تخليق وتفاعلات بعض المركبات الجديدة غير متجانسة الحلقة المتعلقة بالثينو[٣,٢–ب] بيريدين و دراسة التاثير البيولوجي.

عبد الله عبدالكريم الشراعي، فتحية محمد قاسم قائد و إيمان على ثابت

قسم الكيمياء – كلية العلوم التطبيقية – جامعة تعز– اليمن

E. mail: fethiyemohammed@gmail.com

المستخلص. صمم هذا البحث لتحضير بعض مشتقات ٤– اريل–٣– سينو–٥– ايثوكسي كربونيل–٢– ميثيل ثيون من تفاعله مع مركبات الهاليد مثل كلورواستيك اسيد وكلورواستيك كلوريد وايثيل كلورو استيك و كلورو استونيتريل و نتج ٢– مستبدل لسينوثيوبيريدين ٣– ا، ب و٤– ا، ب و٥– ا، ب و ٦– ا، ب حيث تم معاملتها مع إيثوكسيد الصوديوم في الإيثانول و أخضعوا الجزيئات لتخلق ثورب زيغلرو اعطت مستبدلات ٤– اريل–٣– سينو(٣،٢–ب) بيريدين ١٧، ب و٨– ا، ب و٩–ا، ب و ١٠– ا، ب. مركب ١٠أ خضع للتفاعل مع بعض و اعطي بيريدو(٥،٤:٣،٢) ثينو(٣،٢– ب)بيردين. تم استنتاج بنية المركبات المحضرة حديثا من تحليل العنصر وكذلك البيانات الطيفية من (IR، H^1 NMR، C^{13} NMR والكتله الدرية). أيضا، تم اختبار دراسة الأنشطة البيولوجية المتوقعة لجميع المركبات توليفها في المختبر لأنشطة مضادة للميكروبات.

derivatives" *Eur. Chem. Bull.,* **2(**8), 530-537 **(**2013**).**

[15] **Mohareb R. M., and Al-farouk F. O.**," Anti-Tumor and Anti-Leishmanial Evaluations of Novel Thiophene Derivatives Derived from The Reaction of Cyclopentanone with Elemental Sulphur and Cyano-Methylene Reagents", *Mohareb and Al-farouk, Organic Chem Current*, **1:1**, 1-6 (2012).

[16] **Mahmoud A. M**.," Synthesis of Some New Bipyridines, Thieno[2,3-b]pyridines, and Pyrazolo [3,4-b]pyridines ", *Journal of Heterocyclic Chemistry*, **49**, 200-203 (2012).

[17] **Gad-Elkareem M. A. M., Abdel-Fattah A. M. and Elneairy M. A. A**., " Pyridine-2(1H)-thione in heterocyclic synthesis: synthesis and antimicrobial activity of some new thio-substituted ethyl nicotinate, thieno[2,3-b]pyridine and pyridothienopyrimidine derivatives.", *Journal of Sulfur Chemistry,* **32**: 3, 273–286 (2011).

[18] **Kanawade S. B., Patil S. P., Nikam P. S., Gangurde S. A., Jachak M. N., and Toche R. B., "** Synthesis of New Thieno[2,3-d]pyrimidines, Thieno[3,2-e]pyridines, and Thieno[2,3-d][1,3] oxazines.", *Journal of Heterocyclic Chemistry*, **49**,363-369 (2012).

[19] **Buchstaller H. P., Siebert C. D., Steinmetz R., Frank I., Berger M. L., Gottschlich R., Leibrock J., Krug M., Steinhilber D., and Noe C. R** Synthesis of Thieno[2,3-b]Pyridinones Acting as Cytoprotectants and as Inhibitors of [^{3}H]GlycineBinding to the N Methyl-D-aspartate (NMDA) Receptor.", *J. Med. Chem.* **49,** 864-871 **(**2006**).**

[20] **Kidwaj M., Priya ., and Poddar R.,**" Ecofriendly Synthesis of thieno[2,3-b]pyridine derivatives**.**", *Indian Journal of Chemistry,* **49B,**270-273 (2010).

[21] **Puterová,a Z., Krutošíková A., and Végh D** "Gewald reaction: synthesis, properties and applications of substituted 2-aminothiophenes.",*ARKIVOC*, **(i)** ,209-246 (2010).

[22] **Shams H. Z., Mohareb R. M., Helal M. H., and Mahmoud A. E.,** " Novel Synthesis and Antitumor Evaluation of Polyfunctionally Substituted Heterocyclic Compounds Derived from 2-Cyano-N-(3-cyano-4,5,6,7-tetrahydrobenzo[b]thiophen-2-yl)-acetamide.", Molecules, **16**, 52-73 (2011).

1H, CH pyrimidine), 7.9 (s, H, CH triazolo), 7.2 -7.5 (m, 5H, aromatic protons), 4.0 (q, 2H, OCH_2), 2.3 (s, 3H, CH_3 at C_9) and 1.3 (t, 3H, CH_3 of ester). MS at m/z = 389 (M^+, 20 %) and 80 (M^+ -309, 100 %).

Method B

A mixture of 16 (0.75 g, 2 mmol) in tri ethylorthoformate (15 ml) was heated under reflux for 4 h, and then left to cool. The precipitate that formed was collected and recrystallized from ethanol-chloroform mixture to give white needles of: 71 %; m.p: 330 ^{o}c.

Synthesis of 3,9-dimethyl-8-ethoxycarbonyl-7-phenyl[1,2,4]triazolo[3",4"-c]pyrido[3',2':4,5] thieno[2,3-e]pyrimidine (21).

