale yellow crystals of **12**. Yield: 0.8 g (88 %); m.p.: >300°C. IR: ν = 3200 (NH) cm^{-1}. MS: *m/z* = 454 (M^+-1, 35 %), 377 (M^+-1-Ph, 17 %), 351 (M- N=CHPh, 100 %), 77 (Ph^+, 5 %), 69 (CF_3^+, 2 %). Anal. Calcd. For $C_{21}H_{12}F_3N_5S_2$ (455.49): C, 55.38; H, 2.66; N,15.38; S,14.08 %. Found: C, 55.22; H, 2.58; N,15.45; S,14.01 %.

4-(3,5-Dimethylpyrazol-1-yl)-7-(2-thienyl)-9-trifluoromethylpyrido [3',2':4,5] thieno [3,2-d]pyrimidine **(13)**: A mixture of **11** (1.47g, 4 mmol) and acetylacetone (10 ml) was gently heated under reflux for 4 h. The reaction mixture was then triturated with ethanol (15 ml) and left to cool. The precipitated product was collected and recrystallised from ethanol to give yellow crystals of **13**. Yield: 1.5g (86 %); m.p.: 259–260 °C. IR: ν = 1600(C=N) cm^{-1}. ^1H NMR ($CDCl_3$): δ = 9.2 (s, 1H, CH pyrimidine), 8.1 (s, 1H, CH pyridine), 7.9 (m, 1H, CH thienyl), 7.6 (m, 1H, CH thienyl), 7.2 (m, 1H, CH thienyl), 6.1 (s, 1H, CH pyrazole), 2.8(s, 3H, CH_3), 2.4 (s, 3H, CH_3) ppm. Anal. Calcd. For $C_{19}H_{12}F_3N_5S_2$ (431.46): C, 52.89; H, 2.80; N, 16.23; S,14.86 %. Found: C, 52.94; H, 2.83; N,16.22; S,14.44 %.

Ethyl 9-(2-thienyl)-7-trifluoromethyl-[1,2,4]triazolo[4",3"-c]pyrido [3',2':4,5] thieno[2,3-e]pyrimidine-3-acetate **(14)**: Hydrazino compound **11** (1.47 g, 4 mmol) was heated under reflux with diethyl malonate (15 ml) for 6 h. The reaction mixture was then cooled and triturated with ethanol (15 ml). The solid that separated was collected and recrystallised from ethanol as yellow crystals of **14**. Yield: 1.35 g (73 %); m.p.: 340–341° C. IR: ν = 1730 (C=O) cm^{-1}. ^1H NMR (TFA): δ = 9.8 (s, 1H, CH pyrimidine), 8.6 (s, 1H, CH pyridine), 8.3 (m, 1H, CH thienyl), 8.0 (d, 1H, CH thienyl), 7.4 (m, 1H, CH thienyl), 4.3–4.7 (m, 4H, OCH_2 and CH_2CO), 1.3–1.6 (t, 3H, CH_3) ppm. MS : *m/z* = 463 (M^+, 4 %), 69 (CF_3^+, 10 %). Anal. Calcd. For $C_{19}H_{12}F_3N_5O_2S_2$ (463.46): C, 49.24; H, 2.61; N,15.11; S,13.84 %. Found: C, 49.18; H, 2.45; N, 15.17; S, 13.83 %.

9-(2-Thienyl)-7-trifluoromethyl-[1,2,4]triazolo[4",3"-c]pyrido [3',2':4,5] thieno[2,3-c]pyrimidine **(15)**: Compound **11** (1.47g, 4 mmol) in triethyl orthoformate (10 ml) was heated under reflux for 4 h. The precipitate that formed while hot was collected and recrystallised from dioxane as white crystals of **15**. Yield: 1.17 g (76 %); m.p.: > 340° C. IR: ν = 1640 (C=N) cm^{-1}. ^1H NMR (TFA) δ: 9.6 (s, 1H, CH pyrimidine), 9.3 (s, 1H, CH triazole), 8.4 (s, 1H, CH pyridine), 8.2 (m, 1H, CH thienyl), 7.9 (m, 1H, CH thienyl), 7.4 (m, 1H, CH thienyl). MS : *m/z* = 377 (M^+, 100 %), 69 (CF_3^+, 38 %). Anal. Calcd. For $C_{15}H_6F_3N_5S_2$ (377.37): C, 47.74; H, 1.60; N,18.56; S,16.99 %. Found: C, 47.83; H, 1.63; N,18.49; S,16.87 %.

