Heterocyclic Letters
Vol. 6| No.1|15-22| Nov-Jan| 2016
ISSN : (print) 2231–3087 / (online) 2230-9632
CODEN: HLEEAI
http://heteroletters.org

SYNTHESIS OF NOVEL DERIVATIVES OF 3-CYANOPYRIDINE- 2(1*H*)-THIONE, THIENO[2,3,-*b*]PYRIDINE AND PYRIDO[3`,2`:4,5]THIENO[3,2-*d*]PYRIMIDINE

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Abstract: The utility of acetoacetanilide **2** in the synthesis of some new 3-cyanopyridine-2(1*H*)-thione ,3-amino-thieno[2,3-*b*]pyridine and pyrido[3`,2`:4,5]thieno[3,2-*d*]pyrimidine derivatives is reported .Newly synthesized compounds were characterized by elemental analyses and spectral data.

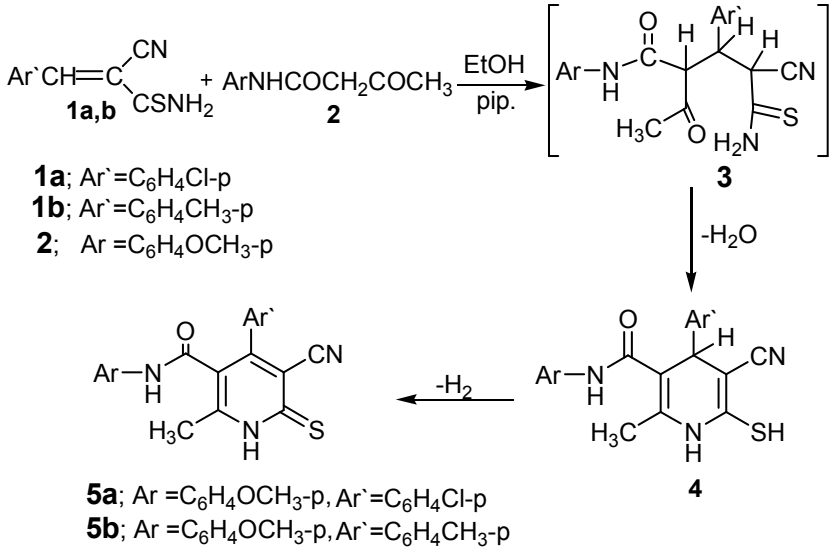
Keywords: Cyanothioacetamide, acetoacetanilide, 3-cyanopyridine-(1*H*) thiones, 3-amino-thieno[2,3-*b*]pyridines, thieno[3,2-*d*]pyrimidines

Introduction

Cyanopyridines are important intermediates in the pharmaceutical industry for the synthesis of nicotinamide, nicotinic acid and isonicotinic acid.[I,II]3-Cyano-2-thioxopyridines are of a great interest due to their synthetic capabilities and also due to the wide spectrum of biological activity.[III] Thieno[2,3-*b*]pyridine derivatives have been reported to furnish anti-inflammatory ,[IV,V] antimicrobial [VI], antihypertensive [VII] and anticancer [VIII] activities. In addition, certain derivatives of thieno[2,3-*b*]pyridine hold promise for the treatment of osteoporosis and serve as tachykinin antagonists, 5-lipoxgenase inhibitors with a broad spectrum of action, antagonists for gonadotropine releasing hormone (GnRH),vasodilators, acetylcholine esterase inhibitors, inhibitors of atherosclerotic coronary artery aneurysm, anticonvulsants and agents for the treatment of Alzheimer's disease.[IX,X] Furthermore , pyridothienopyrimidines were reported to be used for the prophylaxis and therapy of cerebral ischemia [XI,XII], and as central nervous system agents. [XIII] In view of the above and in continuation of our studies on the synthesis of heterocyclic compounds exhibiting biological activity [XIV-XVII], we report herein the synthesis of hitherto unknown 3-cyanopyridine-2(1*H*)-thione, thieno[2,3-*b*]pyridine and pyrido[3`,2`:4,5]thieno[3,2-*d*]pyrimidine derivatives utilizing inexpensive acetoacetanilide intermediate **2** as starting material.

