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Synthetic utility of enaminoester moiety in heterocyclic synthesis

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ABSTRACT

Thieno[2,3-*b*]pyridine-2-carboxylate was utilized to construct a variety of new heterocyclic systems such as thienopyrimidinone, thienopyridine and pyridothienoxazinone derivatives. Treatment of pyridothienoxazinone derivative with some other nitrogen nucleophiles afforded 3-substituted-pyridothienopyramidinone derivatives. Secondary amines such as morpholine, piperidine and *N*-methylaniline reacted smoothly with the oxazinone derivative. When the oxazinone derivative was allowed to react with ethanol containing few drops of pyridine or formamide as a basic catalyst and heated to reflux, afforded thienopyridine ester. All the compounds were fully characterized by means of IR, MS, ^{1}H NMR spectra and elemental analyses.

1. Introduction

Since enaminoester moieties were utilized in synthesis of different heterocyclic systems [1-5] with pronounced biological and pharmaceutical activities such as thienopyrimidine derivatives [6-8]. Therefore, we focused on those derivatives as they were proved to be potential medical agents [9-10] in the plant protection area [11], cancer, and in viral studies [12-15]. Along with some other pyrimidine systems containing an annulated five-membered heteroaromatic ring, thieno pyrimidines are structural analogs of biogenic purines and can be considered as potential nucleic acid antimetabolites. Earlier, various aspects of the chemistry and biology of isomeric thienopyrimidines have been reviewed [16-20]. Various thieno[2,3-*d*]pyrimidine and thieno[3,2-*d*]pyrimidine derivatives show pronounced antitumor [21-23] and radioprotective [24] activities. On the basis of thieno[2,3-*d*]pyrimidine derivatives, immunomodulators [25] and compounds used for prophylaxis and therapy of cerebral ischemia [26], malaria [27-30], tuberculosis [31], Alzheimer's disease [32], Parkinson's disease [33], and other diseases were designed [34,35]. The present work aimed to synthesize some new derivatives of this class of compounds utilizing ethyl-3-amino-5-bromo-4,6-dimethylthieno[2,3-*b*]pyridine-2-carboxy late [1].

2. Experimental

2.1. Instrumentation

All melting points were measured on a Gallenkamp melting point apparatus and are uncorrected. The infrared spectra were recorded using potassium bromide disks on a Pye Unicam SP-3-300 infrared spectrophotometer. ^{1}H NMR experiments were run at 300 MHz on a Varian Mercury VX-300 NMR spectrometer using TMS as internal standard in deuterated chloroform or deuterated dimethylsulphoxide. Chemical shifts are quoted as δ. The mass spectra were recorded on Shimadzu GCMS-QP-1000EX mass spectrometers at 70 eV. All the spectral measurements as well as the elemental analyses were carried out at the Micro analytical Center of Cairo University.

2.2. General procedures

2.2.1. Ethyl 5-bromo-3-(diacetylamino)-4,6-dimethylthieno [2,3-b]pyridine-2-carboxylate (2)

A mixture of enaminoester **1** (1.59 mmol, 0.5 g) and freshly distilled acetic anhydride (20 mL) was heated at reflux for 3 h (Scheme 1). The solid that precipitated upon cooling was recrystallised from light petroleum ether (B.p.: 80-100 °C) to afford diacetylamino derivative **2** as pale yellow crystals. Yield: 56.9 %. M.p.: 158-160 °C. FT-IR (KBr, cm^{-1}): 1745 ν(C=O) (ester), 1715 ν(C=O) (acetyl). ^{1}H NMR (300 MHz, $CDCl_3$): 4.31 (q, *J*=6.9 Hz, 2H, -COOC*H*$_2$-CH$_3$), 2.83 (s, 3H, C*H*$_3$) and 2.60 (s, 3H, C*H*$_3$), 2.33 (s, 6H, -N(COC*H*$_3$)$_2$) and 1.39 (t, *J*=7.2 Hz, 3H, -COOCH$_2$-C*H*$_3$). MS (EI, m/z): 412 (M^+). Anal. Calcd. for $C_{16}H_{17}BrN_2O_4S$: C, 46.50; H, 4.15; N, 6.78. Found: C, 46.34; H, 3.97; N, 6.64.

2.2.2. 8-Bromo-2,7,9-trimethylpyrido[3',2':4,5] thieno[3,2-d] pyrimidin-4 (3H)one (3)

Method A: A suspension of diacetylamino derivative **2** (2.5 mmol, 1 g) in 25% ammonium hydroxide solution (20 mL) was stirred for 5 h at 20 °C. The solid that precipitated was filtered and recrystallised from light petroleum ether (B.p.: 80-100 °C) to afford thienopyrimidinone **3** as white crystals (Scheme 1). Yield: 60.5 %. M.p.: over 360 °C.