A compound 16 (0.75 g, 2 mmol) was heated under reflux for 3 h. in acetylacetone (10 ml). The reaction mixture triturated with ethanol (10 ml) and then left to cool. The precipitate solid was collected and recrystallized from ethanol-chloroform mixture to give white needles of 21. Yield: 78 %; m.p: 321 ^{o}C. Anal. for $C_{21}H_{17}N_5O_2S$; (403.46) Calcd.: C, 62.52; H, 4.25; N, 17.36 %. Found: C, 62.43; H, 4.18; N, 17.15%. IR cm^{-1} 1725 (C=O of ester). ^{1}H NMR $CDCl_3$ at δ = 8.0 (s, 1H, CH pyrimidine), 7.1 -7.6 (m, 5H, aromatic protons), 4.0 (q, 2H, OCH_2), 2.7 (s, 3H, CH_3 triazolo), 2.3 (s, 3H, CH_3 at C_9) and 1.2 (t, 3H, CH_3 of ester). MS at m/z = 403 (M^+, 20 %) and 365 (M^+ -38, 100 %).

4-References:

[1] **Rateb N. M., Abdelaziz S. H., and Zohdi H. F.,** " Synthesis and Antimicrobial Evaluation of Some New Heterocyclic Compounds from Thienopyridine and Pyrazolopyridine Derivatives.", *International Journal of Advanced Research* ,**2:1**, 446-455 (2014).

[2] **Kalaria R., Mittal M., Rajyaguru C., and Upadhyay J.,"** Synthesis, characterization and antimicrobial activity of substituted tetrahydrothieno [2,3-c]pyridin-2-yl)urea derivatives.", *Journal of Chemical and Pharmaceutical Research*, **4(3)**, 1566-1572 (2012).

[3] **Khidre R. E., and Abdel-Wahab B F.**, " Application of Benzoylaceteonitrile in the Synthesis of Pyridines Derivatives.", *Current Organic Chemistry,* **17:2**, 1-16 (2013).

[4] **Hassan A. Y., Sarg M. T., Said M. M., and El-Sebaey S. A.**," Utility of thieno[2,3-b]pyridine derivatives in the synthesis of some condensed heterocyclic compounds with expected biological activity.", *Universal Organic Chemistry,*1-15 (2013).

[5] **Kotb E. R., El-Hashash M. A.,Salama M. A.,Kalf H. S. and Abdel Wahed N. A. M.,** " Synthesis and Reaction of Some Novel Nicotinonitrile Derivatives for Anticancer and Antimicrobial Enaluation" *Acta Chim. Slov.***56**, 908-919 (2009)

[6] **Bakhite E. A.,Abdel-Rahman A. E., Mohamed O. S., and Thabet E. A.,"**Synthesis and Reaction of New Thienopyridines, pyridothienopyrimidines and pyridothienotriazines", *Bull. Korean Chem. Soc***, 23: 11,** 1-6 (2002).

[7] **Abdel-Hafez N. A., Mohamed A. M., Amr A. E., Abdalla M. M., "**Antiarrhythmic Activities of Some Newly Synthesized Tricyclic and Tetracyclic Thienopyridine Derivatives.", *Sci Pharm* ,**77**, 539-553 (2009).

[8] **Rateb N. M.,**" Synthesis and reaction of 4-trifluorometyyl-3-cyanopyridine-2-(1H)-thione one derivatives "**, 32:6**, 611-622 (2011).

[9] **El-Saghier A. M. M.,** " A Simple Synthesis of Some New Thienopyridine and Thienopyrimidine Derivatives " Molecules 7, 756-766 (2002).

[10] **El-Saghier A. M. M., Matough F., Farhat M. F., Saleh N. A., Kreddan K. M., El-Tier S. O., Hussien H. B., "** Synthesis and Biological Evaluation of Some New Thienopyridine and Thienopyrimidine Derivatives.", *Jordan Journal of Chemistry* **3:3**, 223-232 (2008).

[11] **El-Louh A. K., Abdallah S. M., and El-Sawi E. A.**, " Synthesis of Some Aryl Thienopyridine, Pyridothienopyrimidine, and Pyridothienotri azolopyrimidine Derivatives ", *Life Science Journal*, 9(1), 220-2 (2012).

[12] **Queiroz M. R. P., Peixoto D., Calhelha R. C., Pedro S. , Santos T., Lima R. T., Campos J. F., Abreu R. M. V., Ferreira I. C. F. R., Vasconcelos M. H.,** " New di(hetero)arylethers and di(hetero)arylamines in the thieno[3,2-b]pyridine series: Synthesis, growth inhibitory activity on human tumor cell lines and non-tumor cells, effects on cell cycle and on programmed cell death .", **69**, 855-862 (2013).

[13] **Abdel-Fattah A. M., Attaby F. A., and Shaif L. M.,** " Synthesis of Some Fused Heterocyclic Compounds Based on 1(1-Benzofuran- 2-yl)-3-(furan-2-yl)prop-2-en-1-one", *International Journal of Scientific & Engineering Research*, **4 :11**, 1831-1839 (2013).

[14] **El-Sharkawy K. A., Ibrahim R. A.,** " New Approaches for the Synthesis and antitumor evaluation of pyridine, thieno[3,4-c]pyridine, pyrazolo[3,4-b]pyridine and pyrido[3,4-d]pyridazine

Synthesis of 2-ethoxy-5-ethoxycarbonyl-7-methyl-9-phenylpyrido[3',2':4,5]thieno[3,2-e]pyrimidine (15).