Results and discussion

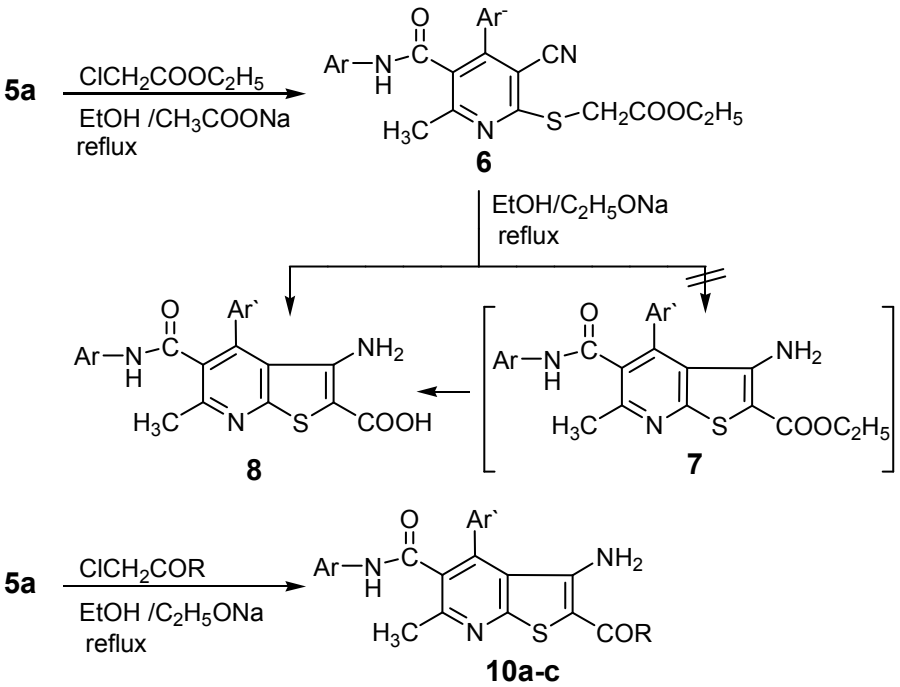
Numerous methods have been reported for the synthesis of 3-cyanopyridine-2(1*H*)-thione derivatives. [XVIII,XIX] The synthesis of 3-cyanopyridine-2(1*H*)-thiones starting from cyclocondensation of cyanothioacetamide with 1,3-diketones in the presence of base has been described in detail in reviews. [XX,XXI] *Hammouda et al*. [XXII] have reported a synthesis of 1,4-dihydrothioxo pyridines **4** from arylmethylenecyanothioacetamides **1** and acetoacetanilide **2**. In our lab, it has been found that cyclization of arylmethylene cyanothioacetamides **1a,b** with acetoacetanilide **2** in ethanol in the presence of a catalytic amount of piperidine at reflux temperature afforded 3-cyanopyridine-2(1*H*)thiones **5a,b** in quantitative yields (Scheme 1**)**. The structures of pyridinethiones **5a,b** were established on the basis of their elemental analysis and spectral data. The IR spectra of pyridinethiones **5a,b** were characterized by the presence of NH, C≡N and C=O groups. The ^{1}H NMR spectrum (DMSO-d_6) of the compound **5a** revealed a singlet at δ 2.48 ppm assigned to the CH_3 protons, a singlet at δ 3.70 ppm assigned to the OCH_3 protons, a singlet at δ 10.18 ppm assigned to the NH proton, a broad singlet at δ 14.42 ppm assigned to the NH proton in addition to the presence of the aromatic protons. The formation of **5** is assumed to proceed via initial formation of the intermediate *Michael* adduct **3** which is then cyclized through elimination of water and autoxidation [XXIII] under the experimental reaction conditions to give the final product **5**.