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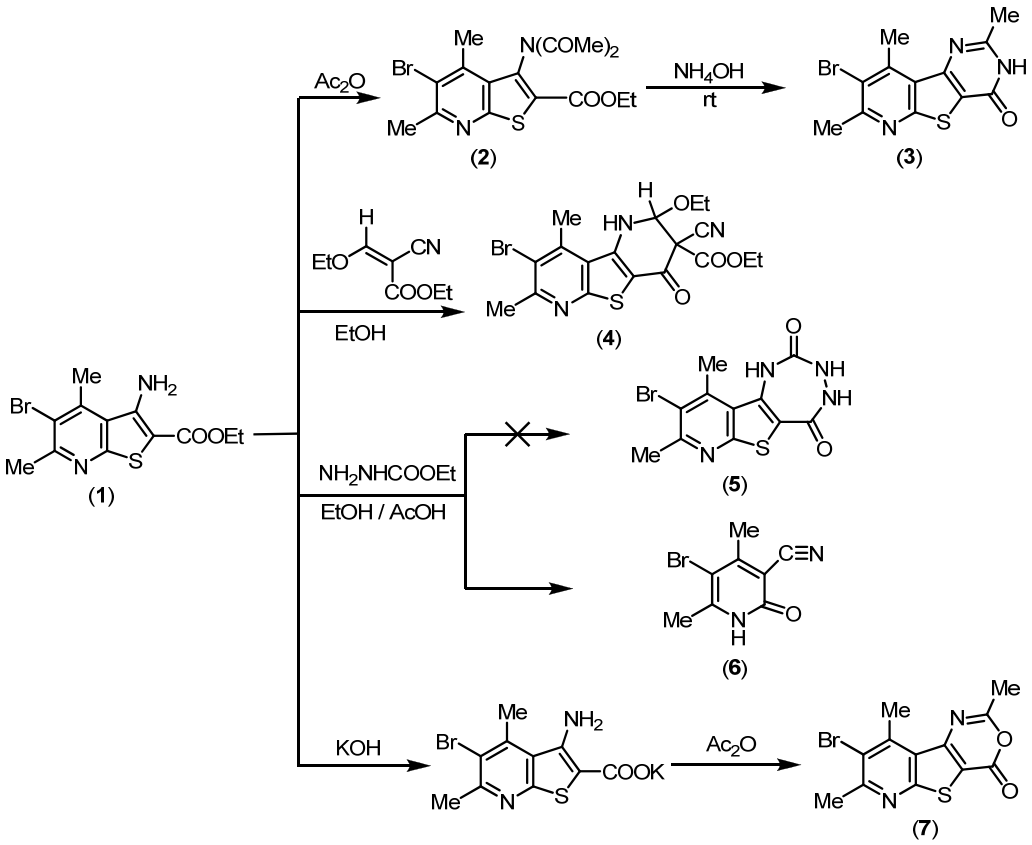


Scheme 1

Method B: A mixture of oxazinone **7** (1.59 mmol, 0.5 g) and ammonium acetate in acetic acid was heated to reflux for 2 h. The solid that precipitated upon cooling was collected by light petroleum ether (B.p.: 80-100 °C) to afford thienopyrimidinone **3** as white crystals (Scheme 2). Yield: 54.8 %. FT-IR (KBr, cm^{-1}): 3350 ν(NH), 1671 ν(C=O). ^{1}H NMR (300 MHz, DMSO-d_6): 7.13 (br s, 1H, exchangeable, N*H*), 6.84 (br s, 1H, exchangeable, O*H*), 2.90 (s, 3H, C*H*$_3$ of pyrimidine ring), 2.77 and 2.50 (two s, 6H, 2C*H*$_3$ of pyridine ring). MS (EI, m/z): 323 (M^+). Anal. Calcd. for $C_{12}H_{10}BrN_3OS$: C, 44.46; H, 3.11; N, 12.96. Found: C, 44.32; H, 2.98; N, 12.85.

2.2.3. Ethyl-8-bromo-3-cyano-2-ethoxy-7,9-dimethyl-4-oxo-1,2,3,4-tetrahydropyrido[2',3':4,5]thieno[2,3-b]pyridine-3-carboxylate (4)