To mixture of compound 10a (3.37 g, 10 mmol) and triethylorthoformate (7 ml) in acetic anhydride (20 ml) was refluxed for 5 h. The precipitate that formed after cooling was collected and recrystallized from ethanol as colorless plates: 60 %; m.p: 240 ^{o}C. Anal. Calcd. for $C_{21}H_{19}N_3O_3S$ (393.46): C, 64.10; H, 4.87; N, 10.68 %. Found: C, 64.15; H, 4.65; N, 10.41%. IR cm-1 1724 (C=O of ester). 1H NMR CDCI3 at δ = 8.0 (s, 1H, CH pyrimidine), 7.0 -7.6 (m, 5H, aromatic protons), 4.1 (q, 4H, 2 OCH2), 2.6 (s, 3H, CH3 at C7), a triplet at δ 1.2 (3H, CH3 at C2) and 0.9 (t, 3H, CH3 of ester). MS at m/z = 393 (M+, 75 %) and 97 (M+ -296, 100 %).

Synthesis of 8-ethoxycarbonyl-4-hydrazino-7-methyl-9-phenylpyrido[3',2':4,5]thieno[3,2-e] pyrimidine (16).

Hydrazine hydrate 99 % (4 ml) was added to a solution of 15 (3.9 g, 10 mmol) in dioxane (20 ml). The reaction mixture was stirred at room temperature for 2 h. The precipitate solid formed was collected and recrystallized from ethanol-chloroform mixture to give fine white needles: 47 %; m.p: 290 ^{o}C. Anal. Calcd. for $C_{19}H_{17}N_5O_2S$ (379.44): C, 60.14; H, 4.52; N, 18.46 %. Found: C, 59.98; H, 4.23; N, 18.62 %. IR cm^{-1} 3450, 3380 (NH-NH_2) and 1710 (C=O of ester). ^{1}H NMR DMSO-d_6 at δ = 8.0 (s,1H, CH pyrimidine), 7.0 - 7.4 (m, 5H, aromatic protons), 4.1 (s, H, NH), 3.9 (q, 2H, OCH_2), 2.5 (s, 3H, CH_3 at C_7), 2.0 (s, 2H, NH_2) and 0.8 (t, 3H, CH_3 of ester). ^{13}C NMR $CDCl_3$ at δ =168 ($C_{pyrim,}$ C_4), 167 ($C_{ester,}$ C=O), 158 ($C_{py,}$ C_6), 155 ($C_{pyrim,}$ C_2), 148 ($C_{py,}$ C_4), 138 ($C_{ph,}$ C_1), 129, 126 ($C_{ph,}$ $C_{2,3,4,5,6}$), 126 ($C_{py,}$ $C_{5,6}$), 125 ($C_{th,}$ $C_{2,3}$),120 ($C_{py,}$ C_3), 60 (C, OCH_2), 14 (C, $ArCH_3$) and 13(C, CH_3). MS at m/z = 378 (M^+-1, 70 %) and 80 (M^+ -299, 100 %).

Synthesis of 3,7-diphenyl-8-ethoxy carbonyl-9-methyl[1,2,4]triazolo[3``,4``-c]pyrido[3',2':4,5] thieno[2,3-e]pyrimidine (17)

To mixture of compound 16 (0.76 g, 2 mmol) and benzaldehyde (0.2 ml, 2 mmol) in ethanol (15 ml), few drops of acetic acide were added. The reaction mixture was heated under reflux for 4 h. The solid that formed on cooling was collected and recrystallized from dioxane to give pale yellow needles of 17. Yield: 52 %; m.p: 335 ^{o}C. Anal. for $C_{26}H_{21}N_5O_2S$ (467.54) Calcd.: C, 66.78; H, 4.52; N, 14. 97%. Found: C, 66.55; H, 4.27; N, 14.55 %. The IR at 3400 - 3350 cm^{-1} for NH and at 1711 cm^{-1} for (C=O of ester). The ^{1}H NMR $CDCI_3$ a singlet at δ 8.0 (1H, CH pyrimidine), a multiplet at δ 7.0 - 7.7 (10H, aromatic protons), a quartet at δ 4.1 (2H, OCH_2), a singlet at δ 3.9 (H, NH), a singlet at δ 2.5 (3H, CH_3 at C_9) and a triplet at δ 1.0 (3H, CH_3 of ester). MS at m/z = 464 (M^+-3, 100 %) which is in agreement with its molecular formula.

Synthesis of 3-ethylacetat-8-ethoxycarbonyl-9-methyl-7-phenyl[1,2,4]triazolo[3``,4``-c]pyrido [3',2':4,5]thieno[2,3-e]pyrimidine (18).

A suspension of compound 16 (0,75 g, 2 mmol) in diethylmalonate (12 ml) was gently heated under reflux for 4 h. The reaction mixture was triturated with ethanol (10 ml) and then left to cool. The formed precipitate was collected and recrystallized from ethanol-chloroform mixture to give as 18 pale yellow needles : 69 %; m.p: 290 ^{o}C. Anal. Calcd. for $C_{24}H_{21}N_5O_4S$ (475.52): C, 60.62; H, 4.45; N, 14.73 %. Found: C, 60.58; H, 4.24; N, 14.54 %. IR cm^{-1} 1710 (2 C=O of ester). ^{1}H NMR $CDCI_3$ at δ 7.9 (s, 1H, CH pyrimidine), 7.2 - 7.5 (m, 5H, aromatic protons), 4.1 (q, 2H, OCH_2), 3.8 (s, 2H, CH_2CO), 2.2 (s, 3H, CH_3 at C_9) and 1.0 (t, 6H, 2 CH_3 of ester). MS at m/z= 475 (M^+, 20 %) and 365 (M^+ -110, 100 %).

