Arabian Journal of Chemistry (2014) 7, 936–946

King Saud University

Arabian Journal of Chemistry

www.ksu.edu.sa
www.sciencedirect.com

ORIGINAL ARTICLE

2nd Heterocyclic Update

Fluorine-containing heterocycles: Part III. Synthesis of some new furo[2,3-b]-, pyrazolo [3,4-b]- and thieno[2,3-b]pyridines with anticipated biological activities

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

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

Received 28 January 2013; accepted 31 May 2014
Available online 18 June 2014

KEYWORDS

Furopyridines;
Pyrazolopyridines;
Thienopyridines;
Pyridothienopyrimidines;
Pyridothienotriazines;
Fluorine-containing compounds

Abstract 3-Cyano-6-(2-thienyl)-4-trifluoromethylpyridine-2(1*H*)-one (**1**) and its thiono analog **2** were prepared by the reaction of (2-thenoyl)-ω,ω,ω-trifluoroacetone with cyanoacetamide or cyanothioacetamide, respectively. Interaction of compound **1** with ethyl chloroacetate or chloroacetamide led to the regioselective formation of *O*-alkylated pyridines **3** and **10**. The latter compounds underwent some successive reactions to furnish the promising furopyridines (**4** and **7–9**) and pyrazolopyridines (**12–15**). The reaction of **2** with chloroacetamides or chloroacetonitrile furnished 2-functionalized 3-amino-6-(2-thienyl)-4-trifluoromethyl-thieno[2,3-*b*]pyridines (**16a**, **b**) which were used as key intermediates in the synthesis of the title thienopyridines. Structures of the newly synthesized compounds were established on the basis of their elemental and spectral (IR, ^{1}H NMR and mass) analyses.

1. Introduction

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 (Hudlicky, 1992). This is due to the unique features of fluorine compounds and foremost their high physiological activity (Filler and Kobayashi, 1981; Welch, 1987). The introduction of fluorine into organic compounds often permits dramatic modification of their chemical and pharmaceutical properties (Nenajdenko et al., 1997). On the other hand, many substituted furopyridines (Clive and Huang, 2002; Hoffman, 1989; Wishka et al., 1998), pyrazolopyridines (Barreiro et al., 2003; De Mello et al., 2004; Menezes et al., 2002) and thienopyridines (Arndts et al., 2000; Bompart et al., 1987; Cho et al., 1998) are reported to possess versatile applications as biologically active compounds. In view of this fact and as a continu-

* Corresponding author. Tel.: +20 1006670292.
Peer review under responsibility of King Saud University.

Production and hosting by Elsevier

1878-5352 © 2014 King Saud University. Production and hosting by Elsevier B.V. All rights reserved.
http://dx.doi.org/10.1016/j.arabjc.2014.05.035

ation of our previous work on fluorine-containing pyridines (Abdel-Monem et al., 2001; Bakhite et al., 2005; Abdel-Rahman et al., 2005), the present project was planned to synthesize other new pyridine derivatives as well as their condensed heterocyclic derivatives and to study their reactions with a variety of reagents hoping to get novel compounds with anticipated biological activities.

2. Experimental

Starting materials were obtained from commercial suppliers and used without further purification. Melting points were determined on a Gallan-Kamp apparatus and are uncorrected. The IR spectra were recorded on a Shimadzu 470 IR-spectrophotometer (KBr; ν_{max} in cm^{-1}). The ^{1}H-NMR spectra were taken on a Varian EM-390, 90 MHz spectrometer or on a Jeol LA 400 MHz FT-NMR spectrometer using TMS as internal standard. Chemical shifts are given in δ ppm and coupling constant (J) is given in Hz. Electron impact (EI) MS spectra were carried out on a JEOL JMS-600 spectrometer. Elemental analyses (C, H, N and S) were performed on an Elemental Analyses system GmbH VARIOEL $V_{2.3}$ 1998 CHNS Mode (Assiut University). The reactions were monitored by TLC.

*2.1. Cyano-6-(2-thienyl)-4-trifluoromethylpyridine-2(1H)-one (**1**)*

To a solution of (2-thenoyl)-ω,ω,ω-trifluoroacetone (4.44 g, 20 mmol) and cyanoacetamide (1.68 g, 20 mmol) in ethanol (50 mL), few drops of piperidine or triethylamine were added. The reaction mixture was refluxed for 4 h and left to cool. The solid which formed was collected and recrystallized from ethanol to give yellow needles of **1**. Yield: 4.0 g (74%); m.p.: 250–251 °C. IR (cm^{-1}): 3100–3000 (NH), 2200 (C≡N), 1650 (C=O). ^{1}H NMR (DMSO-d_6) (400 MHz): δ = 8.17–8.18 (d, J = 4 Hz, 1H, H-5 of thiophene), 7.90–7.91 (d, J = 4 Hz, 1H, H-3 of thiophene), 7.65 (s, 1H, CH pyridine), 7.24–7.25 (t, J = 4 Hz, 1H, H-4 of thiophene). Anal. Calcd. for $C_{11}H_5F_3N_2OS$ (270.23): C, 84.89; H, 1.86; N, 10.37; S, 11.87%. Found: C, 85.92; H, 1.77; N, 10.19; S, 12.06%.

*2.2. 3-Cyano-6-(2-thienyl)-4-trifluoromethylpyridine-2(1H)-thione (**2**)*

It was prepared according to our reported method (Abdel-Monem et al., 2001).

*2.3. Ethyl [3-cyano-6-(2-thienyl)-4-trifluoromethyl-2-pyridyloxy]acetate (**3**)*

Compound **1** (2.7 g, 10 mmol) was dissolved in dry acetone (40 mL). To this solution, ethyl chloroacetate (1.1 mL, 10 mmol), anhyd. potassium carbonate (2.8 g, 20 mmol) and sodium iodide (0.011 g) were added. The reaction mixture was heated at 60 °C for 4 h and then allowed to cool. The precipitate that formed was filtered, washed with water to remove the extra potassium carbonate and recrystallized from ethanol to give compound **3** in the form of white needles. Yield: 3.0 g (84%); m.p.: 126–127 °C. Anal. Calcd. for $C_{15}H_{11}F_3N_2O_3S$ (356.32): C, 50.56; H, 3.11; N, 7.86; S, 8.99%. Found: C, 50.28; H, 3.08; N, 7.91; S, 9.20%. IR (cm^{-1}): 2200 (C≡N), 1740 (C=O). ^{1}H NMR ($CDCl_3$) (90 MHz): δ = 8.1 (d, 1H, H-5 of thiophene), 7.7 (d, 1H, H-3 of thiophene), 7.6 (s, 1H, CH pyridine), 7.2 (t, 1H, H-4 of thiophene), 5.0 (s, 2H, OCH_2CO), 4.1–4.4 (q, 2H, OCH_2), 1.2–1.5 (t, 3H, CH_3).

*2.4. Ethyl 3-amino-6-(2-thienyl)-4-trifluoromethylfuro[2,3-b]pyridine-2-carboxylate (**4**)*

To a solution of compound **3** (3.5 g, 10 mmol) in dry *N,N*-dimethylformamide (40 mL), anhydrous potassium carbonate (1.4 g, 10 mmol) was added. The reaction mixture was heated for 3 h with stirring, maintaining the temperature at 110–120 °C. After cooling, it was poured into crushed ice. The separated solid product was filtered, washed with water, dried in air and crystallized from ethanol to give **4** as yellow crystals; yield: 2.7 g (76%); m.p.: 200–201 °C. Anal. Calcd. for $C_{15}H_{11}F_3N_2O_3S$ (356.32): C, 50.56; H, 3.11; N, 7.86; S, 8.99%. Found: C, 50.34; H, 3.06; N, 8.11; S, 9.32%. IR (cm^{-1}): 3500, 3380 (NH_2), 1660 (C=O). ^{1}H NMR ($CDCl_3$) (90 MHz): δ = 7.9 (m, 2H, H-5 of thiophene and CH pyridine), 7.6 (d, 1H, H-3 of thiophene), 7.2–7.4 (t, 1H, H-4 of thiophene), 5.4 (s, 2H, NH_2), 4.4–4.7 (q, 2H, OCH_2), 1.3–1.6 (t, 3H, CH_3).

*2.5. Effect of sodium ethoxide on the ester (**3**), formation of compound (**5**)*

To a solution of the ester **3** (0.71 g, 2 mmol), in absolute ethanol (5 ml), sodium ethoxide solution (0.1 g sodium in 10 mL abs. ethanol) was added. The reaction mixture was refluxed for 2 h and then left to cool. On dilution with ice-water, the white solid which separated, was collected, dried in air and crystallized from ethanol. It was identified as 3-Cyano-2-ethoxy-6-(2-thienyl)-4-trifluoromethylpyridine (**5**). Yield: 0.4 g (67%); m.p.: 120–122 °C. Anal. Calcd. for $C_{13}H_9F_3N_2OS$ (298.29): C, 52.35; H, 3.04; N, 9.39; S, 10.75%. Found: C, 52.76; H, 3.19; N, 9.27; S, 11.08%. IR (cm^{-1}): 2210 (C≡N). ^{1}H NMR ($CDCl_3$) (90 MHz): δ = 7.9 (s, 1H, H-5 of thiophene), 7.6–7.8 (m, 2H, CH pyridine and H-3 of thiophene), 7.3–7.5 (t, 1H, H-4 of thiophene), 4.6–4.9 (q, 2H, OCH_2), 1.5–1.7 (t, 3H, CH_3).