3-Methyl-9-(2-thienyl)-7-trifluoromethyl-[1,2,4]triazolo[4",3"-c]pyrido[3', 2':4,5]thieno[2,3-c]pyrimidine **(16)**: Compound **11** (1.47 g, 4 mmol) in acetic anhydride (20 ml) was heated under reflux for 4 h. The precipitate that formed while hot was collected and recrystallised from dioxane as white crystals of **16**. Yield: 1.22 g (78 %); m.p.: > 340°C. IR: ν = 1640 (C=N) cm^{-1}. ^1H NMR (TFA) : δ = 9.6 (s, 1H, CH pyrimidine), 8.4 (s, 1H, CH pyridine), 8.2 (m, 1H, CH thienyl), 7.9 (m, 1H, CH thienyl), 7.4 (m, 1H, CH thienyl), 3.0 (s, 3H, CH_3). MS : *m/z* = 391 (M^+, 100 %), 69 (CF_3^+, 64 %). Anal. Calcd. For $C_{16}H_8F_3N_5S_2$ (391.39): C, 49.09; H, 2.06; N, 17.89; S, 16.38 %. Found: C, 49.01; H, 2.28; N, 17.70; S, 16.42 %.

9-(2-Thienyl)-7-trifluoromethyl-[1,2,4]triazolo[2'',3''-c] pyrido[3',2':4,5] thieno[2,3-e]pyrimidine **(19)**: *Method* **(A)**: Compound **11** (1.47 g, 4 mmol) in formic acid 85 % (20 ml) was refluxed for 6 h. The precipitate that formed while hot was collected and recrystallised from an ethanol–chloroform mixture to give white crystals of **19**. Yield: 1.25 g (83 %); m.p.: 297–298° C.. IR: ν = 1600 (C=N) cm^{-1}. ^1H NMR (TFA): δ = 9.7 (s, 1H, CH pyrimidine), 9.3 (s, 1H, CH triazole), 8.5 (s, 1H, CH pyridine), 8.2 (m, 1H, CH thienyl), 7.9 (d, 1H, CH thienyl), 7.4 (m, 1H, CH thienyl). MS: *m/z* = 379 (M+2, 11%), 378 (M+1, 30%), 377 (M^+, 94 %), 376 (M-1, 100 %) 350 (M-HCN, 25 %), 349 (M-1-HCN, 67 %), 69 (CF_3^+, 13 %). Anal. Calcd. For $C_{15}H_6F_3N_5S_2$ (377.37): C, 47.74; H, 1.60; N, 18.56; S,16.99 %. Found: C, 47.62; H, 1.58; N, 18.51; S, 16.86 %.

Method **(B):** Compound **22** (1.47 g, 4 mmol) in formic acid 85% (25 ml) was heated under reflux for 6 h and then left to cool. The precipitate that formed was collected and recrystallised from an ethanol–chloroform mixture to give white needles of **19**.Yield: 1.3 g (86 %); m.p.: 297–298° C; m. m.p.: 297–298° C.

Method **(C)**: Compound **22** (0.73 g, 2 mmol) in triethyl orthoformate (10 ml) was heated under reflux for 4 h and then left to cool. The precipitate that formed was collected and recrystallised from an ethanol–chloroform mixture to give white needles of **19**.Yield: 0.62 g (82 %) ; m.p.: 297–298° C; m. m.p.: 297–298° C.

3.18.2-Methyl-9-(2-thienyl)-7-trifluoromethyl-[1,2,4]triazolo[2",3"-c] pyrido[3',2': 4,5]thieno[2,3-e]pyrimidine **(20)**: *Method* **(A)**: Compound **11** (1.47 g, 4 mmol) in acetic acid 96% (20 ml) was heated under reflux for 6 h. The precipitate that formed on cooling was collected and crystallised from ethanol as white needles of **20**. Yield: 1.32 g (84 %); m.p.: 287–288° C. IR: ν = 1600 (C=N) cm^{-1}. ^1H NMR (TFA): δ = 9.7 (s, 1H, CH pyrimidine), 8.6 (s, 1H, CH pyridine), 8.3 (m, 1H, CH thienyl), 8.0 (d, 1H, CH thienyl), 7.5 (m, 1H, CH thienyl), 3.0 (s, 3H, CH_3). MS: *m/z* = 391.26 (M^+, 100 %), 69 (CF_3^+, 14 %). Anal. Calcd. For $C_{16}H_8F_3N_5S_2$ (391.39): C, 49.09; H, 2.06; N, 17.89; S, 16.38 %. Found: C, 49.28; H, 2.12; N, 17.73; S, 16.35 %.

Method **(B)**: Compound **22** (0.73 g, 2 mmol) in acetic acid 96% (10 ml) was refluxed for 5 h. The crystalline precipitate that formed on cooling was collected by filtration and recrystallised from ethanol as white crystals of **20**. Yield: 0.60 g (77%); m.p.: 287–288°C; m. m.p.: 287–288° C.

Method **(C)**: Compound **22** (0.73 g, 2 mmol) in acetic anhydride (10 ml) was refluxed for 2 h. The crystalline precipitate that formed on cooling was collected by filtration and recrystallised from ethanol as white crystals of **20**. Yield: 0.65 g (83 %); m.p.: 287–288°C; m. m.p.: 287–288° C.