Synthesis of 4-(3,5-dimethyl[1,2,4] pyrazolo-1-yl)-8-ethoxycarbonyl-7-methyl-9-phenylpyrido [3',2':4,5]thieno[2,3-e]pyrimidine (19).

To mixture of 16 (0.75 g, 2 mmol) and acetic anhydride (10 ml) was added and refluxed for 5 h. The crystalline precipitate that formed on cooling was collected by filtration and recrystallized from ethanol as white needles of 19. Yield: 66 %; m.p: 321 ^{o}C. Anal. For $C_{24}H_{21}N_5O_2S$ (443.52) Calcd.: C, 64.99 ; H, 4.76; N, 15.78 %. Found: C, 65.02; H, 4.92 ; N, 15.95 %. The IR at 1718 cm^{-1} for (C=O of ester) with disappearance absorption bands for (NH-NH_2). The ^{1}H NMR $CDCI_3$ a singlet at δ 8.1 (s,1H, CH pyrimidine), 7.2 -7.6 (m, 6H, aromatic and CH pyrazolo protons), 4.0 (q, 2H, OCH_2), 2.8 (s, 6H, CH_3 at $C_{3,5}$ pyrazolo), 2.6 (s, 3H, CH_3 at C_9) and 1.0 (t, 3H, CH_3 of ester). MS at m/z= 443 (M^+, 50 %) and 365 (M^+ -114, 100 %).

Synthesis of 8-ethoxycarbonyl-9-methyl-7-phenyl [1,2,4]triazolo [3``,4``-c]pyrido [3',2':4,5]thieno [2,3-e]pyrimidine (20).

Method A

Compound 16 (0.75 g, 2 mmol) in 85% formic acid (20 ml) was heated under reflux for 6 h, and then left to cool. The precipitate solid was collected and recrystallized from ethanol-chloroform mixture to give white needles: 77 %; m.p: 330 ^{o}C. Anal. Calcd. for $C_{20}H_{15}N_5O_2S$ (389.43): C, 61.68; H, 3.88; N, 17.98 %. Found: C, 61.49; H, 3.65; N, 17.62 %. IR cm^{-1} 1720 (C=O of ester). The ^{1}H NMR ($CDCI_3$) at δ= 8.3 (s,

ethanol-chloroform mixture to give canary yellow needles of 10a,b.

3-Amino-2-carbamoyl-5-ethoxycarbonyl-6-methyl-4-phenylthieno[2,3-b]pyridine 10a.

Prepared from 9a. Yield: 81 %; m.p: 300 ^{o}C. Anal. Calcd. for $C_{18}H_{17}N_3O_3S$ (355.42): C, 60.83;H, 4.82; N, 11.82 %. Found: C, 60.59; H, 4.68; N, 11.71 %. IR cm^{-1} 3440, 3360 (NH_2), 1700 (C=O groups). The ^{1}H NMR $CDCl_3$ at δ 6.9 - 7.5 (m,7H, aromatic and amid protons), 4.2 (q, 2H, OCH_2), 3.8 (s, 2H, NH_2), 2.3 (s, 3H, CH_3 at C_6) and 0.9 (t, 3H, CH_3 of ester). The ^{13}C NMR $CDCl_3$ at δ = 169 ($C_{amide,}$ C=O), 167 ($C_{ester,}$ C=O), 158 ($C_{py,}$ C_6), 148 ($C_{py,}$ C_4), 146 ($C_{th,}$ C_2), 136 ($C_{ph,}$ C_1),137 ($C_{th,}$ C_3), 134 ($C_{ph,}$ C_4), 128, 129 ($C_{ph,}$ $C_{2,3,5,6}$), 120 ($C_{py,}$ C_5), 60 (C, OCH_2), 14 (C, $ArCH_3$) and 13(C, CH_3). MS at m/z = 337 (M^+-18, 100 %).

3-Amino-2-carbamoyl-4-(4-chlolrophenyl)-5-ethoxycarbonyl-6-methylthieno[2,3-b]pyridine 10b.

Prepared from 9b.Yield: 80 %; m.p: 320 ^{o}C. Anal. Calcd for $C_{18}H_{16}ClN_3O_3S$ (389.64).: C, 55.46; H, 4.14; N, 10.78 %.Found: C, 55.32 ; H, 3.99; N, 10.53 %. IR (cm^{-1}) 3440, 3360 (NH_2), 1700 (CO groups). ^{1}H NMR ($CDCl_3$) at δ = 7.1 - 7.7 (m, 6H, aromatic and amid protons), 3.9 - 4.1 (q & s, 4H, OCH_2 , NH_2), 2.7 (s, 3H, CH_3 at C_6) and 1.0 (t, 3H, CH_3 of ester). MS at m/z = 371 (M^+, 95 %) and 190 (M^+-199, 100 %).

Method B

To a suspension of compounds 2a,b in sodium ethoxide solution (0.35 g sodium in 40 ml abs. ethanol), chloro acetonitrile (10 mmol) was added. The resulting mixture was refluxed for 20 min. The formed precipitate was collected and recrystallized from ethanol-chloroform mixture to give compounds 10a,b (yield; 57 - 60 %). These products were identical in all aspects to those described in method A.