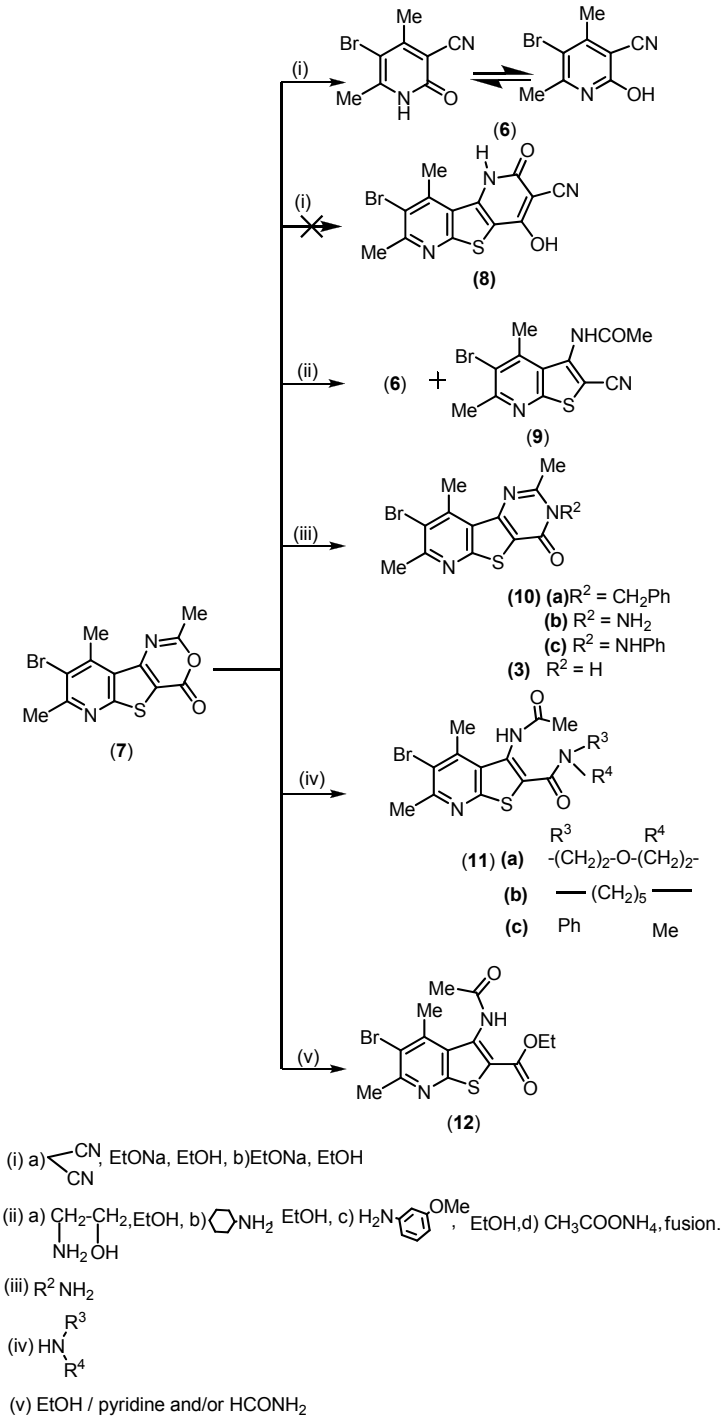
To a solution of enaminoester **1** (3 mmol, 0.98 g) in ethanol (20 mL), 2-ethoxymethylene-cyanoacetate (3 mmol, 0.5 g) was added and the reaction mixture was heated to reflux for 6 h then left to cool. The solid crude product that separated out was collected by suction, dried and then recrystallised from ethanol to afford compound **4** as yellow crystals (Scheme 1), Yield: 63.4 %. M.p.: over 300 °C. FT-IR (KBr, cm^{-1}): 3340 ν(NH), 2223 ν(C≡N), 1653 broad band of ν(C=O) (ester, the lowering in value is due to hydrogen bonding) and 1620 ν(C=O) (pyridone). ^{1}H NMR (300 MHz, $CDCl_3$): 6.20 (br s, 1H, exchangeable, N*H*), 4.35 (q, *J*=7.2 Hz ,4H, 2-(-OC*H*$_2$-CH$_3$)), 2.91 & 2.78 (two s, 6H, 2C*H*$_3$ of pyridine ring), 2.61 (d, *J*=3.9 Hz, 1H, -NH-C*H*-) and 1.39 (t, *J*=7.2 Hz, 6H, 2-(-OCH$_2$-C*H*$_3$)). MS (EI, m/z): 451 (M^+). Anal. Calcd. for $C_{18}H_{18}BrN_3O_4S$: C, 47.80; H, 4.01; N, 9.29. Found: C, 47.73; H, 4.21; N, 9.07.

2.2.4. 5-Bromo-4,6-dimethyl-2-oxo-1,2-dihydro pyridine-3-carbonitrile (6)

A mixture of thienopyridine **1** (2.3 mmol, 0.75 g) and ethyl carbazate (2.3 mmol, 0.24 g) in ethanol (15 mL) containing (0.1 mL) glacial acetic acid was heated to reflux for 10 h. The solid that precipitated upon cooling was filtered off, dried and then recrystallised from ethanol to afford cyanopyridone **6** as yellow crystals (Scheme 1). M.p.: 264 °C [Lit.: 260 °C].

2.2.5. 8-Bromo-2,7,9-trimethyl-4H-pyrido[3',2': 4,5]thieno [3,2-d][1,3] oxazin-4-one (7)

A suspension of enaminoester **1** (1.5 mmol, 0.5 g) in 10% aqueous alcoholic potassium hydroxide (10 mL) was stirred at 40 °C for 5 h. The solid crude product that separated out was collected by suction, dried and washed with ethanol to afford a potassium salt of the enaminoester **1.** A mixture of the latter compound (3 mmol, 1 g) and freshly distilled acetic anhydride (20 mL) was heated to reflux for 3 h. The solid that precipitated upon cooling was recrystallised from light petroleum ether (B.p.: 80-100 °C) to afford oxazinone **7** as white crystals (Scheme 1). Yield: 58.7 %. M.p.: 250-252 °C. FT-IR (KBr, cm^{-1}): 1756 ν(C=O) (lactone). ^{1}H NMR (300 MHz, $CDCl_3$): 3.09 (s, 3H, C*H*$_3$, oxazinone ring), 2.86 and 2.59 (two s, 6H, 2C*H*$_3$ of pyridine ring). MS (EI, m/z): 324 (M^+). Anal. Calcd. for $C_{12}H_9BrN_2O_2S$: C, 44.32; H, 2.79; N, 8.61. Found: C, 44.05; H, 2.65; N, 8.49.