*2.6. [3-Cyano-6-(2-thienyl)-4-trifluoromethyl-2-pyridyloxy]acethydrazide (**6**)*

A mixture of ester **3** (0.7 g, 2 mmol) and an equimolar quantity of hydrazine hydrate 99% (0.1 mL, 2 mmol) in ethanol (15 mL) was stirred at room temperature for 24 h. The precipitated product was collected and recrystallized from ethanol to give white crystals of **6**. Yield: 0.6 g (87%); m.p.: 180–181 °C. Anal. Calcd. for $C_{13}H_9F_3N_4O_2S$ (342.30): C, 45.62; H, 2.65; N, 16.37; S, 9.37%. Found: C, 45.55; H, 2.48; N, 16.52; S, 9.16%. IR (cm^{-1}): 3400, 3300, 3250 ($NHNH_2$), 2200 (C≡N), 1665(C=O). ^{1}H NMR (DMSO-d_6) (90 MHz): δ = 9.5 (s, 1H, NH), δ 8.1 (d,1H, H-5 of thiophene), 7.9 (d, 1H, H-3 of thiophene), 7.5 (s, 1H, CH pyridine), 7.2 (t, 1H, H-4 of thiophene), 5.0 (s, 2H, OCH_2), 4.5 (s, 2H, NH_2).

*2.7. 3-Amino-6-(2-thienyl)-4-trifluoromethylfuro[2,3-b]pyridine-2-carbohydrazide (**7**)*

A mixture of compound **4** (1.4 g, 4 mmol) and hydrazine hydrate 99% (0.5 mL, 10 mmol) in ethanol was heated under

reflux for 3 h and then left to cool. The precipitated solid was collected and recrystallized from ethanol to give yellow needles of **7**. Yield: 1.0 g (73%); m.p.: 236–237 °C. Anal. Calcd. for $C_{13}H_9F_3N_4O_2S$ (342.30): C, 45.62; H, 2.65; N, 16.37; S, 9.37%. Found: C, 45.32; H, 2.73; N, 16.70; S, 9.58%. IR (cm^{-1}): 3420, 3300, 3150 (NH_2, $NHNH_2$), 1630 (C═O). ^1H NMR (DMSO-d_6) (90 MHz): δ = 9.2 (s, 1H, NH), 8.0 (d, 1H, H-5 of thiophene), 7.6 (m, 2H, H-3 of thiophene and CH pyridine), 7.1 (t, 1H, H-4 of thiophene), 6.0 (s, 2H, NH_2), 4.6 (s, 2H, NH_2).

2.8. N-(4-Methoxybenzylidene)-3-amino-6-(2-thienyl)-4-trifluoromethylfuro[2,3-b] pyridine-2-carbohydrazide (8)

A mixture of compound 7 (1.36 g, 4 mmol) and 4-methoxybenzaldehyde (0.5 mL, 4 mmol) in ethanol (20 mL) was refluxed for 4 h. The product was collected and recrystallized from ethanol to give **8** in the form of yellow needles. Yield: 1.5 g (81%); m.p.: 218–219 °C. Anal. Calcd. for C21H15F3N4O3S (460.43): C, 54.78; H, 3.28; N, 12.17; S, 6.96%. Found: C, 54.90; H, 3.33 N, 11.92; S, 6.70%. IR (cm^{-1}): 3490, 3300, 3150 (NH_2, NH), 1630 (C═O). ^1H NMR (DMSO-d6) (90 MHz): δ = 9.1 (s, 1H, N═CH), 8.9 (s, 1H, CH pyrimidinone), 7.4–8.4 (m, 8H: 4 aromatic protons, 3 CH thiophene and CH pyridine), 5.6 (2H, 2H, NH2), 4.0 (s, 3H, OCH3).

2.9. 3-(4-Methoxybenzylideneamino)-7-(2-thienyl)-9-trifluoromethylpyridio[3′,2′:4,5] furo[3,2-d]pyrimidine-4(3H)-one (9)

A mixture of **8** (0.9 g, 2 mmol) and triethyl orthoformate (1 mL) in redistilled acetic anhydride (15 mL) was heated under reflux for 3 h. The solid that formed on cooling was collected and recrystallized from an ethanol-chloroform mixture to give white crystals of **9**, yield: 0.65 g (69%); m.p.: 293–294 °C. Anal. Calcd. for $C_{22}H_{13}F_3N_4O_3S$ (470.43): C, 56.17; H, 2.97; N, 11.91; S, 6.82%. Found: C, 56.11; H, 2.73; N, 12.03; S, 6.77%. IR (cm^{-1}): 1670 cm^{-1} for (C═O).^1H NMR (TFA) (90 MHz): δ = 9.0 (s, 1H, N═CH), 8.9 (s, 1H, CH pyrimidinone), 7.4–8.4 (m, 8H: 4 aromatic protons, 3 CH thiophene and CH pyridine), 4.0 (s, 3H, OCH_3).

2.10. [3-Cyano-6-(2-thienyl)-4-trifluoromethyl-2-pyridyloxy]acetamide (10)

Compound **1** (2.7 g, 10 mmol) was dissolved in dry acetone (30 mL). To the homogeneous solution, chloroacetamide (0.94 g, 10 mmol), anhydrous potassium carbonate (2.8 g, 20 mmol) and a pinch of sodium iodide (0.011 g) were added. The reaction mixture was refluxed for 6 h at 60 °C and cooled to room temperature. The separated salt was filtered off and washed with acetone (30 mL). The total filtrate was concentrated under vacuum and the residue treated with water. The separated white solid was filtered, dried in air and crystallized from ethanol to give white crystals of **10**. Yield: 2.8 g (85%); m.p.: 264–265 °C. Anal. Calcd. for $C_{13}H_8F_3N_3O_2S$ (327.28): C, 47.71; H, 2.46; N, 12.84; S, 9.80%. Found: C, 47.93; H, 2.75; N, 11.98; S, 9.60%. IR (cm^{-1}): 3400, 3200 (NH_2), 2180 (CN), 1660 (C═O). ^1H NMR (DMSO-d_6) (400 MHz): δ = 8.22–8.23 (d, J = 4 Hz, 1H, H-5 of thiophene), 8.07 (s, 1H, CH pyridine), 7.91–7.92 (d, J = 4 Hz, 1H, H-3 of thiophene), 7.63 (s, 1H, NH of NH_2), 7.31 (s, 1H, NH of NH_2), 7.24–7.26 (t, J = 4 Hz, 1H, H-4 of thiophene), 4.93 (s, 2H, OCH_2).

2.11. 3-Amino-6-(2-thienyl)-4-trifluoromethyl-lH-pyrazolo[3,4-b]pyridine (12)

2.11.1. Method (A)

Compound **10** (1.6 g, 5 mmol) was suspended in excess of hydrazine hydrate (8 mL) and the reaction mixture was refluxed for 6 h. It was then cooled to room temperature, poured onto crushed ice and the separated solid was filtered, washed with water, dried in air and crystallized from ethanol to give **12** in the form of yellow plates. Yield: 1.3 g (91%); m.p: 231–232 °C. Anal. Calcd. for $C_{11}H_7F_3N_4S$ (284.26): C, 46.48; H, 2.48; N, 19.71; S, 11.28%. Found: C, 46.37; H, 2.54; N, 19.89; S, 11.17%. IR (cm^{-1}): 3480, 3320, 3200 (NH_2, NH). ^1H NMR ($CDCl_3$) (90 MHz): δ = 12.4 (s,1H, NH), 7.9 (d, 1H, H-5 of thiophene), 7.7 (m, 2H, H-3 of thiophene and CH pyridine), 7.2–7.4 (t, 1H, H-4 of thiophene), 4.4 (s, 2H, NH_2). MS: 284 (M^+, 4%), 283 $(M-1)^+$, 100%).

2.11.2. Method (B)

Compound **13** (1.5 g, 5 mmol) in excess amount of hydrazine hydrate (2 mL, 40 mmol) was heated under reflux for 4 h. The reaction mixture was triturated with ethanol (10 mL) and left to cool. The precipitated solid was collected and recrystallized from ethanol to give yellow needles of **12**. Yield: 1.35 g (95%). This product was identical in all aspects to that described in method A.

2.12. 3-Cyano-2-methylthio-6-(2-thienyl)-4-trifluoromethyl pyridine (13)

A mixture of **2** (1.43 g, 5 mmol), methyl iodide (5 mmol) and sodium acetate trihydrate (0.75 g, 5 mmol) in ethanol (15 mL) was heated under reflux for 1 h. The precipitate that formed on cooling was collected and recrystallized from ethanol as fine white needles of **13**. Yield: 1.4 g (93%); m.p. 147–148 °C. Anal. Calcd. for $C_{12}H_7F_3N_2S_2$ (300.33): C, 47.99; H, 2.35; N, 9.33; S, 21.35%. Found: C, 47.82; H, 2.53; N, 9.55; S, 21.29%. IR (cm^{-1}): 2200 (C≡N).^1H NMR ($CDCl_3$) (90 MHz): δ = 7.9 (d, 1H, H-5 of thiophene), 7.7 (m, 2H, H-3 of thiophene and CH pyridine), 7.2–7.4 (t, 1H, H-4 of thiophene), 2.7 (s, 3H, SCH_3).