Synthesis of 2,4-dithioxo-8-ethoxy carbonyl-7-methyl-9-phenyl-1,2,3,4-tetrahydropyrido [3`,2`:4,5]thieno[3,2-e]pyrimidine (11).

A mixture of 10a (1.01 g, 3 mmol) and carbon disulphide (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: 51 %; m.p: 310 ^{o}C. Anal. Calcd. for $C_{19}H_{15}N_3O_2S_3$ (413.54): C, 55.18; H, 3.66 ; N, 10.16 %. Found: C, 54.89 ; H, 3.46 ; N, 10.33 %. IR cm^{-1} 3420, 3360 (2 NH) and 1712 (C=O of ester). ^{1}H NMR $CDCI_3$ a multiplet at δ 7.1 - 7.6 (m, 5H, aromatic protons), (q & s 4H, OCH_2 , 2NH), 2.6 (s, 3H, CH_3 at C_7) and 1.0 (t, 3H, CH_3 of ester). ^{13}C NMR $CDCl_3$ at δ = 186 (2 C=S), 167 ($C_{ester,}$ C=O), 158 ($C_{py,}$ C_6), 148 ($C_{py,}$ C_4), 138 ($C_{ph,}$ C_1), 129 ($C_{ph,}$ $C_{2,3,4,5,6}$),127 ($C_{th,}$ $C_{3,5}$), 126 ($C_{th,}$ $C_{2,5}$), 125 ($C_{py,}$ C_6), 122 ($C_{py,}$ C_5), 60 (C, OCH_2), 14 (C, $ArCH_3$) and 13 (C, CH_3). MS at m/z = 413 (M^+, 54 %) and 52 (M^+-361, 100 %).

Synthesis of 2,4-diethylsulfanyl-8-ethoxycarbonyl -7-methyl-9-phenylpyrido[3',2':4,5]thieno[3,2-e] pyrimidine (12).

To a suspension of compound 11 (0.83 g, 2 mmol) in ethanolic sodium hydroxide solution 4 % (10 ml, 1 mmol), ethyl iodide (0.4 ml, 6 mmol) was added. The resulting mixture was refluxed for 2 h. and then left to cool. The precipitate solid was collected and recrystallized from ethanol to give white needles: 58 %; m.p:302 ^{o}C. Anal. Calcd. for $C_{23}H_{23}N_3O_2S_3$ (469.64): C, 58.82; H, 4.94; N, 8.95 %. Found: C, 58.59 ; H, 4.70 ; N, 8.63 %. IR cm-1 1711 (C=O of ester). 1H NMR CDCI3 at δ 7.1 -7.4 (m, 5H, aromatic protons), 4.0 (q, 2H, OCH2), 2.9 (s,4H, 2 SCH2), 2.4 (s, 3H, CH3 at C7), 1.4 (t, 6H, CH3 at C2,4) and 0.8 (t, 3H, CH3 of ester). MS at m/z = 470 (M+ +1, 15 %) and 64 (M+-405, 100 %).

Synthesis of 4-amino-8-ethoxy carbonyl-7-methyl-9-phenylpyrido[3',2':4,5]thieno[3,2-e] pyrimidine (13).

Compound 10a (0.67 g, 2 mmol) in formamide (10 mmol) was heated under reflux for 4 h. The solid that formed while hot was collected and recrystallized from ethanol-chloroform mixture to give white crystals of: 59 %; m.p: 320 ^{o}C. Anal. Calcd. for $C_{19}H_{15}N_4O_2S$ (364.42): C, 62.62; H, 4.43; N, 15.37%. Found: C, 62.35; H, 4.25; N, 15.12 %. IR cm-1 3420, 3360 for (NH2) and 1710 (C=O of ester). 1H NMR CDCI3 at δ = 7.0 -8.0 (m, 6H, aromatic protons), 4.1 (s, 2H, NH2), 3.9 (q, 2H, OCH2), 2.8 (s, 3H, CH3 at C7) and 1.0 (t, 3H, CH3 of ester). MS at m/z = 363 (M+-1, 20%) and 80 (M+ -285, 100 %).

Synthesis of 4-amino-3,9-diphenyl-8-ethoxycarbonyl-7-methyl-2-thioxopyrido[3',2':4,5] thieno[3,2-e]pyrimidine (14).

A mixture of compound 10a (0.67 g, 2 mmol) and phenylisothiocyanate (0.25 ml, 2 mmol) in pyridine (10 ml) was gently heated under reflux for 6 h. The precipitate that formed was collected and recrystallized from acetic acid to give orange crystals: 55 %; m.p: 308 ^{o}C. Anal. Calcd. for $C_{25}H_{20}N_4O_2S_2$ (472.58): C, 63.54; H, 4.27; N, 11.86 %. Found: C, 63.35; H, 4.02; N, 11.69 %. IR cm-1 3430, 3360 (NH2), 1710 (C=O of ester). 1H NMR CDCI3 at δ = 7.0 - 7.7 (m, 10H, aromatic protons), 4.2 - 3.9 (q & s 4H, NH2 , OCH2), 2.6 (s, 3H, CH3 at C7) and 1.2 (t, 3H, CH3 of ester). MS at m/z = 472 (M+, 35 %) and 80 (M+ -392, 100 %).