Scheme 2

2.2.6. N-(5-Bromo-2-cyano-4,6-dimethylthieno [2,3-b] pyridin-3-yl) acetamide (9)

Method A: To a hot solution of oxazinone **7** (2 mmol, 0.65 g) in ethanol (20 mL), some nitrogen nucleophiles namely, ethanolamine, cyclohexylamine and/or *m*-anisidine (4 mmol) was added. The reaction mixture was heated to reflux for 3 h, allowed to cool. The solid product that formed was collected and dried. TLC experiment showed that there were two spots indicating the presence of two products which were separated by fractional crystallization from light petroleum ether (B.p.: 80-100 °C) to afford 3-acetylamino-thienopyridine **9** as white crystals (Scheme 2). Yield: 48.7 %. M.p.: 238-240 °C, and cyanopyridone **6** from ethanol as yellow crystals. M.p.: 270-272 °C. Compound **9**: FT-IR (KBr, cm^{-1}): 3300 ν(OH), 3142 ν(NH), 2226 ν(C≡N), 1669 ν(C=O) (amide) and 1643 ν(C=O) (pyridone). MS (EI, m/z): 323 (M^+). Anal. Calcd. for $C_{12}H_{10}BrN_3OS$: C, 44.46; H, 3.11; N, 12.96. Found: C, 44.15; H, 2.95; N, 12.69.

Method B: A mixture of oxazinone **7** (2 mmol, 0.65 g) and ammonium acetate (4 mmol, 0.31 g) was fused for 1.5 h, left to cool and washed with water. The solid that precipitated was collected then dried. TLC experiment showed that there were two spots indicating the presence of two products which were separated by fractional crystallization from light petroleum ether (B.p.: 80-100 °C) to afford 3-acetylamino-thienopyridine **9** as

white crystals. M.p.: 238-240 °C and cyanopyridone **6** from ethanol as yellow crystals (Scheme 2). M.p.: 264 °C [Lit.: 260 °C].

2.2.7. 3-Benzyl-8-bromo-2,7,9-trimethylpyrido [3',2':4,5] thieno[3,2-d] pyrimidin-4(3H)-one (10a).

To a hot solution of oxazinone **7** (2 mmol, 0.65 g) in ethanol (20 mL), benzylamine (4 mmol, 0.43 g) was added. The reaction mixture was heated to reflux for 3 h, allowed to cool. The solid product that formed was collected, dried and recrystallised from light petroleum ether (B.p.: 80-100 °C) to afford 3-benzylpyrimidinone derivative **10a** as yellow crystals (Scheme 2). Yield: 57.6 %. M.p.: 220-222 °C, FT-IR (KBr, cm^{-1}): 1666 ν(C=O) (cyclic amide). ^{1}H NMR (300 MHz, $CDCl_3$): 7.38-7.24 (m, 5H, Ar-*H*), 5.48 (s, 2H, -N-C*H*$_2$-Ph), 3.12 (s, 3H, C*H*$_3$), 2.85 and 2.64 (two s, 6H, 2 C*H*$_3$). MS (EI, m/z): 413 (M^+). Anal. Calc. for $C_{19}H_{16}BrN_3OS$: C, 55.08; H, 3.89; N, 10.14. Found: C, 54.97; H, 3.73; N, 9.96.

2.2.8. 3-Amino-8-bromo-2,7,9-trimethylpyrido [3',2':4,5] thieno[3,2-d] pyrimidin-4(3H)-one (10b) or 3-anilino-8-bromo-2,7,9-trimethyl pyrido[3',2':4,5]thieno[3,2-d]pyrimidin-4(3H)-one (10c)

To a solution of oxazinone **7** (2 mmol, 0.65 g) in ethanol (20 mL), the appropriate nitrogen nucleophiles namely hydrazine hydrate and/or phenyl hydrazine (4 mmol) was added. The reaction mixture was stirred at room temperature for 2 h. The solid product that formed was collected, dried and recrystallised from dioxane to afford 3-aminopyrimidinone **10b** as grey crystals (Scheme 2). Yield: 65.3 %. M.p.: 260-263 °C, FT-IR (KBr, cm^{-1}): 3310, 3243 ν(NH_2) and 1671 ν(C=O). ^{1}H NMR (300 MHz, DMSO-d_6): 6.02 (s, 2H, exchangeable, N*H*$_2$), 2.75 (s, 3H, C*H*$_3$), 2.68 and 2.5 (two s, 6H, 2C*H*$_3$). MS (EI, m/z): 338 (M^+). Anal. Calcd. for $C_{12}H_{11}BrN_4OS$: C, 42.49; H, 3.27; N, 16.52. Found: C, 42.36; H, 3.02; N, 16.34.

Compound **10c** recrystallised from ethanol to give 3-anilinopyrimidinone as pale yellow crystals (Scheme 2). Yield: 45.3 %. M.p.: 240-242 °C. FT-IR (KBr, cm^{-1}): 3278 ν(NH) and 1665 ν(C=O). ^{1}H NMR (300 MHz, $CDCl_3$): 7.59 (s, 1H, exchangeable, N*H*), 7.30-7.04 (m, *J*=7.5 Hz, 5H, Ar-*H*), 3.17 (s, 3H, C*H*$_3$), 2.74 and 2.72 (two s, 6H, 2C*H*$_3$). MS (EI, m/z): 414 (M^+). Anal. Calcd. for $C_{18}H_{15}BrN_4OS$: C, 52.06; H, 3.64; N, 13.49. Found: C, 51.89; H, 3.48; N, 13.18.