2.13. 2,4-Dimethyl-8-(2-thienyl)-10-trifluoromethylpyridio[2′,3′:3,4]pyrazolo[1,5-a] pyrimidine (14)

A mixture of **12** (0.85 g, 3 mmol) and acetylacetone (0.3 mL, 3 mmol) in glacial acetic acid (10 mL) was refluxed for 4 h and then allowed to cool. The precipitate that formed was collected and recrystallized from ethanol to give **14** in the form of pale yellow crystals. Yield: 0.8 g (76%); m.p.: 205–206 °C. Anal. Calcd. for $C_{16}H_{11}F_3N_4S$ (348.35): C, 55.17; H, 3.18; N, 16.08; S, 9.21%. Found: C, 55.32; H, 3.13; N, 16.19; S, 9.45%. IR (cm^{-1}): 1600 (C═N).^1H NMR ($CDCl_3$) (400 MHz): δ = 7.85–7.86 (d, J = 4 Hz, 1H, H-5 of

thiophene), 7.82 (s, 1H, CH pyridine), 7.52–7.53 (s, J = 4 Hz, 1H, H-3 of thiophene), 7.15–7.17 (t, J = 4 Hz, 1H, H-5 of thiophene), 7.07 (s, 1H, CH pyrimidine), 2.95 (s, 3H, CH_3 at C-2), 2.73 (s, 3H, CH_3 at C-4).

*2.14. 2-Methyl-8-(2-thienyl)-10-trifluoromethylpyridio [2′,3′:3,4]pyrazolo[1,5-a] pyrimidine-4(1H)-one (**15**)*

A mixture of **12** (0.85 g, 3 mmol) and ethyl acetoacetate (0.4 mL, 5 mmol) in glacial acetic acid (10 mL) was refluxed for 5 h. The solid product that formed after cooling was collected and recrystallized from dioxane as orange crystals of **15**. Yield: 0.9 g (85%); m.p.: 213–214 °C. Anal. Calcd. for $C_{15}H_9F_3N_4OS$ (350.32): C, 51.43; H, 2.59; N, 15.99; S, 9.15%. Found: C, 51.38; H, 2.71; N, 16.18; S, 9.21%. IR (cm^{-1}): 3200 (NH), 1700 (C═O).^{1}H NMR ($CDCl_3$) (400 MHz): δ = 7.86–7.87 (d, J = 4 Hz, 1H, H-5 of thiophene), 7.85 (s, 1H, CH pyridine), 7.52–7.54 (d, J = 4 Hz, 1H, H-3 of thiophene), 7.17–7.20 (t, J = 4 Hz, 1H, H-4 of thiophene), 7.10 (s, 1H, CH pyrimidine), 3.2 (s, 3H, CH_3).

*2.15. 2-Methyl-7-(2-thienyl)-9-trifluoromethylpyrido[3′,2′:4,5] thieno[3,2-d]pyrimidine-4-(3H)-one (**17**)*

Compound **16a** (1.71 g, 5 mmol) in acetic anhydride (15 mL) was heated under reflux for 3 h. The product that formed on cooling was collected and recrystallized from ethanol to give **17** in the form of white crystals. Yield: 1.0 g (55%), m.p.: > 360 °C. Anal. Calcd. for $C_{15}H_8F_3N_3OS_2$ (367.37): C, 49.04; H, 2.19; N, 11.44; S, 17.46%. Found: C, 49.28; H, 2.17; N, 11.36; S, 17.82%. IR (cm^{-1}): 3500–3200 (NH), 1660 (C═O).^{1}H NMR (TFA) (90 MHz): δ = 8.5 (s, 1H, CH pyridine), 8.3 (d, 1H, CH thiophene), 8.0 (d, 1H, CH thiophene), 7.5 (t, 1H, CH thiophene), 3.1 (s, 3H, CH_3).

*2.16. 2-Chloromethyl-7-(2-thienyl)-9-trifluoromethylpyrido [3′,2′:4,5]thieno[3,2-d] pyrimidine-4-(3H)-one (**18**)*

Compound **16a** (1.71 g, 5 mmol) in chloroacetyl chloride (10 mL) was heated on a water bath for 3 h. The product that formed on cooling was collected and recrystallized from ethanol to give **18** in the form of white crystals. Yield: 1.8 g (89%), m.p.: > 360 °C. Anal. Calcd. for $C_{15}H_7ClF_3N_3OS_2$ (401.82): C, 44.84; H, 1.76; N, 10.46; S, 15.96%. Found: C, 45.01; H, 1.52; N, 10.26; S, 16.07%. IR (cm^{-1}): 3500–3200 (NH), 1660 (C═O). ^{1}H NMR (TFA) (90 MHz): δ = 8.6 (s, 1H, CH pyridine), 8.4 (d, 1H, CH thiophene), 8.1 (d, 1H, CH thiophene), 7.6 (t, 1H, CH thiophene), 4.5 (s, 2H, CH_2Cl).

*2.17. Reaction of compound **16a** with aromatic aldehydes, formation of tetrahydro-pyridothienopyrimidinones (**19a-d**)*

A mixture of **16a** (0.68 g, 2 mmol) and the respective aldehyde (2 mmol) in ethanol (15 mL) containing few drops of HCl was heated under reflux for 3 h. The product that formed on cooling was collected and recrystallized from acetic acid as yellow needles of **19a–d**.

*2.17.1. 2-(4-Hydroxyphenyl)-4-oxo-7-(2-thienyl)-9-trifluoromethyl-1,2,3,4-tetrahydro-pyrido[3′,2′:4,5]thieno[3,2-d]pyrimidine (**19a**)*

Prepared by using 4-hydroxybenzaldehyde. Yield: 87%; m.p.: 325–326 °C. Anal. Calcd. for $C_{20}H_{12}F_3N_3OS_2$ (431.46): C, 55.68; H, 2.80; N, 9.74; S, 14.86%. Found: C, 55.72; H, 2.91; N, 9.55; S, 14.50%. IR (cm^{-1}): 3400, 3200 (2NH), 1650 (C═O). ^{1}H NMR (TFA) (90 MHz): δ = 8.3–8.5 (m, 2H, CH pyridine and CH thiophene), 8.1 (d, 1H, CH thiophene), 7.3–7.6 (m, 3H: 2H aromatic and CH thiophene), 7.0–7.2 (d, 2H, aromatic), 6.3 (s, 1H, CH of tetrahydropyrimidine).

*2.17.2. 2-(3,4-Dihydroxyphenyl)-4-oxo-7-(2-thienyl)-9-trifluor omethyl-1,2,3,4-tetra-hydropyrido[3′,2′:4,5]thieno[3,2-d] pyrimidine (**19b**)*

Prepared by using 3,4-dihydroxybenzaldehyde. Yield: 80%; m.p.: 319–320 °C. Anal. Calcd. for $C_{20}H_{12}F_3N_3O_3S_2$ (463.46): C, 51.83; H, 2.61; N, 9.07; S, 13.84%. Found: C, 51.68; H, 2.73; N, 8.95; S, 13.63%. IR (cm^{-1}): 3400, 3200 (2NH), 1650 (C═O). ^{1}H NMR (TFA) (90 MHz): δ = 8.4–8.6 (m, 2H, CH pyridine and CH thiophene), 8.3 (d, 1H, CH thiophene), 7.5 (t, 1H, CH thiophene), 7.4 (s, 1H, aromatic proton), 7.1–7.2 (d, 2H, aromatic protons), 6.3 (s, 1H, CH of tetrahydropyrimidine).

*2.17.3. 2-(3-Hydroxy-4-methoxyphenyl)-4-oxo-7-(2-thienyl) -9-trifluoromethyl-1,2,3,4-tetrahydropyrido[3′,2′:4,5]thieno [3,2-d]pyrimidine (**19c**)*

Prepared by using 3-hydroxy-4-methoxybenzaldehyde. Yield: 78%; m.p.: 307–308 °C. Anal. Calcd. for $C_{21}H_{14}F_3N_3O_3S_2$ (477.48): C, 52.82; H, 2.96; N, 8.80; S, 13.43%. Found: C, 52.90; H, 2.78; N, 8.95; S, 13.25%. IR (cm^{-1}): 3400, 3200 (2NH), 1650 (C═O). ^{1}H NMR (TFA) (90 MHz): δ 8.5–8.6 (m, 2H, CH pyridine and CH thiophene), 8.3 (d, 1H, CH thiophene), δ 7.6 (t, 1H, CH thiophene), δ 7.4 (s, 1H, aromatic), 7.2–7.3 (d, 2H, aromatic), 6.4 (s, 1H, CH of tetrahydropyrimidine), 4.0 (s, 3H, OCH_3).

*2.17.4. 2-(3,4-Methylenedioxyphenyl)-4-oxo-7-(2-thienyl)-9-trifluoromethyl-1,2,3,4-tetrahydropyrido[3′,2′:4,5]thieno[3,2-d]pyrimidine (**19d**)*

Prepared by using piperonal. Yield 83%; m.p.: 316–317 °C. Anal. Calcd. for $C_{21}H_{12}F_3N_3O_3S_2$ (475.47): C, 53.05; H, 2.54; N, 8.84; S, 13.49%. Found: C, 53.15; H, 2.42; N, 8.64; S, 13.40%. IR (cm^{-1}): 3400, 3200 (2NH), 1650 (C═O). ^{1}H NMR (TFA) (90 MHz): δ 8.2–8.4 (m, 2H, CH pyridine and CH thiophene), 8.1 (d, 1H, CH thiophene), 7.4 (t, 1H, CH thiophene), 6.8–7.2 (m, 3H, aromatic), 6.2 (s, 1H, CH of tetrahydropyrimidine), 5.9 (s, 2H, OCH_2O).