Scheme 1. Synthesis of 3-cyanopyridine-2(1*H*) thiones **5a,b**

The polyfunctionally substituted 3-aminothieno[2,3-*b*]pyridine derivatives were obtained by cyclization of 3-cyanopyridine-2(1*H*)thiones **5a** with halo carbonyl compounds. Treatment of compound **5a** with ethyl chloroacetate under reflux in the presence of anhydrous sodium acetate gave 2-ethoxycarbonyl methylthiopyridine derivative **6** on the basis of analytical and spectral data. The structure **6** was supported on the basis of microanalysis and spectral data . The IR spectrum showed the presence of absorption peak at 1740 cm^{-1} due to carbonyl group and at 2210 cm^{-1} for the C≡N absorption. The ^{1}H NMR ($CDCl_3$) spectrum showed singlet signal at δ 4.00 ppm for SCH_2 in addition to the presence of the ethoxy moiety. Cyclization of compound **6** by refluxing in ethanol in the presence of sodium ethoxide afforded 3-amino-thieno[2,3-*b*]pyridine derivative **8** instead of the expected compound **7**. The molecular structure of

compound **8** was assigned by analytical and spectral data. The IR spectrum showed the disappearance of C≡N group and on the other hand, showed the presence of absorption peaks at 3356, 3490 cm^{-1} due to stretching vibration of NH_2 group and at 1670,1684 cm^{-1} for the two C=O absorption. Its ^1H NMR spectrum (DMSO-d_6) indicated the absence of ethoxy fragment. The formation of thieno[2,3-*b*]pyridine **8** is assumed to proceed via *Thorpe-Ziegler cyclization* [XXIV] followed by base hydrolysis of the ester group. Cycloalkylation of compound **5a** with α-halocarbonyl compounds **9a-**c in ethanol in the presence of sodium ethoxide under reflux yielded the corresponding thieno[2,3-*b*]pyridines **10a-c**, via initial alkylation followed by heterocyclization through *Thorpe-Ziegler cyclization*[XXIV], (Scheme 2). The IR spectra of compounds **10a-c** indicated the absence of the C≡N band and contains the characteristic absorption peaks for the NH_2 and C=O groups. The ^1H NMR spectrum of compound **10a** (DMSO-d_6) revealed signals at δ 2.34, 2.73, 3.74 and 6.27-7.46 ppm which were assigned to the methyl, acetyl, methoxy and aromatic protons, respectively.