2.2.9. N-[5-Bromo-4,6-dimethyl-2-(morpholin-4-ylcarbonyl) thieno[2,3-b]pyridin-3-yl] acetamide (11a), N-(5-bromo-4,6-dimethyl-2-(piperidine-1-carbonyl)thieno[2,3-b] pyridin -3-yl) acetamide (11b) and 3-acetamido-5-bromo-N,4,6-trimethyl-N-phenylthieno[2,3-b]pyridine-2-carboxamide (11c)

To a solution of oxazinone **7** (2 mmol, 0.65 g) in ethanol (20 mL), the appropriate secondary amines such as morpholine, piperidine and *N*-methylaniline (4 mmol) was added. The reaction mixture was heated to reflux temperature for 2 h. The solid product that formed was collected, dried and recrystallised from ethanol to afford **11a-c** as white crystals (Scheme 2).

Compound **11a:** Yield: 44.2 %. M.p.: >300 °C. FT-IR (KBr, cm^{-1}): 3182 ν(NH) and 1696 ν(C=O). ^{1}H NMR (300 MHz, $CDCl_3$): 9.55 (s, 1H, exchangeable, N*H*), 3.73 & 3.67 (two br s, 8H, morpholine nucleus), 2.73 (s, 3H, C*H*$_3$), 2.61 and 2.22 (two s, 6H, 2C*H*$_3$). MS (EI, m/z): 411 (M^+). Anal. Calcd. for $C_{16}H_{18}BrN_3O_3S$: C, 46.61; H, 4.40; N, 10.19. Found: C, 46.43; H, 4.15; N, 9.95.

Compound **11b:** Yield: 54.7 %. M.p.: 240-242 °C, FT-IR (KBr, cm^{-1}): 3189 ν(NH) and 1699 and 1654 ν(C=O) (amide). ^{1}H NMR (300 MHz, $CDCl_3$): 9.44 (s, 1H, exchangeable, N*H*), 3.65-3.60 (s, 10H, piperidine nucleus), 2.74 (s, 3H, C*H*$_3$) and 2.54 and 2.20 (two s, 6H, 2C*H*$_3$). MS (EI, m/z): 409 (M^+). Anal. Calcd. for $C_{17}H_{20}BrN_3O_2S$: C, 49.76; H, 4.91; N, 10.24. Found: C, 49.62; H, 4.86; N, 10.06.

Compound **11c:** Yield: 55.6 %. M.p.: 172-174 °C, FT-IR (KBr, cm^{-1}): 3223 ν(NH) and 1699 ν(C=O). ^{1}H NMR (300 MHz, $CDCl_3$): 9.29 (s, 1H, exchangeable, N*H*), 7.34-7.27 (m, 5H, -Ar-*H*), 3.49 (s, 3H, -CO-N-C*H*$_3$), 2.70 & 2.68 (two s, 6H, 2C*H*$_3$) and 2.29 (s, 3H, -NH-COC*H*$_3$). MS (EI, m/z): 431 (M^+). Anal. Calcd. for $C_{19}H_{18}BrN_3O_2S$: C, 52.78; H, 4.20; N, 9.72. Found: C, 52.53; H, 4.01; N, 9.53.

2.2.10. Ethyl 3-(acetylamino)-5-bromo-4,6-dimethylthieno [2,3-b]pyridine -2-carboxylate (12)

A mixture of oxazinone **7** (2 mmol, 0.65 g) and pyridine and/or formamide (few drops) in ethanol was heated to reflux for 10 h then left to cool. The solid crude product that separated out was collected by suction, dried and then recrystallised from light petroleum ether (B.p.: 60-80 °C) to afford compound **12** as yellow crystals (Scheme 2). Yield: 46.3 %. M.p.: 198-200 °C. FT-IR (KBr, cm^{-1}): 3265 ν(NH), 1716 ν(C=O) (ester) and 1672 ν(C=O) (amide). ^{1}H NMR (300 MHz, $CDCl_3$): 8.85 (s, 1H, exchangeable, N*H*), 4.41 (q, *J*=7.2 Hz, 2H,-COOC*H*$_2$-CH$_3$,), 2.81 (s, 3H, -NH-COC*H*$_3$), 2.68 & 2.25 (two s, 6H, 2C*H*$_3$) and 1.43 (t, *J*=7.2 Hz, 3H, -COOCH$_2$-C*H*$_3$). MS (EI, m/z): 470 (M^+). Anal. Calcd. for $C_{14}H_{15}BrN_2O_3S$: C, 45.29; H, 4.07; N, 7.55. Found: C, 44.98; H, 4.21; N, 7.34.