EthylN-(2-cyano-6-(2-thienyl)-4-trifluoromethylthieno[2,3-b]pyridin-3-yl) methanimidate **(21)**:

A mixture of compound **5** (3.25 g, 10 mmol), triethyl orthoformate (7 ml) and acetic anhydride (20 ml) was refluxed for 5 h. The precipitate that formed after cooling was collected and recrystallised from ethanol as white plates of **21**. Yield: 3.56 g (93 %); m.p.: 158–159° C. IR: ν = 2200 (C≡N), 1620 (C=N) cm^{-1}. ^1H NMR ($CDCl_3$) : δ = 8.0 (s, 2H, 2CH: N=CH and CH pyridine), 7.8 (m, 1H, CH thienyl), 7.6 (d, 1H, CH thienyl), 7.3 (m, 1H, CH thienyl), 4.3–4.6 (q, 2H, OCH_2), 1.2–1.5 (t, 3H, CH_3). Anal. Calcd. For $C_{16}H_{10}F_3N_3OS_2$ (381.39): C, 50.39; H, 2.64; N,11.02; S,16.81 %. Found: C, 50.32; H, 2.70; N,11.11; S,16.93 %.

3-Amino-3,4-dihydro-4-imino-7-(2-thienyl)-9-trifluoromethyl-pyrido[3',2':4,5] thieno[3,2-d]pyrimidine **(22)**: To a suspension of compound **21** (1.52 g, 4 mmol) in dioxane (10 ml), hydrazine hydrate 99% (2 ml) was added. The reaction mixture was stirred at room temperature for 3 h. The solid that formed was collected and recrystallised from ethanol–chloroform mixture to give fine white needles of **22**. Yield: 1.25 g (85 %); m.p.: 290–291° C. IR: ν = 3490, 3300 (NH_2), 3150 (NH), 1650 (C=N) cm^{-1}.^1H NMR (DMSO-d_6)): δ = 9.3 (s, 1H, CH pyrimidine), 8.2 (s, 1H, CH pyridine), 7.9 (m, 1H, CH thienyl), 7.7 (d, 1H, CH thienyl), 7.1 (m, 1H, CH thienyl), 5.8 (s, 2H, NH_2). MS: *m/z* = 367.25 (M^+, 96 %), 352 (M-NH, 32 %), 32 (S^+, 100 %), 18 (N_2^+, 100%). Anal. Calcd. For $C_{14}H_8F_3N_5S_2$ (367.38): C, 45.77; H, 2.19; N,19.06; S,17.46 %. Found: C, 45.78; H, 2.13; N, 19.09; S,17.39 %.

Ethyl 9-(2-thienyl)-7-trifluoromethyl-[1,2,4]triazolo[2",3"-c]pyrido [3',2':4,5]thieno[2,3-e]pyrimidin-2-acetate **(23)**: A suspension of compound **22** (0.73 g, 2 mmol) in diethyl malonate (12 ml) was gently heated under reflux for 4 h. The reaction mixture was triturated with ethanol (15 ml) and then allowed to cool. The formed precipitate was collected and recrystallised from an ethanol–chloroform mixture as pale yellow needles of **23**. Yield: 0.68 g (73 %); m.p.: 296° C. IR: ν = 1730 (C=O), 1600 (C=N) cm^{-1}. ^1H NMR (TFA): δ = 9.8 (s, 1H, CH pyrimidine), 8.6 (s, 1H, CH pyridine), 8.3 (m, 1H, CH thienyl), 8.0 (d, 1H, CH thienyl), 7.4 (m, 1H, CH thienyl), ,4.3–4.5 (m, 4H, OCH_2 and CH_2CO), 1.3–1.6 (t, 3H, CH_3). MS: *m/z* = 463 (M^+, 100 %), 391 (M-$CO_2C_2H_5$, 93 %), 69 (CF_3^+, 22 %). Anal. Calcd. For $C_{19}H_{12}F_3N_5O_2S_2$ (463.46): C, 49.24; H, 2.61; N, 15.11; S,13.84 %. Found: C, 49.11; H, 2.82; N, 15.31; S,14.00 %.

Reaction of compound **22** *with acetylacetone*: Compound **22** (0.73 g, 2 mmol) in acetylacetone (10 ml) was refluxed for 3 h. The reaction mixture was triturated with ethanol (10 ml) and then left to cool. The formed crystalline precipitate was collected by filtration and recrystallised from ethanol as white crystals of **20**. Yield: 0.64 g (82 %); m.p.: 287–288° C; m. m.p.: 287–288° C.

3-Benzylideneamino-3,4-dihydro-4-imino-7-(2-thienyl)-9-trifluoromethyl-pyrido[3',2':4,5]thieno[3,2-d]pyrimidine **(25)**: To a mixture of compound **22** (0.78 g, 2 mmol) and benzaldehyde (0.2 ml, 0.002 mol) in ethanol (15 ml), few drops of acetic acid were added. The reaction mixture was heated under reflux for 4 h. The solid that

formed on cooling was collected and recrystallised from dioxane to give yellow crystals of **22**. Yield: 0.77 g (85 %); m.p.: >300° C. %. IR: ν = 3200 (NH), 1600 (C=N) cm^{-1}. Anal. Calcd. For $C_{21}H_{12}F_3N_5S_2$ (455.49): C, 55.38; H, 2.66; N,15.38; S,14.08 %. Found: C, 55.52; H, 2.43; N,15.11; S,13.82 %.

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