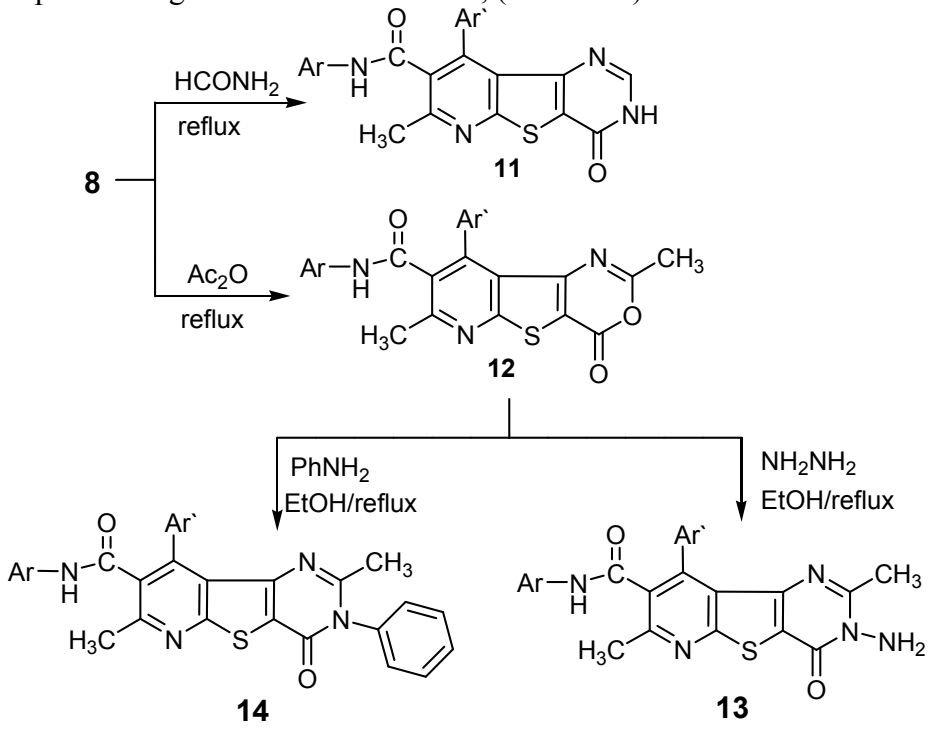


6 and **8**; Ar = $C_6H_4OCH_3$-p, Ar` = C_6H_4-Cl-p
10a; Ar = $C_6H_4OCH_3$-p, Ar` = C_6H_4-Cl-p, R = CH_3
10b; Ar = $C_6H_4OCH_3$-p, Ar` = C_6H_4-Cl-p, R = $CH_3C_6H_4NH$-p
10c; Ar = $C_6H_4OCH_3$-p, Ar` = C_6H_4-Cl-p, R = $OCH_3C_6H_4NH$-p

Scheme 2. Synthesis of 3-cyano-6-methylpyridine **6** and thieno[2,3-*b*]pyridine **8** , **10a-c** derivatives

Thieno[2,3-*b*]pyridine **8** bearing latent functional substituents were useful for the syntheses of pyrido[3`,2`:4,5]thieno[3,2-*d*]pyrimidine derivatives. Refluxing of compound **8** with formamide[XXIII] gave the corresponding pyrido[3`,2`:4,5]thieno[3,2-*d*]pyrimidine derivative **11.** The pyrido [3`,2`:4,5] thieno[3,2-*d*]oxazine-4-one derivative **12** was achieved by refluxing of compound **8** with acetic anhydride, via initial acetylation of the amino group followed by

intramolecular cyclization by elimination of water molecule. Condensation of oxazinone **12** with hydrazine hydrate in refluxing ethanol gave 3-aminopyrido[3`,2`:4,5]thieno[3,2-*d*]pyrimidine-4-one **13 .**Similarly, oxazinone derivative **12** underwent ring transformation into the pyrimidinone derivative **14** upon heating with aniline in ethanol, (Scheme 3).



Scheme 3. Synthesis of pyrido[3`,2`:4,5]thieno[3,2-*d*]pyrimidines **11,12,13** and **14**

Experimental

Melting points were determined on a digital Gallen-Kamp MFB-595 instrument and are uncorrected. IR spectra (KBr) were measured on a Shimadzu 440 spectrometer. ^{1}HNMR spectra were recorded in deuterated dimethylsulfoxide (DMSO-d_6) on a Varian Gemini 300 (300 MHz) spectrometer using tetramehylsilane (TMS) as an internal standard; chemical shifts are reported as δ units. Mass spectra were performed on a Shimadzu GSMS-QP 1000 Ex mass spectrometer at 70eV. The elemental analyses were carried out at the Microanalytical Center, Cairo University, Cairo (Egypt).

3.1. General procedure for the synthesis of 3-cyanopyridine-2(1*H*)-thione 5a,b

A mixture of compound **1** (0.01 mol), acetoacetanilide **2** (0.01 mol) and piperidine (0.3 ml) in ethanol (30 ml) was refluxed for 24 h. The solid product which produced on heating was collected and recrystallized from the proper solvent to give **5a,b**.

3.1.1.4-(4-Chlorophenyl)-3-cyano-6-methyl-5-(4-methoxyphenyl)carbamoyl-pyridine-2(1H)thione 5a. This compound was obtained as yellow crystals from ethanol; yield 83 %; m.p. 300 -1 ^{0}C. IR (KBr, cm^{-1}): 3191(NH), 3061 (CH-arom.), 2832(CH-aliph), 2227 (C≡N), 1638 (C=O). ^{1}HNMR (300 MHz, DMSO-d_6, δ/ppm): 2.48 (s, 3H, CH_3),3.7(s,3H, OCH_3), 6.8-7.5 (m,

8H, Ar-H), 10.18 (s, 1H, NH, exchangeable with D_2O),14.42 (broad,1H,NH,exchangeable with D_2O). Anal., for $C_{21}H_{16}ClN_3O_2S$ (409.90) calcd.: C, 61.54; H, 3.93; N, 10.25. Found: C, 61.50; H, 3.90; N, 10.00%.