2.2.11. (3-Amino-5-bromo-4,6-dimethylthieno[2,3-b]pyridin-2-yl)(3,5-dimethyl-1H-pyrazol-1-yl)methanone (14)

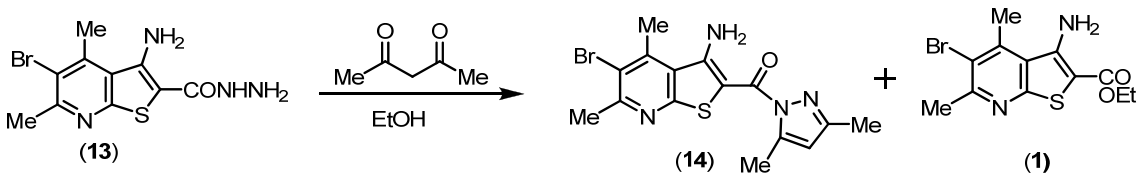
A mixture of thienopyridine **13** (2 mmol, 0.63 g) and acetyl acetone (4 mmol, 0.4 mL) in ethanol (20 mL) was heated to reflux for 10 h. TLC experiment showed that there were two spots indicating the presence of two products which were separated by fractional crystallization from light petroleum ether (B.p.: 60-80 °C) to afford 3,5-dimethyl-pyrazole derivative **14** as yellow crystals. Yield: 46.5 %. M.p.: 168-170 °C, and enaminoester **1** as yellow crystals (Scheme 3). M.p.: 202-204 °C from light petroleum ether (B.p.: 80-100 °C). Compound **14**: FT-IR (KBr, cm^{-1}): 3337, 3312 ν(NH_2), 1634 ν(C=O) (amide). ^{1}H NMR spectrum (300 MHz, $CDCl_3$): 7.15 (br s, 2H, exchangeable, N*H*$_2$), 2.94 and 2.92 (two s, 6 H, 2C*H*$_3$ of pyrazole ring), 2.79 and 2.78 (two s, 6H, 2C*H*$_3$ of pyridine) and 6.01 (s, 1 H, -C*H*- of pyrazole ring). MS (EI, m/z): 378 (M^+). Anal. Calcd. for $C_{15}H_{15}BrN_4OS$: C, 47.50; H, 3.99; N, 14.77. Found: C, 44.88; H, 4.20; N, 14.84.

3. Results and discussion

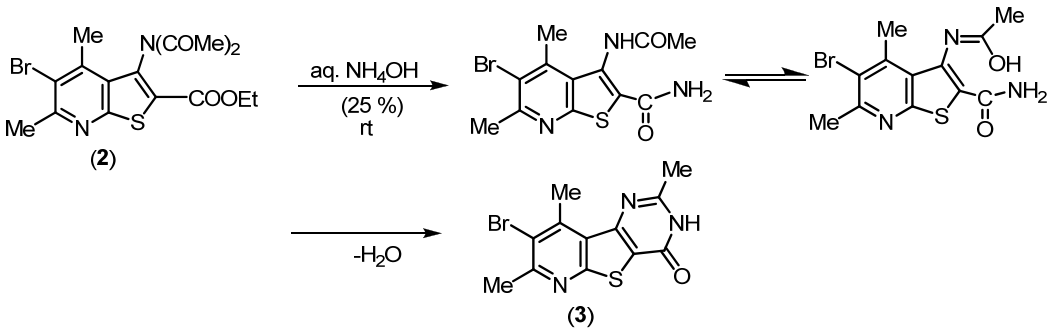
Acetylation of the enaminoester **1** [1] gave the diacetyl derivative **2** as the sole product. The structure of diacetyl derivative **2** was confirmed by elemental analysis as well as by spectral data (IR, ^{1}H NMR and MS) and chemically proved from the isolation of thienopyrimidinone **3** when the diacetyl-amino derivative **2** was stirred at room temperature with ammonia solution (Scheme 1).

Compound **3** was formed from the hydrolysis of one of the acetyl groups as well as the ester functionality to give the corresponding carboxamide which is cyclized as shown in (Scheme 4).

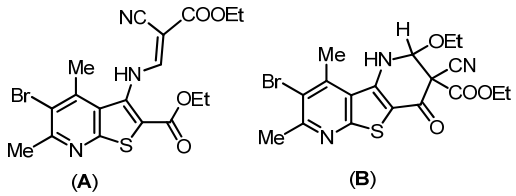
It was a point of interest to study the reaction of enaminoester **1** with 2-ethoxymethylene-cyanoacetate in refluxing ethanolic solution because it might proceed by substitution or addition to furnish **A** or **B,** respectively (Scheme 5).



Scheme 3

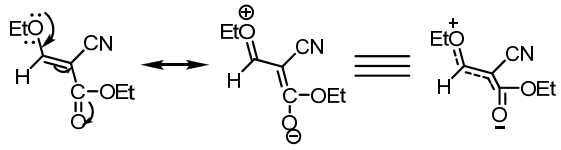


Scheme 4



Scheme 5

The reaction afforded a yellow solid product which was identified as 4-oxo-tetrahydropyridothienopyridine **4** (Scheme 1). The confirmatory evidence was obtained from the ^{1}H NMR spectrum which exhibited a signal for CH aliphatic at δ 2.61 but didn't show a signal of CH olefinic. It was found that the reaction proceeded *via* addition not substitution since the first requires only the breaking of the π-bond whereas the second needs the cleavage of the stronger C-OEt σ-bond which has some partial double bond character due to the mesomeric effect of the ethoxyl group (Scheme 6).



Scheme 6

Aiming to construct a new seven-membered heterocyclic system namely, triazepindione **5** [3, 36] intended to utilize the bifunctional ethyl carbazate reagent is allowed to react with enaminoester **1**. Instead of the expected triazepindione **5** the cyanopyridone **6** was obtained which had been assigned from its melting point (M.p.) and mixed melting point measurements [37] (M.p. of compound **6** is 264 °C [Lit.: 260 °C) as well as its spectral data (IR, ^{1}H NMR, MS) (Scheme 1).