4.1 (q, 4H, 2 OCH_2), 3.4 (s, 2H, SCH_2), 2.4 (s, 3H, CH_3 at C_6) and 0.9 (t, 6H, 2 CH_3 of ester). ^{13}C NMR (DMSO-d_6) at δ =172, 167($C_{ester,}$ 2C=O), 165 ($C_{py,}$ C_2), 162 ($C_{py,}$ C_6), 153($C_{py,}$ C_4), 136($C_{ph,}$ C_1), 134($C_{ph,}$ C_4), 128, 129($C_{ph,}$ $C_{2,3,5,6}$), 122 ($C_{py,}$ C_5), 118 (C, CN), 100 ($C_{py,}$ C_3), 60 (C, OCH_2), 14 (C, $ArCH_3$) and 13(C, CH_3). The mass at m/z = 417 (M^+-1, 70 %) and 345 (M^+-73, 100 %).

Synthesis of 3-amino-4-aryl-2,5-diethoxy carbonyl-6-methylthieno [2,3-b]pyridine 8a,b.

Method A

Compounds 7a,b were suspended in sodium ethoxide solution (0.05 g) sodium in 30 ml abs. ethanol) and heated under reflux for 5 min. The solid that formed while hot was collected and recrystallized from ethanol-chloroform mixture to give yellow crystals of 8a,b.

3-Amino-2,5-diethoxycarbonyl-6-methyl-4-phenyl thieno[2,3-b]pyridine 8a.

Prepared from 7a. Yield: 56 %; m.p: 190 ^oC. Anal. Calcd. for $C_{20}H_{20}N_2O_4S$ (384.46): C, 62.48; H, 5.24; N, 7.29 %. Found: C, 62.60; H, 5.34; N, 7.31 %. IR cm^{-1} 3420, 3320 (NH_2) and 1720 (2 C=O of ester). The ^1H NMR DMSO-d_6 at δ = 7.3 - 7.6 (m, 5H, aromatic protons), 4.2 (s, 2H, NH_2), 4.0 (q, 4H, 2 OCH_2), 2.5 (s, 3H, CH_3 at C_6) and 0.9 (t, 6H, 2 CH_3 of ester). MS at m/z = 384 (M^+, 80 %) and 57 (M^+-327, 100 %).

3-Amino-4-(4-chlorophenyl)-2,5-diethoxycarbonyl-6-methylthieno[2,3-b]pyridine 8b.

Prepared from 7b. Yield: 60 %; m.p: 220 ^oC. Anal. Calcd. for $C_{20}H_{19}ClN_2O_4S$ (418.90): C, 57.35; H, 4.57; N, 6.69 %. Found: C, 57.23; H, 4.39; N, 6.59 %. IR (cm^{-1}) 3420, 3320 (NH_2) and 1720 (2 C=O of ester). ^1H NMR (DMSO-d6) at δ =7.3 - 7.6 (m, 4H, aromatic protons), 4.0 (s, 2H, 2 NH_2), a quartet at δ 3.8 (4H, 2 OCH_2), 2.5 (s, 3H, CH_3 at C_6) and 0.8 (t, 6H, 2 CH_3 of ester). ^{13}C NMR ($CDCl_3$) at δ = 172, 164 ($C_{ester,}$ 2 C=O), 162 ($C_{py,}$ C_6), 148 ($C_{py,}$ C_4), 153 ($C_{py,}$ C_4), 148 ($C_{py,}$ C_4), 138 ($C_{ph,}$ C_1), 134 ($C_{th,}$ $C_{2,3}$), 134 ($C_{ph,}$ C_4), 129 ($C_{ph,}$ $C_{2,3,5,6}$), 60 (C, OCH_2), 14 (C, $ArCH_3$) and 13(C, CH_3). MS at m/z = 418 (M^+, 70 %) and 346 (M^+-72, 100 %).

Method B

To a suspension of 2a,b (10 mmol) in sodium ethoxide solution (0.35 g sodium in 40 ml abs. ethanol), ethyl chloroacetate (10 mmol) was added. The resulting mixture was refluxed for 20 min. The yellow precipitate formed was collected and recrystallized from ethanol-chloroform mixture to give compounds 8a,b (yield; 60 - 55 %). These products were identical in all aspects to those described in method A.

Synthesis of 4-aryl-3-cyano-2-cyanomethyl sulfanyl-5-ethoxycarbonyl-6-methylthieno[2,3-b] pyridine 9a,b.

To a suspended 2a,b (20 mmol) and sodium acetate tri hydrate (3 g, 22 mmol) in ethanol (50 ml), chloro acetonitrile (20 mmol) was added. The resulting mixture was heated under reflux for 2 h . The precipitate that formed on cooling was collected and recrystallized from ethanol as pale yellow needles of 9a,b.

3-Cyano-2-cyanomethylsulfanyl-5-ethoxycarbonyl-6-methyl-4-phenylpyridine 9a.

Prepared from 2a. Yield: 80 %; m.p: 120 ^oC. Anal. for $C_{18}H_{15}N_3O_2S$ (337.40) Calcd.: C, 64.08; H, 4.48; N,12.45 %. Found: C, 64.12; H, 4.36; N,12.28 %. IR at 2230, 2220 cm^{-1} for (2 C≡N) and at 1735 cm^{-1} for (C=O of ester). ^1H NMR (DMSO-d_6) at δ = 7.4 - 7.6 (m, 5H, aromatic protons), 4.0 (q, 2H, OCH_2), 3.8 (s, 2H, SCH_2), 2.6 (s, 3H, CH_3 at C_6) and a triplet at δ 0.9 (3H,CH_3 of ester). ^{13}C NMR DMSO-d_6 at δ =169 ($C_{amide,}$ C=O), 167($C_{ester,}$ C=O), 148 ($C_{py,}$ C_4), 138 ($C_{ph,}$ C_1), 137 ($C_{py,}$ C_6), 128, 129($C_{ph,}$ $C_{2,3,4,5,6}$), 120 ($C_{py,}$ C_5), 118 (CN), 98 ($C_{py,}$ C_3), 60 (C, OCH_2), 14 (C, $ArCH_3$) and 13(C, CH_3). MS at m/z = 337 (M^+, 60 %) and 308 (M^+-29, 100 %).