*2.18. 4-Amino-7-(2-thienyl)-9-trifluoromethylpyrido[3′,2′:4,5] thieno[3,2-d]pyrimidine (**20**)*

Compound **16b** (0.65 g, 2 mmol) in formamide (10 mL) was heated under reflux for 4 h. The solid that formed while hot was collected and recrystallized from an ethanol-chloroform mixture to give white crystals of **20**.Yield: 0.58 g (83%); m.p.: 309–310 °C. Anal. Calcd. for $C_{14}H_7F_3N_4S_2$ (352.36): C, 47.72; H, 2.00; N, 15.90; S, 18.20%. Found: C, 47.63; H, 2.13; N, 15.84; S, 18.43%. IR (cm^{-1}): 3190, 3100 (NH_2),

1640 (C═N). ^{1}H NMR (DMSO-d_6) (90 MHz): δ = 8.8 (s, 1H, CH pyrimidine), 8.0 (s, 1H, CH pyridine), 7.8 (m, 1H, CH thiophene), 7.5 (m, 3H: NH_2 and CH thiophene), 7.2 (m, 1H, CH thiophene), MS: 352.4 (M^+, 100%).

*2.19. 4-Imino-3-phenyl-1,2,3,4-tetrahydro-7-(2-thienyl)-2-thio xo-9-trifluoromethyl-pyrido[3′,2′:4,5]thieno [3,2-d]pyrimidine (**21**)*

A mixture of compound **16b** (0.65 g, 2 mmol) and phenyl *iso*-thiocyanate (0.25 ml, 2 mmol) in pyridine (10 mL) was gently heated under reflux for 6 h. The solid that formed on cooling was collected and recrystallized from acetic acid to give orange crystals of **21**. Yield: 0.83 g (90%); m.p.: > 360 °C. Anal. Calcd. for $C_{20}H_{11}F_3N_4S_3$ (460.52): C, 52.16; H, 2.41; N, 12.17; S, 20.89%. Found: C, 51.85; H, 2.35; N, 12.28; S, 20.71%. IR (cm^{-1}): 3380, 3200 (2NH), 1600 (C═N). ^{1}HNMR (DMSO-d_6) (90 MHz): δ = 10.0 (s, 1H, NH), 8.3 (s, 1H, CH pyridine), 8.0 (d, 1H, CH thiophene), 7.7 (d, 1H, CH thiophene), 7.2–7.5 (m, 6H, aromatic protons and CH thiophene).

*2.20. 3-Amino-2-(Δ^1-imidazolin-2-yl)-6-(2-thienyl)-4-trifluoro methylthieno[2,3-b]pyridine (**22**)*

To a suspension of **16b** (1.62 g, 5 mmol) in ethylene diamine (5 mL), carbon disulfide (0.2 mL) was added drop wise. The reaction mixture was heated on a water bath for 2 h and then triturated with ethanol (10 mL). The solid that formed was collected and recrystallized from an ethanol-chloroform mixture to give yellow crystals of **22**. Yield: 1.6 g (87%); m.p.: 200–201 °C. Anal. Calcd. for $C_{15}H_{11}F_3N_4S_2$ (368.40): C, 48.90; H, 3.01; N, 15.21; S, 17.41%. Found: C, 48.76; H, 3.11; N, 15.32; S, 17.30%. IR (cm^{-1}): 3500–3250 (NH and NH_2), 1600 (C═N). ^{1}H NMR ($CDCl_3$) (90 MHz): δ = 8.0 (s, 1H, CH pyridine), 7.8 (d, 1H, CH thiophene), 7.5 (d, 1H, CH thiophene), 7.2 (t, 1H, CH thiophene), 6.7 (s, 2H, NH_2), 3.7 (s, 4H, $(CH_2)_2$). MS: 368.0 (M^+, 100%).

*2.21. 3-Amino-2-(3,4,5,6-tetrahydropyrimidin-2-yl)-6-(2-thien yl)-4-trifluoromethyl-thieno[2,3-b]pyridine (**23**)*

It was prepared from **16b** and propylenediamine in analogy to the above procedure. It was recrystallized from chloroform to give yellow needles of **23**. Yield: 1.5 g (78%); m.p.: 190–191 °C. Anal. Calcd. for $C_{16}H_{13}F_3N_4S_2$ (382.43): C, 50.25; H, 3.43; N, 14.65; S, 16.77%. Found: C, 50.45; H, 3.29; N, 14.56; S, 16.90%. IR (cm^{-1}): 3500, 3400 (NH_2), 3100 (NH), 1600 (C═N). ^{1}H NMR ($CDCl_3$) (90 MHz): δ = 7.9 (s, 1H, CH pyridine), 7.8 (m, 1H, CH thiophene), 7.6 (m, 1H, CH thiophene), 7.2 (t, 1H, CH thiophene), 6.7 (s, 2H, NH_2), 3.4–3.7 (t, 4H, $2NCH_2$), 1.8 (m, 2H, CH_2). MS: 382.25 (M^+, 100%).

*2.22. 3-Amino-2-(1H-tetrazol-5-yl)-6-(2-thienyl)-4-trifluorome thylthieno[2,3-b] pyridine (**24**)*

A solution of compound **16b** (1.62 g, 5 mmol), sodium azide (0.4 g, 6 mmol) and ammonium chloride (0.32 g, 6 mmol) in DMF (15 mL) was heated on a water bath for 5 h. The reaction mixture was cooled, diluted with water and acidified with dilute acetic acid. The solid that formed was collected and crystallized from ethanol to give yellow crystals of **24**. Yield: 1.55 g (84%); m.p.: 255–256 °C. Anal. Calcd. for $C_{13}H_7F_3N_6S_2$ (368.36): C, 42.39; H, 1.92; N, 22.81; S, 17.41%. Found: C, 42.70; H, 2.25; N, 22.99; S, 17.57%. IR (cm^{-1}): 3500–3300 (NH, NH_2), 1620 (C═N). ^{1}H NMR (DMSO-*d6*) (90 MHz): δ = 8.9 (s, 1H, NH), δ 7.4–8.4 (m, 8H: 4 aromatic protons, 3CH thiophene and CH pyridine), 6.1 (s, 1H, CH), 5.1 (s, 2H, CH_2), 4.5 (s, 2H, CH_2). MS: 368.0 (M^+, 100%).

*2.23. 2,3-Dihydro-9-(2-thienyl)-7-trifluoromethyl-imidazo [1″,2″-c]pyrido[3′,2′:4,5] thieno[2,3-e]pyrimidine (**25**)*

Compound **22** (0.73 g, 2 mmol) in triethyl orthoformate (10 ml) was heated under reflux for 3 h. The precipitate that formed while hot was collected and recrystallized from acetic acid to give white needles of **25**. Yield: 0.7 g (92%); m.p.: 307–308 °C. Anal. Calcd. for $C_{16}H_9F_3N_4S_2$ (378.40): C, 50.79; H, 2.40; N, 14.81; S, 16.95%. Found: C, 50.58; H, 2.22; N, 14.75; S, 17.08%. IR (cm^{-1}): 1630 (C═N). ^{1}H NMR (TFA) (90 MHz): δ = 8.8 (s, 1H, CH pyrimidine), 8.0 (s, 1H, CH pyridine), 7.8 (m, 1H, CH thiophene), 7.5 (m, 1H, CH thiophene), 7.2 (m, 1H, CH thiophene), 5.1 (s, 2H, CH_2), 4.5 (s, 2H, CH_2). MS: 378.1 (M^+, 28%).

*2.24. 5-(4-Chlorophenyl)-2,3,5,6-tetrahydro-9-(2-thienyl)-7-tri fluoromethylimidazo [1″,2″-c]pyrido[3′,2′:4,5]thieno[2,3-e] pyrimidine (**26**)*

To a mixture of compound **22** (0.73 g, 2 mmol) and 4-chlorobenzaldehyde (0.28 g, 2 mmol) in ethanol (15 mL), few drops of piperidine were added. The reaction mixture was heated under reflux for 4 h. The solid that formed while hot was collected and recrystallized from dioxane to give yellow crystals of **26**. Yield: 0.9 g (92%); m.p.: 224–225 °C. Anal. Calcd. for $C_{22}H_{14}ClF_3N_4S_2$ (490.95): C, 53.82; H, 2.87; N, 11.41; S, 13.06%. Found: C, 53.98; H, 2.75; N, 11.52; S, 12.97%. IR (cm^{-1}): 3330 (NH). ^{1}H NMR (DMSO-*d6*) (90 MHz): δ = 8.8 (s, 1H, NH), 7.3–8.4 (m, 8H: 4 aromatic protons, 3CH thiophene and CH pyridine), 6.1 (s, 1H, CH), 4.2 (s, 2H, CH_2), 3.7 (s, 2H, CH_2). MS: 490 (M^+, 4%).

*2.25. 2,3,5,6-Tetrahydro-9-(2-thienyl)-5-thioxo-7-trifluoro methyl-pyrimido[1″,2″-c] pyrido[3′,2′:4,5]thieno[2,3-e] pyrimidine (**27**)*

A mixture of compound **22** (0.73 g, 2 mmol) and carbon disulfide (1 mL) in pyridine (10 mL) was heated under reflux on a water bath for 8 h. The solid that formed while hot was collected and recrystallized from DMF to give orange crystals of **27**. Yield: 0.62 g (76%); m.p.: > 360 °C. Anal. Calcd. for $C_{16}H_9F_3N_4S_3$ (410.46): C, 46.82; H, 2.21; N, 13.65; S, 23.44%. Found: C, 46.58; H, 2.52; N, 13.74; S, 23.21%. IR (cm^{-1}): 3250 (NH), 1610 (C═N). ^{1}H NMR (TFA) (90 MHz): δ = 8.0 (s, 1H, CH pyridine), 7.8 (m, 1H, CH thiophene), 7.5 (m, 1H, CH thiophene), 7.2 (m, 1H, CH thiophene), 5.1 (s, 2H, CH_2), 4.5 (s, 2H, CH_2). MS: 410 (M^+, 100%).