A new fused tricyclic system containing the oxazinone moiety **7** was obtained through the effect of acetic anhydride on the potassium salt of the enaminoester **1** resulting by saponification of the ester **1** using aqueous alcoholic potassium hydroxide (Scheme 1).

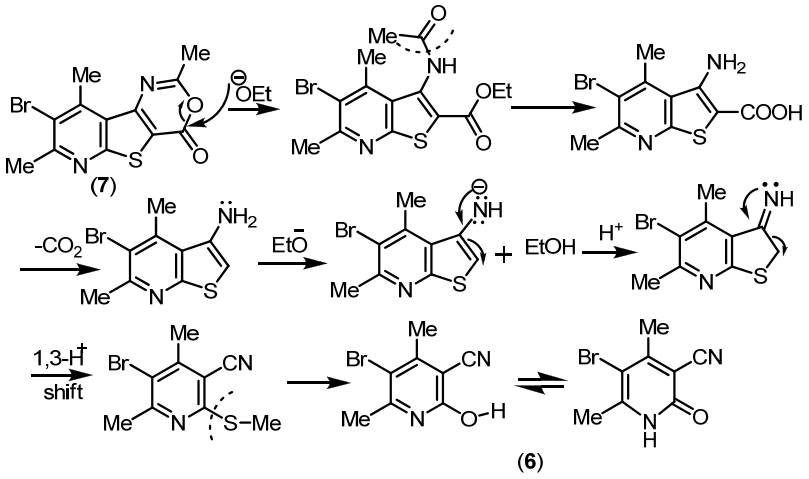
The present investigation was extended to study the behaviour of pyridothienoxazinone **7** towards carbon nucleophiles exemplified by malononitrile in the presence of sodium ethoxide. Thus when oxazinone **7** was allowed to react with ethanolic solution of malononitrile containing sodium ethoxide as a basic catalyst, the expected [38] fused tricyclic system **8** was not isolated. Surprisingly the cyano pyridone **6** was isolated as the sole product even when the reaction was conducted in the absence of malononitrile under the same conditions (Scheme 2).

When oxazinone **7** reacted with some nitrogen nucleophiles namely, ethanolamine, cyclohexylamine and/or *m*-anisidine in ethanol heated to reflux or fused with ammonium acetate, it afforded a mixture of the cyanopyridone **6** together with 3-acetylaminothienopyridine **9** which were separated by fractional crystallization (Scheme 2).

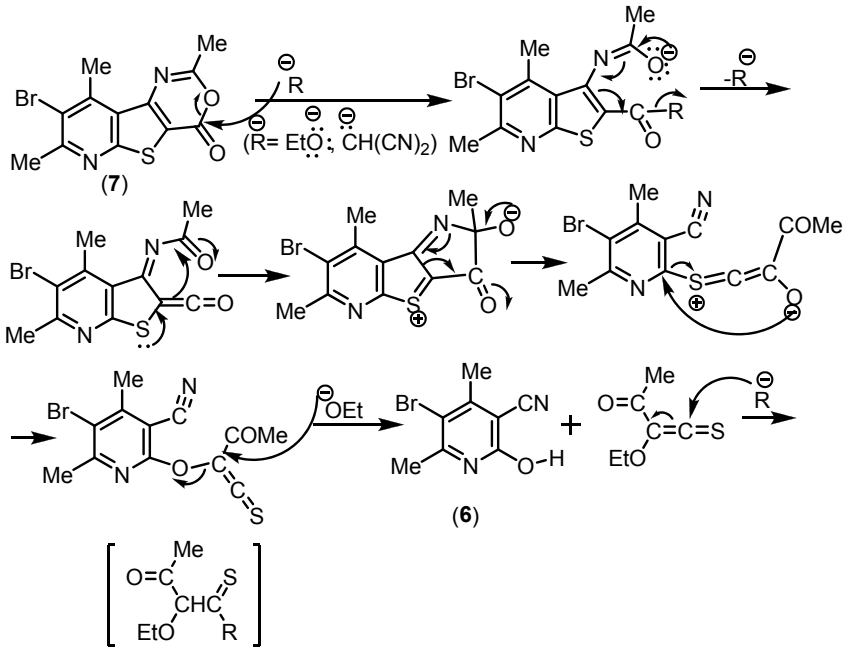
The interpretation of the formation of cyanopyridone **6** could be exhibited in two alternative proposed mechanisms.

Mechanism 1: In this mechanism we neglect the participation of malononitrile since we obtained compound **6** not only in the case of the reaction with malononitrile/sodium ethoxide mixture but also in case of the reaction with sodium ethoxide alone (Scheme 7). The mechanism 1 included base–catalyzed ring opening of the thiophene nucleus [39,40].

Mechanism 2: This mechanism takes into consideration the attack of the nucleophile whether it was the carbanion derived from malononitrile through abstraction of a proton from the active methylene group present or the ethoxide anion itself in case of conducting the reaction in the absence of malononitrile (Scheme 8).



Scheme 7



Scheme 8

Interpretation of the formation of the products resulted from the reaction of nitrogen nucleophiles with oxazinone **7** is shown in Scheme 9.