3.1.2. 3-Cyano-6-methyl-4-(p-tolyl)-5-(4-methoxyphenyl)carbamoyl-pyridine 2(1H)thiones 5b.This compound was obtained as yellow crystals from ethanol; yield 79 %; m.p. 305-6 ^{0}C. IR (KBr, cm^{-1}): 3128, 3368 (2NH), 3050 (CH-arom.), 2930 (CH-aliph.), 2228 (C≡N),1638 (C=O). ^{1}HNMR (300 MHz, DMSO-d_6, δ/ppm): 2.23 (s, 3H, CH_3), 2.28 (s, 3H, CH_3),3.67 (s, 3H, OCH_3), 6.79-7.37 (m, 8H, Ar-H), 10.19 ,14.30 (2s, 2H, 2NH, exchangeable with D_2O**)**. Anal., for $C_{22}H_{19}N_3O_2S$ (389.48) calcd.: C, 67.85; H, 4.92; N, 10.79. Found: C, 67.60; H, 4.70; N, 10.50%.

3.2. ***3-Cyano-2-ethoxycarbonylmethylthio-4- (chlorophenyl)-5 -(4-methoxy phenyl) carbamoyl-6-methyl-pyridine 6.*** A mixture of compound **5a** (0.01 mol), ethyl chloroacetate (0.01 mol) and sodium acetate (1 gm) in ethanol (30 ml) was refluxed for 12 h, then allowed to cool. The solid product was collected and recrystallized from ethanol to give (**6**; 88%) as yellow crystals, m.p. 180-1 ^{0}C. IR (KBr, cm^{-1}): 3210 (NH), 3050 (CH-arom.), 2950 (CH-aliph.), 2224 (C≡N) , 1740,1638 (2C=O). ^{1}HNMR (300 MHz, $CDCl_3$, δ/ppm): 1.28 (t, 3H, CH_3), 1.64 (s, 3H, CH_3), 3.75 (s, 3H, OCH_3), 4.0 (s, 2H, SCH_2),4.23 (q, 2H, CH_2), 6.5-7.4 (m, 9H, Ar-H and NH). Anal., for $C_{25}H_{22}ClN_3O_4S$ (495.99) calcd.: C, 60.54; H, 4.47; N, 8.47. Found: C, 60.30; H, 4.20; N, 8.30%.

3.3. 3-*Amino-4-(4-chlorophenyl)-5-(4-methoxyphenyl)carbamoyl-6-methylthieno [2,3-b]pyridine-2-carboxylic acid 8.*A sample of compound **6** (0.01 mol) and sodium ethoxide (0.3 g Na in 25 ml ethanol) was refluxed for 2 h, then allowed to cool and poured into cold water (40 ml) and acidified with HCl. The product so formed was collected, and recrystallized from ethanol to give (**8**; 70%) as yellow crystals, m.p. 260 -1 ^{0}C. IR (KBr, cm^{-1}): 3356, 3490 (OH/NH_2),), 3050 (CH-arom.), 2950 (CH-aliph.), 1670,1648 (2 C=O).^{1}HNMR (300 MHz, DMSO-d_6, δ/ppm): 2.50 (s, 3H, CH_3),3.71 (s, 2H, NH_2,, exchangeable with D_2O),3.79 (s, 3H, OCH_3), 5.6 (s, 1H, OH, exchangeable with D_2O), 6.8-7.6 (m, 8H, Ar-H), 10.23 (s, 1H, NH, exchangeable with D_2O). Anal., for $C_{23}H_{18}ClN_3O_4S$ (467.93) calcd.: C, 59.04; H, 3.88; N, 8.98. Found: C, 59.00; H, 4.00; N, 8.80%.

3.4. General procedure for the synthesis of thieno[2,3-b]pyridines 10a-c.

A mixture of compound **5a** (0.01 mol), halo compound (0.01 mol) and sodium ethoxide (0.01 mole) in ethanol (30 ml) was refluxed for 1 h, the solid product which produced on heating was collected and recrystallized from ethanol to give **10a-c**.