4-(4-Chlolrophenyl)-3-cyano-2-cyanomethyl sulfanyl-5-ethoxycarbonyl-6-methylpyridine 9b.

Prepared from 2b. Yield: 64 %; m.p: 130 ^oC. Anal. Calcd. for $C_{18}H_{14}ClN_3O_2S$ (371.85): C, 58.14; H, 3.79; N, 11.30 %. Found: C, 58.01; H, 3.58; N, 11.24 %. IR cm^{-1} 2230, 2220 (2 C≡N) and 1735 (C=O of ester). ^1H NMR ($CDCl_3$) at δ = 7.3-7.5 (m, 4H, aromatic protons), 4 (q, 2H, OCH_2), 3.8 (s, 2H, SCH_2), 2.6 (s, 3H, CH_3 at C_6) and 0.9 (t, 3H, CH_3 of ester). ^{13}C NMR DMSO-d_6 at δ =169 ($C_{amide,}$ C=O), 167 ($C_{ester,}$ C=O), 162 ($C_{py,}$ C_6),152 148 ($C_{py,}$ C_4), 146 ($C_{th,}$ C_2), 138($C_{ph,}$ C_1), 134 ($C_{ph,}$ C_4), 128, 129($C_{ph,}$ $C_{2,3,5,6}$), 120 ($C_{py,}$ C_5), 118 (CN), 98 ($C_{py,}$ C_3), 60 (C, OCH_2), 14 (C, $ArCH_3$) and 13(C, CH_3). MS at m/z = 370 (M^+-1, 100 %).

Synthesis of 3-amino-4-aryl-2-carbamoyl-5-ethoxycarbonyl-6-methylthieno[2,3-b]pyridine 10a,b.

Method A

Compounds 9a,b were suspended in sodium ethoxide solution (0.12 g sodium in 30 ml abs. ethanol) and heated under reflux for 5 min. The solid that formed while hot was collected and recrystallized from

2-chlorocarbonylmethylsulfanyl-3-cyano-5-ethoxycarbonyl-6-methyl -4-phenylpyridine 5a.

Prepared from 2a. Yield: 56 %; m.p: 110 ^{o}C. Anal. for $C_{18}H_{15}ClN_2O_3S$ (374.85) Calcd.: C, 57.68; H, 4.03; N, 7.46 %. Found: C, 57.46 ; H, 3.91; N, 7.25 %. The IR (cm^{-1}) 2210 (C≡N), 1780 (COCl) and 1720 (C=O of ester). ^{1}H NMR (DMSO-d_6) at δ = 7.1 - 7.4 (m, 5H, aromatic protons), 4.2 (q, 2H, OCH_2), 3.9 (s, 2H, SCH_2), 2.7 (s, 3H, CH_3 at C_6) and 0.9 (t, 3H, CH3 of ester). ^{13}C NMR (DMSO-d_6) at δ =172 ($C_{,}$ COCl), 167 ($C_{ester,}$ C=O), 165 ($C_{py,}$ C_2), 162 ($C_{py,}$ C_6), 152 ($C_{py,}$ C_4), 136 ($C_{ph,}$ C_1), 129 ($C_{ph,}$ $C_{2,3,4,5,6}$), 118 (C, CN), 118 ($C_{py,}$ C_5), 100 ($C_{py,}$ C_3), 60 (C, OCH_2), 14 (C, $ArCH_3$) and 13(C, CH_3). MS at m/z = 374 (M^+, 40 %) and 91 (M^+-283, 100 %).

2-Chlorocarbonylmethylsulfanyl-4-(4-chloro phenyl)-3-cyano-5-ethoxycarbonyl-6-methyl pyridine 5b.

Prepared from 2b. Yield: 64 %; m.p: 190 ^{o}C. Anal. for $C_{18}H_{14}Cl_2N_2O_3S$ (409.29) Calcd.: C, 52.82; H, 3.45; N, 6.84 %. Found: C, 52.64; H, 3.28; N, 6.67 %. The IR at 2210 cm^{-1} for (C≡N), 1780 cm^{-1} for (COCl) and 1720 cm^{-1} for (C=O of ester). The ^{1}H NMR $CDCl_3$ at δ = 7.2 -7.5 (m, 4H, aromatic protons), 4.2 (q, 2H, OCH_2), 3.8 (s, 2H, SCH_2), 2.5 (s, 3H, CH_3 at C_6) and 1.0 (t, 3H, CH_3 of ester). The ^{13}C NMR ($CDCl_3$) at δ =172($C_{,}$ COCl), 167($C_{ester,}$ C=O), 162 ($C_{py,}$ C_2), 153($C_{py,}$ C_4), 136 ($C_{ph,}$ C_1), 134 ($C_{ph,}$ C_4), 128, 129 ($C_{ph,}$, $C_{2,3,5,6}$), 120 ($C_{py,}$ C_5), 118 (C, CN), 100 ($C_{py,}$ C_3), 60 (C, OCH_2), 14 (C, $ArCH_3$) and 13(C, CH_3). MS at m/z = 409 (M^+, 30 %) and 64 (M^+-345, 100 %).