On the other hand, treatment of pyridothienoxazinone derivative **7** with some other nitrogen nucleophiles namely benzylamine in ethanolic solution heated to reflux , hydrazine hydrate and/or phenyl hydrazine in ethanolic solution at room temperature or with ammonium acetate in acetic acid heated to reflux afforded 3-substituted pyridothieno pyrimidinone (**10 a-c**) and **3,** respectively [41] (Scheme 2).

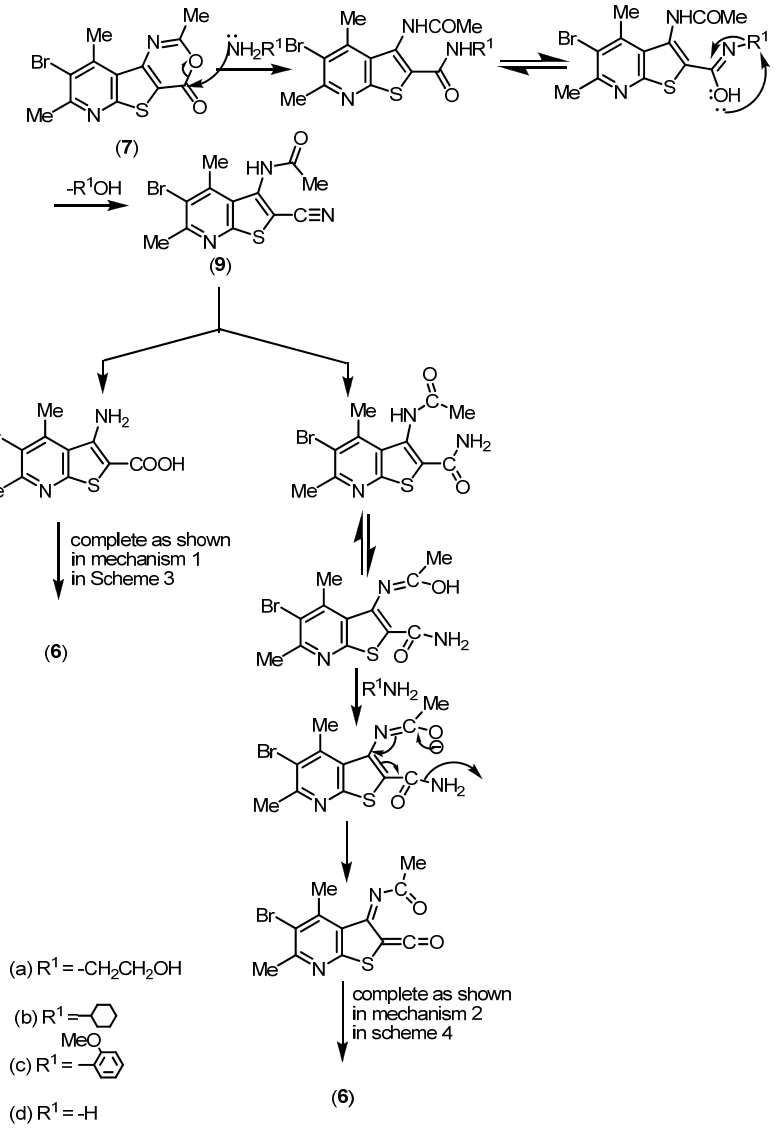
Secondary amines such as morpholine, piperidine and *N*-methylaniline reacted smoothly with oxazinone derivative **7** through nucleophilic attack at electronically deficient carbonyl carbon atom followed by ring opening to give (**11 a-c**), respectively (Scheme 2).

Oxygen nucleophiles exemplified by ethanol in the presence of basic catalyst, namely, pyridine or formamide resulted in oxazinone ring cleavage through the attack of ethoxide anion on the electronically deficient carbonyl carbon of oxazinone **7** to create ester functionality in position 2 of thienopyridine moiety [42]. Thus when the oxazinone derivative **7** was subjected to react with ethanol in pyridine as a catalytic base, ethyl 3-(acetylamino)-5-bromo-4,6-dimethylthieno [2,3-*b*]pyridine-2-carboxylate (**12**) was formed (Scheme 2).

According to the pronounced biological activity [43] of pyrazole derivatives, the author intended to construct a new thienopyridine containing pyrazole ring *via* the reaction of the hydrazide derivative **13** [1] with acetyl acetone in an ethanolic solutions which afforded a mixture of the unexpected enaminoester **1** and 3,5-dimethylpyrazole derivative **14** in the ratio of 2:1, respectively. The latter products were separated by fractional crystallization (Scheme 3).

4. Conclusion

Ethyl thieno[2,3-*b*]pyridine-2-carboxylate has two centers; the amino group (nucleophilic center) and the ethoxycarbonyl group (electrophilic center). The interaction of the above mentioned compound with electrophiles, e.g., activated double bond or acetic anhydride results in aza-Michael adduct *via* addition of the amino group on the double bond and oxazinone nucleus (annelation) *via* ring closure respectively. With hydrazine hydrate, the corresponding hydrazide was formed



Scheme 9

via tetrahedral mechanism which involves ethoxycarbonyl group. We can claim that ethyl thieno[2,3-*b*]pyridine-2-carboxylate is a scaffold for building up many fused heterocyclic systems of anticipated biological activities by reaction with different reagents.

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