*2.26. 2,3-Dihydro-9-(2-thienyl)-7-trifluoromethyl-imidazo [1″,2″-c]pyrido[3′,2′:4,5] thieno[2,3-e][1,2,3]triazine (**28**)*

Sodium nitrite solution 10% (5 mL) was added to a solution of **22** (0.73 g, 2 mmol) in conc. H_2SO_4 (5 mL) and acetic acid (5 mL) at 0 °C during 5 min with stirring. The reaction mixture was allowed to stand at room temperature for 30 min. The solid that precipitated on dilution with water was collected and crystallized from ethanol to give white needles of **28**. Yield: 0.65 g (85%); m.p.: 279–280 °C. Anal. Calcd. for $C_{15}H_8F_3N_5S2$ (379.39): C, 47.49; H, 2.13; N, 18.46; S, 16.90%. Found:
C, 47.36; H, 2.02; N, 18.37; S, 17.08%. IR(cm^{-1}): 1640 cm^{-1} for (C═N). ^{1}H NMR (TFA) (90 MHz): δ = 8.8 (s, 1H, CH pyrimidine), 8.0 (s, 1H, CH pyridine), 7.8 (m, 1H, CH thiophene), 7.5 (m, 1H, CH thiophene), 7.2 (m, 1H, CH thiophene), 5.1 (s, 2H, CH_2), 4.5 (s, 2H, CH_2). MS: 380.21 (M^+, 10%).

*2.27. 3,4-Dihydro-10-(2-thienyl)-8-trifluoromethyl-2H-pyri mido[1″,2″-c]pyrido[3′,2′: 4,5]thieno[2,3-e]pyrimidine (**29**)*

Compound **23** (0.76 g, 2 mmol) in triethyl orthoformate (10 ml) was heated under reflux for 3 h. The precipitate that formed while hot was collected and recrystallized from acetic acid to give white needles of **29**. Yield: 0.74 g (94%); m.p.: 309–310 °C. Anal. Calcd. for $C_{17}H_{11}F_3N_4S_2$ (392.42): C, 52.03; H, 2.83; N, 14.28; S, 16.34%. Found: C, 52.25; H, 2.56; N, 14.20; S, 16.31%. IR (cm^{-1}): 1630 (C═N).^{1}H NMR (TFA) (90 MHz): δ = 8.8 (s, 1H, CH pyrimidine), δ 7.9 (s, 1H, CH pyridine), 7.8 (m, 1H, CH thiophene), 7.6 (m, 1H, CH thiophene), 7.2 (t, 1H, CH thiophene), 3.4–3.7 (t, 4H, $2NCH_2$), 1.8 (m, 2H, CH_2). MS: 391.81 (M^+, 100%).

*2.28. 6-(4-Chlorophenyl)-3,4,6,7-tetrahydro-10-(2-thienyl)-8-tr ifluoromethyl-2H-pyrimido[1″,2″-c]pyrido[3′,2′:4,5]thieno [2,3-e]pyrimidine (**30**)*

To a mixture of compound **23** (0.76 g, 2 mmol) and 4-chlorobenzaldehyde (0.28 g, 2 mmol) in ethanol (15 mL), few drops of piperidine were added. The reaction mixture was heated under reflux for 4 h. The solid that formed while hot was collected and recrystallized from dioxane to give yellow crystals of **30**. Yield: 0.8 g (79%); m.p.: 249–250 °C. Anal. Calcd. for $C_{23}H_{16}ClF_3N_4S_2$ (504.98): C, 54.70; H, 3.19; N, 11.09; S, 12.70%. Found: C, 54.53; H, 3.12; N, 11.27; S, 12.86%. IR (cm^{-1}): 3330(NH).^{1}H NMR (TFA) (90 MHz): δ = 8.8 (m, 1H, CH thiophene), 8.2–8.4 (m, 7H: 4 aromatic protons, 2CH thiophene and CH pyridine), 6.1 (s, 1H, CH), 3.5–3.8 (t, 4H, $2NCH_2$), 1.9 (m, 2H, CH_2).

*2.29. 3,4,6,7-Tetrahydro-10-(2-thienyl)-6-thioxo-8-trifluoro methyl-2H-pyrimido[1″,2″-c]pyrido[3′,2′:4,5] thieno[2,3-e] pyrimidine (**31**)*

A mixture of compound **23** (0.76 g, 2 mmol) and carbon disulfide (1 mL) in pyridine (10 mL) was heated under reflux on a water bath for 8 h. The solid that formed while hot was collected and recrystallized from DMF to give orange crystals of **31**. Yield: 0.68 g (80%); m.p.: > 360 °C. Anal. Calcd. for $C_{17}H_{11}F_3N_4S_3$ (424.49): C, 48.10; H, 2.61; N, 13.20; S, 22.66%. Found: C, 48.32; H, 2.75; N, 13.38; S, 22.56%. IR (cm^{-1}): 3300 (NH), 1610 (C═N). ^{1}H NMR (TFA) (90 MHz): δ = 7.9 (s, 1H, CH pyridine), 7.8 (m, 1H, CH thiophene), 7.6 (m, 1H, CH thiophene), 7.2 (t, 1H, CH thiophene), 3.4–3.7 (t, 4H, $2NCH_2$), 1.8 (m, 2H, CH_2). MS: 424.04 (M^+, 100%).

*2.30. 3,4-Dihydro-10-(2-thienyl)-8-trifluoromethyl-2H-pyrim ido[1″,2″-c]pyrido[3′,2′: 4,5]thieno[2,3-e][1,2,3] triazine (**32**)*

Sodium nitrite solution 10% (5 mL) was added to a solution of **23** (2 mmol) in conc. H_2SO_4 (5 mL) and acetic acid (5 mL) at 0 °C during 5 min with stirring. The reaction mixture was allowed to stand at room temperature for 30 min. The solid that precipitated on dilution with water was collected and crystallized from ethanol to give white needles of **32**. Yield: 0.65 g (83%); m.p.: 252–253 °C. Anal. Calcd. for $C_{16}H_{10}F_3N_5S_2$ (393.41): C, 48.85; H, 2.56; N, 17.80; S, 16.30%. Found: C, 48.72; H, 2.81; N, 17.63; S, 16.18% IR (cm^{-1}): 1640 (C═N). ^{1}H NMR ($CDCl_3$) (90 MHz): δ = 7.9 (s, 1H, CH pyridine), 7.8 (m, 1H, CH thiophene), 7.6 (m, 1H, CH thiophene), 7.2 (t, 1H, CH thiophene), 3.4–3.7 (t, 4H, $2NCH_2$), δ 2.0 (m, 2H, CH_2). MS: 393.86 (M^+, 86%).

*2.31. Reaction of 3-amino-2-(1H-tetrazol-5-yl)-6-(2-thienyl) -4-trifluoromethylthieno [2,3-b]pyridine (**24**) with triethyl orthoformate*

Compound **24** (0.74 g, 2 mmol) in triethyl orthoformate (10 mL) was heated under reflux for 2 h. The precipitate that formed while hot was collected and recrystallized from ethanol to give white needles. This product was assigned as *4-azido-7-(2-thienyl)-9-trifluoromethylpyrido[3′,2′:4,5]thieno[3,2-d] pyrimidine* (**34**). Yield: 0.65 g (86%); m.p.: 229–230 °C (dec.) Anal. Calcd. for $C_{14}H_5F_3N_6S_2$ (378.36): C, 44.44; H, 1.33; N, 22.21; S, 16.95%. Found: C, 44.35; H, 1.48; N, 21.91; S, 17.12%. IR (cm^{-1}): 2150 (N_3). ^{1}H NMR (TFA) (90 MHz): δ = 8.8 (s, 1H, CH pyrimidine), δ 8.0 (s, 1H, CH pyridine), 7.8 (d, 1H, CH thiophene), 7.5 (d, 1H, CH thiophene), 7.2 (t, 1H, CH thiophene). MS: 378 (M^+, 54%).

*2.32. 5-(4-Chlorophenyl)-5,6-dihydro-9-(2-thienyl)-7-triflu oromethyltetrazolo[1″,5″-c] pyrido[3′,2′:4,5]thieno[2,3-e] pyrimidine (**35**)*

To a mixture of compound **24** (0.74 g, 2 mmol) and 4-chlorobenzaldehyde (0.28 g, 2 mmol) in ethanol (15 mL), few drops of piperidine were added. The reaction mixture was heated under reflux for 2 h. The solid that formed on cooling was collected and recrystallized from ethanol to give pale yellow crystals of **35**.Yield: 0.8 g (81%); m.p.: 241–242 °C. Anal. Calcd. for $C_{20}H_{10}ClF_3N_6S_2$ (490.91): C, 48.93; H, 2.05; N, 17.12; S, 13.06%. Found: C, 48.89; H, 2.26; N, 17.34; S, 12.96%. IR (cm^{-1}): 3400 (NH). ^{1}H NMR (DMSO-*d6*) (90 MHz): δ = 8.8 (s, 1H, NH), δ 7.3–8.4 (m, 8H: 4 aromatic protons, 3CH thiophene and CH pyridine), 6.1 (s, 1H, CH). MS: 490 (M^+-1, 69%).