3.4.1.*2-Acetyl-3-amino-4-(4-chlorophenyl)-6-methyl-5-(4-methoxyphenyl) carbamoyl-thieno[2,3-b]pyridine 10a.* This compound was obtained as yellow crystals from ethanol; yield75%; m.p.258-9^{0}C .IR(KBr,cm^{-1}):3257,3477 ((NH/NH_2), 3042 (CH-arom.) 2954(CH-aliph.),1666,1632 (2C=O),^{1}HNMR (300 MHz, $CDCl_3$, δ/ppm): 2.34 (s, 3H, CH_3), 2.73 (s, 3H, CH_3), 3.74 (s, 3H, OCH_3), 6.2-7.46 (m, 11H, Ar-H, NH and NH_2). Anal., for $C_{24}H_{20}ClN_3O_3S$ (465.96) calcd.: C, 61.87; H, 4.33; N, 9.02. Found: C, 61.80; H, 4.20; N, 9.00%.

3.4.2.3-*Amino-4-(4-chlorophenyl)-6-methyl-5-(4-methoxyphenyl)carbamoyl-2-(p-tolyl)carbamoyl-thieno[2,3-b]pyridine 10b.*This compound was obtained as yellow crystals from ethanol; yield 70 %; m.p. 275-6^{0}C.IR(KBr,cm^{-1}):3259,3485(NH/NH_2), 2923 (CH-aliph.),1635 (CO). ^{1}HNMR (300 MHz, $CDCl_3$, δ/ppm): 2.25 (s, 3H, CH_3),2.57 (s, 3H, CH_3), 3.78 (s, 3H, OCH_3),5.60 (s, 2H, NH_2,exchangeable with D_2O), 6.78-7.46 (m, 12H, Ar-H), 8.01 (broad, 2H, 2NH, exchangeable with D_2O). Anal., for $C_{30}H_{25}ClN_4O_3S$ (557.08) calcd.: C, 64.68; H, 4.52; N, 10.06. Found: C, 64.50; H, 4.30; N, 10.10%.

3.4.3.3-Amino-4-(4-chlorophenyl)-6-methyl-2,5-bis[(4-methoxyphenyl) carbamoyl] -thieno[2,3-b]pyridine 10c.This compound was obtained as yellow crystals from ethanol; yield 74 %; m.p.280-1^{0}C.IR(KBr,cm^{-1}):3310,3480(NH/NH_2),2950(CH-liph.)1670,1645 (2C=O).^{1}HNMR (300 MHz, $CDCl_3$, δ/ppm): 2.30 (s, 3H, CH_3), 3.36,3.78 (2s, 6H, 2OCH_3),5.80 (s, 2H, NH_2,exchangeable with D_2O), 6.78-7.62 (m, 12H, Ar-H), 8.51 (broad, 1H, NH, exchangeable with D_2O), 9.21 (s, 1H, NH, exchangeable with D_2O). Anal., for $C_{30}H_{25}ClN_4O_4S$ (573.08) calcd.: C, 62.88; H, 4.40; N, 9.78. Found: C, 62.65; H, 4.50; N, 9.50%.

3.5.9-(4-Chlorophenyl)-8-(4-methoxyphenyl)carbamoyl-7-methyl-pyrido [3`,2`:4,5]thieno[3,2-d]pyrimidine-4(3H)-one 11. A solution of compound **8** (0.01 mol) in formamide (5 ml) was refluxed for 5 h, then allowed to cool and poured into cold water (40 ml). The solid product was collected and recrystallized from benzene to give (**11**; 60%) as brown crystals, m.p. 120-1 ^{0}C. IR (KBr, cm^{-1}): 3436,3405 (2NH),1670,1638 (2C=O). ^{1}HNMR (300 MHz, $CDCl_3$, δ/ppm): 2.45 (s,3H, CH_3), 3.83 (s, 3H, OCH_3), 6.64-7.70 (m, 9H,Ar-H), 8.56, 9.51 (2s, 2H, 2NH, exchangeable with D_2O). Anal., for $C_{24}H_{17}ClN_4O_3S$ (476.95) calcd.: C, 60.44; H, 3.59; N, 11.75. Found: C, 60.20; H, 3.40; N, 11.50%.