*2.33. 9-(2-Thienyl)-7-trifluoromethyltetrazolo[1″,5″-c] pyrido[3′,2′:4,5]thieno[2,3-e] [1,2,3]triazine (**36**)*

Sodium nitrite solution 10% (5 mL) was added to a solution of **24** (0.74 g, 2 mmol) in conc. H_2SO_4 (5 mL) and acetic acid (5 mL) at 0 °C during 5 min with stirring. The reaction mixture was allowed to stand at room temperature for 30 min. The solid that precipitated on dilution with water was collected and crystallized from ethanol to give white needles of **36**.Yield: 0.6 g (79%); m.p.: 179–180 °C (dec.). Anal. Calcd. for $C_{13}H_4F_3N_7S_2$ (379.35): C, 41.16; H, 1.06; N, 25.85; S, 16.91%. Found: C, 41.25; H, 1.29; N, 25.61; S, 16.78%. IR(cm^{-1}): 1600 (C═N).^{1}H NMR (TFA) (90 MHz): δ = 8.0 (s, 1H, CH pyridine), 7.8 (m, 1H, CH thiophene), 7.5 (t, 1H, CH thiophene), 7.2 (m, 1H, CH thiophene). MS: 378 ($M^+ - 1$, 0.5%).

3. Results and discussion

The wide synthetic utility of several 3-cyanopyridine-2(1*H*)-one (Kaigorodova et al., 2004; Litvinov et al., 1992; Wagner and Prantz, 1993) and 3-cyanopyridine-2(1*H*)-thione derivatives (Bakhite, 2003) promoted us to use 3-cyano-6-(2-thienyl)-4-trifluoromethylpyridine-2(1*H*)-one (**1**) and its thiono analog (**2**) as starting compounds in this investigation.

Thus, on treatment of (2-thenoyl)-ω,ω,ω-trifluoroacetone with cyanoacetamide in the presence of triethylamine or piperidine as a basic catalyst, a regioselective cyclo-condensation reaction occurred and 3-cyano-6-(2-thienyl-4-trifluoromethyl-pyridine-2(1H)-one (1) was obtained as a sole product. Under the same conditions, the reaction of (2-thenoyl)-ω,ω,ω-trifluoroacetone with cyanothioacetamide produced 3-cyano-6-(2-thienyl)-4-trifluoromethylpyridine-2(1*H*)-thione (**2**) (Abdel-Monem et al., 2001) (Scheme 1).

When compound **1** was allowed to react with ethyl chloroacetate, in dry acetone containing slightly excess amount of anhyd. potassium carbonate and catalytic amount of sodium iodide for 4 h, ethyl (3-cyano-6-(2-thienyl)-4-trifluoromethyl-2-pyridyloxy)acetate (**3**) was obtained exclusively. This is in agreement with the earlier reports (Narsaiah et al., 1994; Von Gewald and Jgnsch, 1976) which state that when an *o*-substituent offers steric hindrance, only *O*-alkylation takes place and not *N*-alkylation. On heating of the open ester **3** in DMF containing anhyd. potassium carbonate at 110–120 °C, it underwent intramolecular *Thorpe-Ziegler* cyclization to give ethyl 3-amino-6-(2-thienyl)-4-trifluoromethylfuro[2,3-*b*]pyridine-2-carboxylate (**4**) (Scheme 2).

An attempt to cyclize the open ester **3** to furopyridine **4**, using sodium ethoxide as a basic catalyst in boiling ethanol, failed and instead, 3-cyano-2-ethoxy-6-(2-thienyl)-4-trifluoromethylpyridine (**5**) was obtained as a sole product. This may be due to the relatively high electrophilicity of the carbon atom number **2** of pyridine derivative **3** (Scheme 2). Treatment of ester **3** with hydrazine hydrate in ethanol at room temperature produced (3-cyano-6-(2-thienyl)-4-trifluoromethyl-2-pyridyloxy) acethydrazide (**6**) whereas the cyclized hydrazide, 3-amino-6-(2-thienyl)-4-trifluoromethylfuro[2,3-*b*]pyridine-2-carbohydrazide (**7**) was obtained *via* hydrazinolysis of the corresponding ester **4** using hydrazine hydrate in boiling ethanol. The direct condensation of **7** with an equimolar amount of 4-methoxy-benzaldehyde in boiling ethanol led to the formation of compound **8**. Treatment of **8** with triethyl orthoformate in the presence of acetic anhydride furnished pyridofuropyrimidine derivative **9** (Scheme 2).

In the same manner, reaction of 3-cyanopyridine-2(1*H*)-one (**1**) with chloroacetamide, in dry acetone containing slightly excess amount of anhyd. potassium carbonate and catalytic amount of sodium iodide, resulted in the selective formation of (3-cyano-6-(2-thienyl)-4-trifluoromethyl-2-pyridyloxy)acetamide (**10**) (Scheme 3).

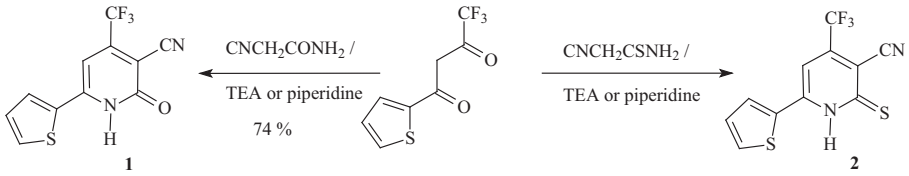
An attempt to cyclize compound **10** into the corresponding furopyridine **11**, by refluxing with hydrazine hydrate under neat conditions failed and instead, pyrazolo[3,4-b]pyridine **12** was obtained (Chandra Sheker Reddy et al., 1997). The structure of **12** was confirmed by an independent route *via* methylation of pyridinethione **2** followed by hydrazinolysis of the resulting 2-methylthiopyridine **13**. Treatment of **12** with acetylacetone or ethyl acetoacetate in the presence of acetic acid led to the formation of pyridofuropyrimidine derivatives **14** and **15** respectively (Scheme 3).

On the other hand, 2-functionalized 3-amino-6-(2-thienyl)-4-trifluoromethylthieno[2,3-*b*]pyridines **16a,b** were obtained, by reacting 3-cyano-pyridine-2(1*H*)-thione **2** with chloroacetamide or chloroacetonitrile according to our reported procedures (Bakhite et al., 2005) (Scheme 4).

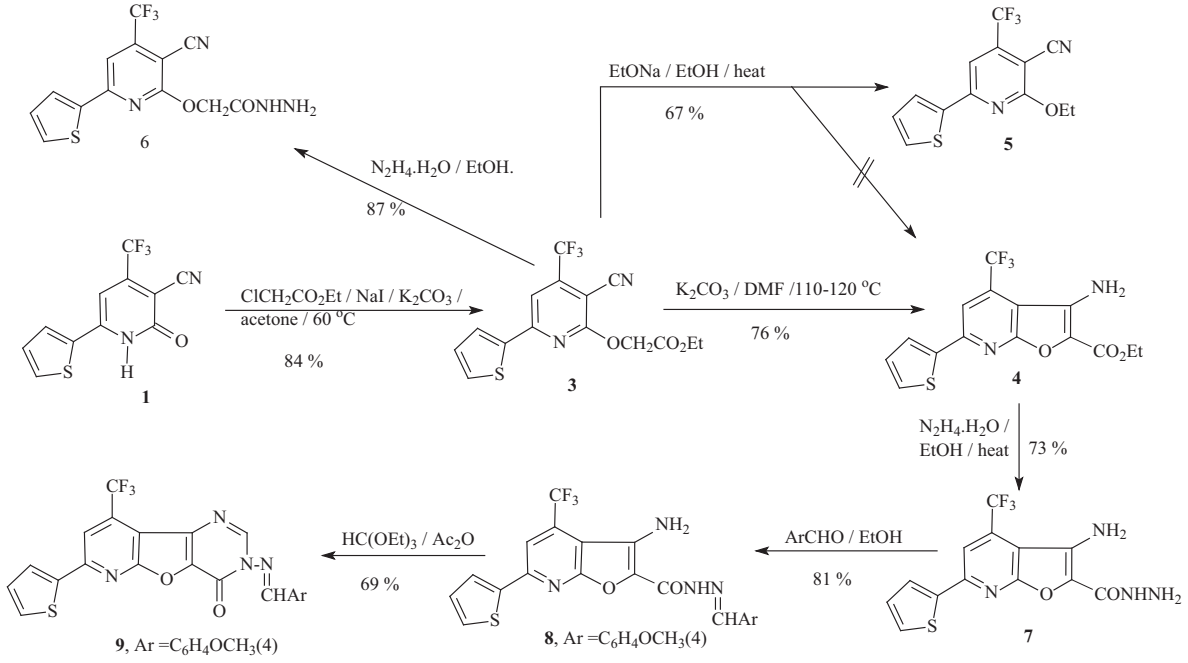
Compounds **16a,b** were used as precursors for new pyridothienopyrimidines as well as pyridothienotriazines *via* some successive reactions.

Heating β-aminoamide **16a** with acetic anhydride at reflux temperature led to the formation of pyridothienopyrimidine-4(3*H*)-one **17**. In the same manner, the reaction of **16a** with chloroacetyl chloride at 100 °C produced 2-chloromethyl derivative **18** in good yield. When compound **16a** was allowed to react with some aromatic aldehydes of biological significance namely; 4-hydroxybenzaldehyde, 3,4-dihydroxybenzaldehyde, vanillin or piperonal in ethanol containing few drops of conc. HCl, a cyclocondensation reaction occurred and the products which were obtained identified as 2-aryl-4-oxo-1,2,3,4-tetrahydro-7-(2-thienyl)-9-trifluoromethylpyrido[3′,2′:4,5]thieno[3,2-*d*]pyrimidines (**19a–d**) (Scheme 5).

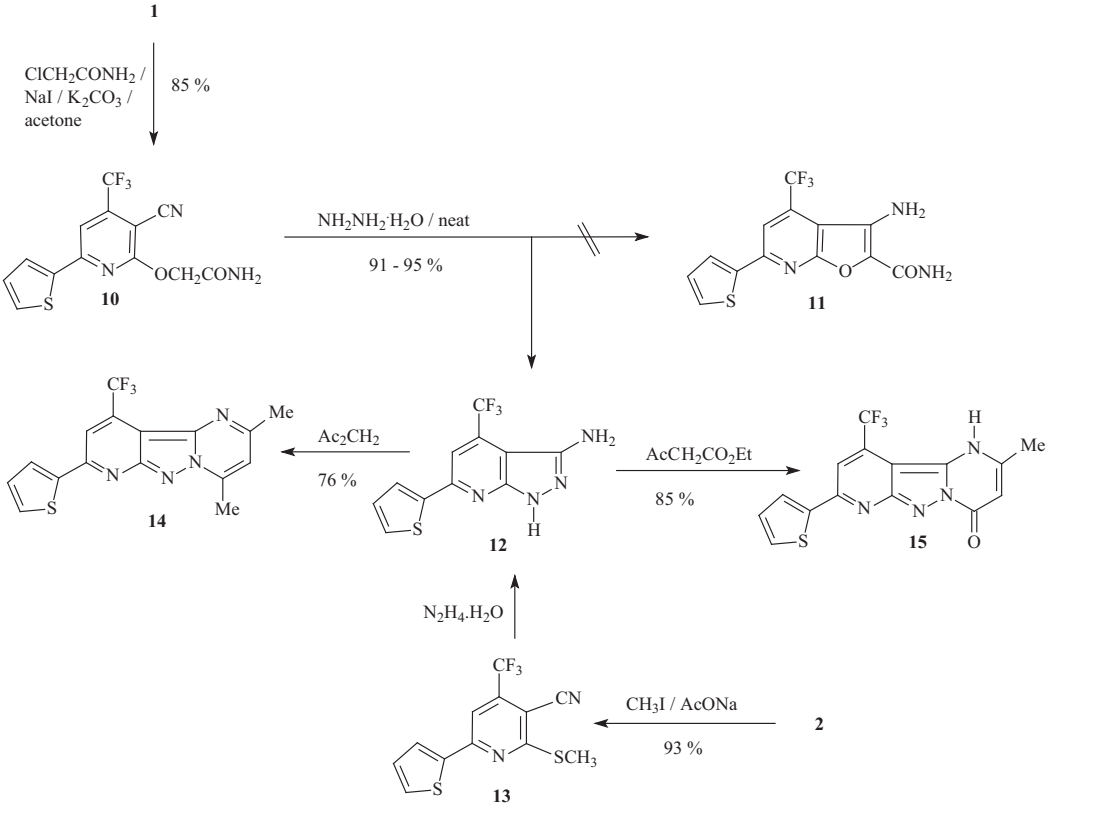
Refluxing of compound **16b** in formamide yielded 4-aminopyrimidine derivative **20**. The reaction of **16b** with phenyl isothiocyanate in the presence of pyridine yielded tetrahydropyridothienopyrimidine **21** (Scheme 6).



Scheme 1 Synthesis of compounds **1** and **2**.



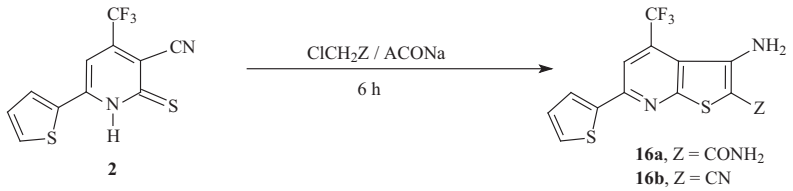
Scheme 2 Synthesis of compounds **3–9**.



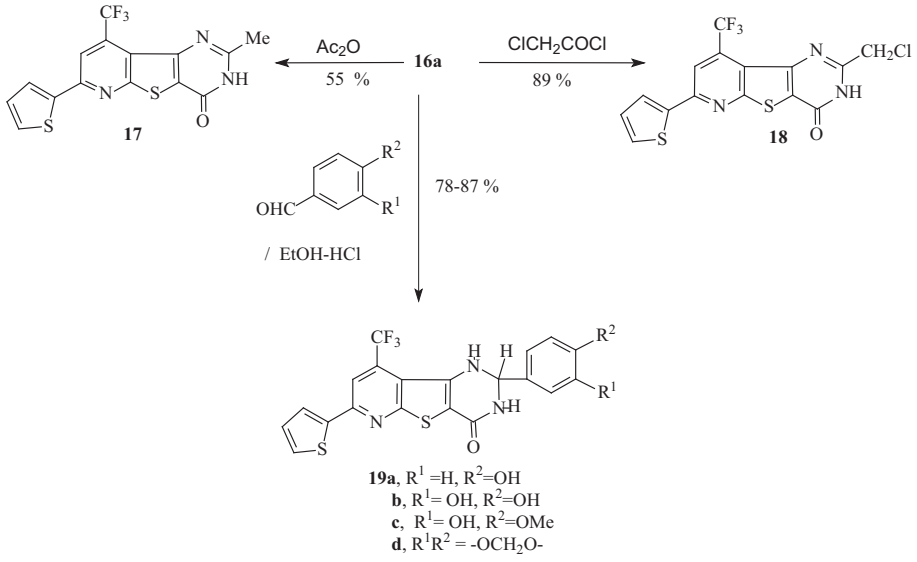
Scheme 3 Synthesis of compounds **10–15**.

Incorporating imidazolinyl, tetrahydropyrimidinyl or tetrazolyl moiety into thienopyridine structure was successfully attempted by converting the nitrile group of **16b** into imidazolinyl, tetrahydropyrimidinyl or tetrazolyl residue followed by some successive reactions.

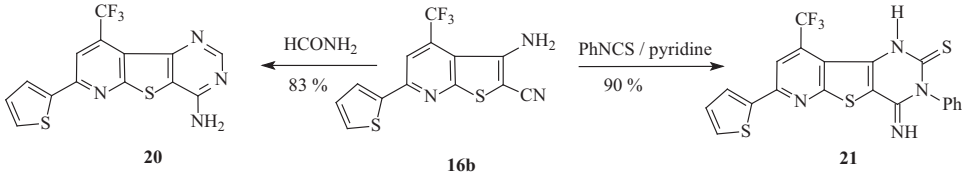
Thus, the reaction of **16b** with ethylenediamine in the presence of carbon disulfide gave 3-amino-2-(Δ^1-imidazolin-2-yl)-6-(2-thienyl)-4-trifluoromethylthieno[2,3-*b*] pyridine (**22**) in a good yield. Similarly, the reaction of **16b** with propylenediamine under the same (above) condition afforded 3-amino-2-



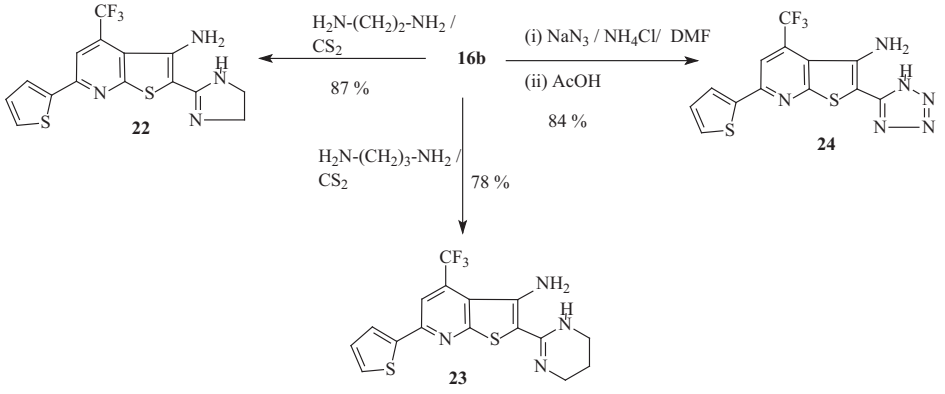
Scheme 4 Synthesis of compounds **16a,b**.



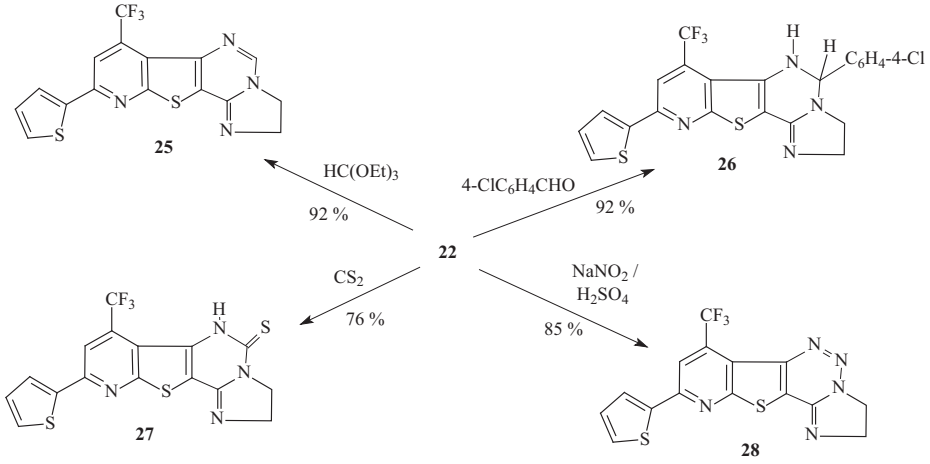
Scheme 5 Synthesis of compounds **17–19**.