3.6.9-(4-Chlorophenyl)-8-(4-methoxyphenyl)carbamoyl-2,7-dimethyl pyrido[3`,2`:4,5]thieno[3,2-d]oxazine-4-one 12.A sample of compound **8** (0.01 mol) in acetic anhydride (5 ml) was refluxed for 12 h, then allowed to cool. The solid product so formed was collected and recrystallized from ethanol to give (**12**; 60%) as yellow crystals,m.p.210-1^{0}C.IR(KBr,cm^{-1}):3350(NH),2950 (CH-aliph.),1723,1630 (2C=O) . ^{1}HNMR (300 MHz, $CDCl_3$, δ/ppm): 2.10 (s, 3H, CH_3), 2.70 (s, 3H, CH_3), 3.85 (s, 3H, OCH_3),6.77-7.46 (m, 9H, Ar-H and NH). Anal., for $C_{25}H_{18}ClN_3O_4S$ (491.96) calcd.: C, 61.04; H, 3.69; N, 8.54. Found: C, 61.00; H, 3.50; N, 8.50%.

3.7.General procedure for the synthesis of pyrido[3`,2`:4,5]thieno[3,2-*d*] pyrimidines 13 and 14 .

A mixture of compound **12** (0.01 mol) and hydrazine hydrate or phenyl hydrazine (0.012 mol) in ethanol (30 ml) was refluxed for 30 min, then allowed to cool. The solid product so formed was collected and recrystallized from ethanol to give **13** and **14**.

3.7.1.3-Amino-9-(4-chlorophenyl)-2,7-dimethyl-8-(4-methoxyphenyl)carbamo-ylpyrido[3`,2`:4,5]thieno[3,2-d]pyrimidine-4-one 13. This compound was obtained as pale yellow crystals; yield 80%; m.p.260-1^{0}C.IR (KBr,cm^{-1}) :3264,3450 (NH/NH_2), 2930 (CH-aliph.),1670,1652 (2C=O),. ^{1}HNMR (300 MHz, $CDCl_3$, δ/ppm):2.16,2.33 (2s,6H,2CH_3),3.77 (s, 3H, OCH_3), 3.83 (s,2H, NH_2 ,exchangeable with D_2O),5.43 (s, 1H, NH, exchangeable with D_2O), 6.95-7.85 (m, 8H, Ar-H). Anal., for $C_{25}H_{20}ClN_5O_3S$ (505.99) calcd.: C, 59.35; H, 3.98; N, 13.84. Found: C, 59.10; H, 3.70; N, 13.60%.

3.7.2.9-(4-Chlorophenyl)-2,7-dimethyl-8-(4-methoxyphenyl)carbamoyl-3-phenyl-pyrido[3`,2`:4,5]thieno[3,2-d]pyrimidine-4-one 14.This compound was obtained as yellow crystals; yield 85%; m.p. 300-1^{0}C. IR (KBr, cm^{-1}):3260(NH),2980 (CH-aliph.),1700,1656 (2C=O),;. ^{1}HNMR (300 MHz, $CDCl_3$, δ/ppm): 2.49 (s, 3H, CH_3), 2.65 (s, 3H, CH_3), 3.79 (s, 3H, OCH_3), 6.67-7.29 (m, 13H, Ar-H), 7.77 (s, 1H, NH, exchangeable with D_2O). Anal., for $C_{31}H_{23}ClN_4O_3S$ (567.07) calcd.: C, 65.46; H, 4.09; N, 9.88. Found: C, 65.30; H, 4.00; N, 9.60%.

Conclusions

In conclusion, acetoacetanilide **2** has been shown to be a useful building block for the synthesis of some new 3-cyanopyridine-2(1*H*)-thione , 3-aminothieno[2,3-*b*]pyridine and pyrido[3`,2`:4,5]thieno[3,2-*d*]pyramidine derivatives.

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Received on November 13, 2015.