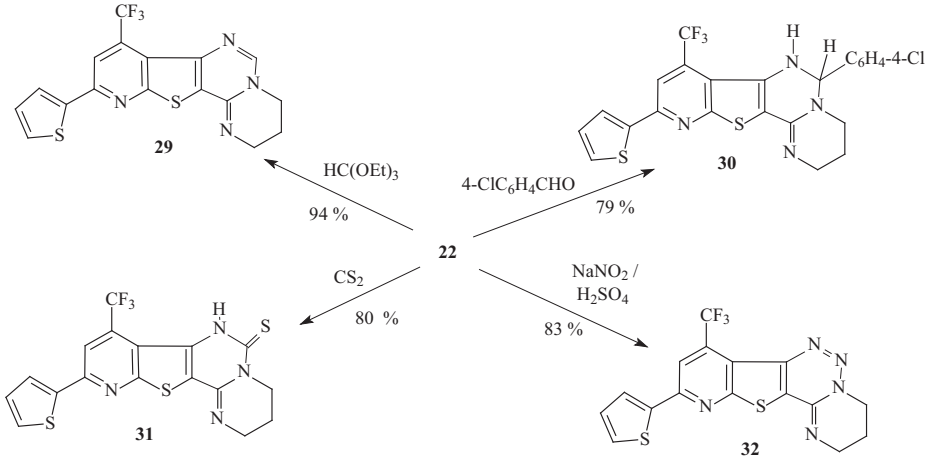
Scheme 6 Synthesis of compounds **20** and **21**.



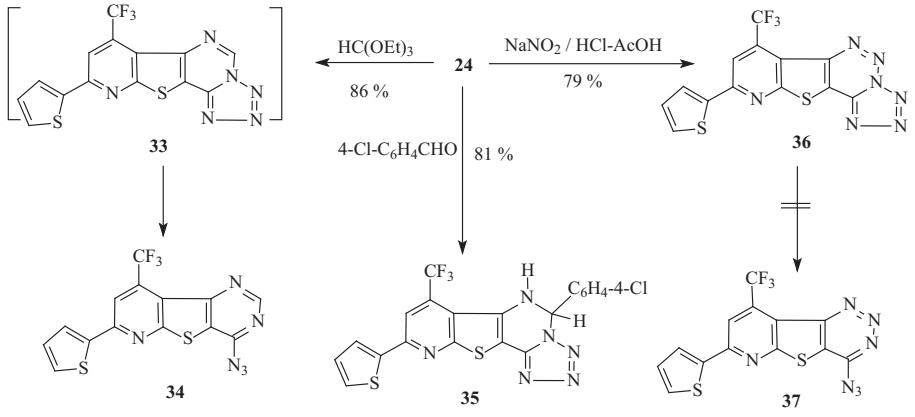
Scheme 7 Synthesis of compounds **22–24**.



Scheme 8 Synthesis of compounds **25–28**.



Scheme 9 Synthesis of compounds **29–32**.



Scheme 10 Synthesis of compounds **33–37**.

(3,4,5,6-tetrahydropyrimidin-2-yl)-6-(2-thienyl)-4-trifluoromethylthieno[2,3-*b*]pyridine (**23**). On treatment of **16b** with sodium azide and ammonium chloride in hot DMF followed by acidification of the reaction mixture resulted in the formation of the tetrazolyl compound **24** (Scheme 7).

The reaction of **22** with triethyl orthoformate, 4-chlorobenzaldehyde, and/ or carbon disulfide gave imidazo[1″,2″-*c*]pyrido[3′,2′:4,5]thieno[2,3-*e*]pyrimidine derivatives **25**, **26** and **27** respectively. On treatment of **22** with nitrous acid, it underwent diazotization followed by self coupling to furnish

heterocyclopyrido [3′,2′:4,5]thieno[2,3-*e*][1,2,3]triazine derivatives **28** in excellent yield (Scheme 8).

By the same procedure, pyrimido[1″,2″-*c*]pyrido[3′,2′:4,5] thieno[2,3-*e*]pyrimidine derivatives **30**, **31** and **32** were prepared starting from compound **23**. On treatment of **23** with nitrous acid, it underwent diazotization followed by self coupling to give heterocyclopyrido[3′,2′:4,5]thieno[2,3-*e*][1,2,3]triazine derivatives **32** (Scheme 9).

In contrast, the reaction of tetrazolyl derivative **24** with triethyl orthoformate produced the azidopyrimidine **34** rather than the expected tetrazolopyrimidine **33** (Scheme 10). When compound **24** was allowed to react with 4-chlorobenzaldehyde, the tetrazolo-pyridothienopyrimidine derivative **35** was obtained in high yield. The reaction of tetrazolyl derivative **24** with nitrous acid gave tetrazolotriazine **36**. The latter compound does not isomerize to azidotriazine **37**. (Scheme 10).

The structure of all newly synthesized compounds was confirmed on the basis of their elemental analyses (experimental part) and spectral data.

4. Conclusion

In the present work, 3-cyano-6-(2-thienyl)-4-trifluoromethylpyridine-2(1*H*)-one (1) was prepared and used as a precursor for synthesizing the target fluorine-containing pyridines, furopyridines and pyrazolopyridines. Also, 2-functionalized 3-amino-6-(2-thienyl)-4-trifluoromethylthieno[2,3-*b*]pyridines (**16a,b**) underwent several successive reactions to afford the desired thienopyridines and pyridothienopyrimidines bearing trifluoromethyl residue.

References

Abdel-Monem, M.I., Mohamed, O.S., Bakhite, E.A., 2001. Pharmazie 56 (1), 41.

Abdel-Rahman, A.E., Bakhite, E.A., Al-Taifi, E.A., 2005. J. Chem. Res., 461.

Arndts, D., Loesel, W., Palluk, R., 2000. PCT Int. Appl. WO, 00, 44, 725, Chem. Abstr. 133, 135237.

Bakhite, E.A.-G., 2003. Phosphorus, Sulfur and Silicon 178, 929.

Bakhite, E.A., Abdel-Rahman, A.E., Al-Taifi, E.A., 2005. J. Chem. Res., 147.

Barreiro, E.J., Camara, C.A., Verli, H., Brazil-Más, L., Castro, N.G., Cintra, W.M., Aracava, Y., Rodrigues, C.R., Fraga, C.A.M., 2003. J. Med. Chem. 46, 1144.

Bompart, J., Giral, L., Malicorne, G., Puygrenier, M., 1987. Eur. J. Med. Chem. 22, 139.

Chandra Sheker Reddy, A., Narsaiah, B., Venkataratnam, R.V., 1997. J. Fluorine Chem. 86, 127.

Cho, N., Harada, M., Imaeda, T., Imada, T., Matsumoto, H., Hayase, Y., Sasaki, S., Furuya, S., Suzuki, N., Okubo, S., Ogi, K., Endo, S., Onda, H., Fujino, M., 1998. J. Med. Chem. 41, 4190.

Clive, D.L.J., Huang, X., 2002. Tetrahedron 58, 10243.

De Mello, H., Echevarria, A., Bernardino, A.M., Canto-Cavalheiro, M., Leon, L.L., 2004. J. Med. Chem. 47, 5427.

Filler, A., Kobayashi, Y., 1981. Biomedical Aspects of Fluorine Chemistry. Kodansha Ltd., Tokyo.

Hoffman Jr., J.M., 1989. U.S. Patent 4,808,595. Chem. Abstr. 111, 115159.

Hudlicky, M., 1992. Chemistry of Organic Fluorine Compounds. Ellis Horwood Ltd., Chichester.

Kaigorodova, E.A., Vasilin, V.K., Sidorova, E.A., Zavodnik, V.E., Krapivin, G.D., 2004. Chem. Heterocycl. Compd. 40 (11), 1442.

Litvinov, V.P., Rodinovskaya, L.A., Sharanin, Yu.A., Shestopalov, A.M., Senning, A., 1992. Sulfur Rep. 13, 1.

Menezes, C.M.S., Sant' Anna, C.M.R., Rodrigues, C.R., Barreiro, E.J., 2002. J. Mol. Struct. 579, 31.

Narsaiah, B., Sivaprasad, A., Venkataratnam, R.V., 1994. J. Fluorine Chem. 67, 87.

Nenajdenko, V.G., Sanin, A.V., Balenkova, E.S., 1997. Molecules 2, 186.

Von Gewald, K., Jgnsch, H.J., 1976. J. Prakt. Chem. 318, 313.

Wagner, G., Prantz, J., 1993. Pharmazie 48 (4), 250.

Welch, J.T., 1987. Tetrahedron 43, 3123.

Wishka, D.G., Graber, D.R., Seest, E.P., Dolak, L.A., Han, F., Watt, W., Morris, J., 1998. J. Org. Chem. 63, 7851.