Synthesis of 3-amino-4-aryl-2-chlorocarbonyl-5-ethoxycarbonyl-6-methylthieno[2,3-b]pyridine 5a,b.

Method A

Compounds 5a,b (10 mmol) were suspended in sodium ethoxide solution (0.05 g, sodium in 30 ml abs. ethanol) and heated under reflux for 5min. The solid that formed while hot was collected and recrystallized from ethanol-chloroform mixture to give yellow crystals of 6a,b.

3-Amino-2-chlorocarbonyl-5-ethoxycarbonyl-6-methyl-4-phenyl thieno [2,3-b]pyridine 6a.

Prepared from 5a. Yield: 66 %; m.p: 260 ^{o}C. Anal. Calcd. for $C_{18}H_{15}ClN_2O_3S$ (374.85): C, 57.68; H, 4.03; N, 7.46%. Found: C, 57.50 ; H, 3.96; N, 7.37 %. IR cm^{-1} 3450, 3400 (NH_2), 1780 (COCl) and 1720 (C=O of ester). MS at m/z = 373 (M^+-1, 15 %) and 311 (M^+-63, 100 %).

3-Amino-2-chlorocarbonyl-4-(4-chlorophenyl)-5-ethoxycarbonyl-6-methylthieno[2,3-b]pyridine 6b.

Prepared from 5b. Yield: 70%; m.p: 270 ^{o}C. Anal. Calcd. for $C_{18}H_{14}Cl_2N_2O_3S$ (409.29): C, 52.82; H, 3.45; N, 6.84 %. Found: C, 52.83; H, 3.42; N, 6.78 % . IR (cm^{-1}) 3450, 3400 (NH_2), 1780 (COCl) and 1720 (C=O of ester). MS at m/z = 409 (M^+, 15 %) and 270 (M^+-139, 100 %).

Method B

To a suspension of compounds 2a,b (10 mmol) in sodium ethoxide solution (0.35 g sodium in 40 ml abs. ethanol), chloroacetochloride (10 mmol) was added. The resulting mixture was refluxed for 20 min. The yellow precipitate formed was collected and recrystallized from ethanol-chloroform mixture to give compounds 6a,b (yield 54 - 60 %).These products were identical in all aspects to those described in method A.

Synthesis of 4-aryl-3-cyano-5-ethoxycarbonyl-2-ethoxycarbonylmethylsulfanyl-6-methylpyridine 7a,b.

To a mixture of compounds 2a,b (10 mmol), ethyl chloroacetate (2.2 ml, 10 mmol) and sodium acetate tri hydrate (3 g, 22 mmol) in ethanol (60 ml) was heated under reflux for 3 h. The precipitate that formed on cooling was filtered, washed with water and recrystallized from ethanol to give pale yellow crystals of compounds 7a,b.

3-Cyano-5-ethoxycarbonyl-2-ethoxycarbonyl methylsulfanyl-6-methyl-4-phenylpyridine 7a.

Prepared from 2a. Yield: 59 %; m.p: 110 ^{o}C. Anal. Calcd. for $C_{20}H_{20}N_2O_4S$ (384.46): C, 62.48; H, 5.24; N, 7.29 %. Found: C, 62.22; H, 5.01; N, 7.05 %. IR cm^{-1} 2220 (C≡N), 1724 (2 C=O of ester). ^{1}H NMR (DMSO-d_6) δ = 7.2 - 7.5 (m, 5H, aromatic protons), 4.1 (q, 4H, 2 OCH_2), a 3.4 (s, 2H, SCH_2), 2.4 (s, 3H, CH_3 at C_6) and 0.9 (t, 6H, 2 CH_3 of ester). ^{13}C NMR (DMSO-d_6) at δ =171, 167 ($C_{ester,}$ 2 C=O), 165 ($C_{py,}$ C_2), 162 ($C_{py,}$ C_6), 152 ($C_{py,}$ C_4), 136 ($C_{ph,}$ C_1), 138 ($C_{ph,}$ C_4), 126, 129 ($C_{ph,}$ $C_{2,3,5,6}$), 118 ($C_{py,}$ C_5), 118 (C, CN), 100 ($C_{py,}$ C_3), 60 (C, OCH_2), 14 (C, $ArCH_3$) and 13(C, CH_3). MS at m/z = 383 (M^+-1, 100 %).

4-(4-Chlorophenyl)-3-cyano-5-ethoxycarbonyl-2-ethoxycarbonyl methylsulfanyl-6-methyl pyridine 7b.

Prepared from 2b. Yield: 64 %; m.p: 120 ^{o}C. Anal. Calcd. for $C_{20}H_{19}ClN_2O_4S$ (418.90) : C, 57.35; H, 4.57; N, 6.69 %. Found: C, 57.18; H, 4.26; N, 6.45 %. IR cm^{-1} 2220 (C≡N), 1724 (2 C=O of ester). ^{1}H NMR (DMSO-d_6) at δ 7.2 - 7.5 (m, 5H, aromatic protons),

and 1620 (C=C $_{aromatic}$). ^{1}H NMR ($CDCl_3$) at δ = 7.2-7.5 (m, 4H, aromatic protons), 4.1 (q, 2H, OCH_2), 2.8 (s, 1H, NH), 2.7 (s, 3H, CH_3 at C_6) and 1.0 (t, 3H, CH_3 of ester). ^{13}C NMR ($CDCl_3$) at δ = 185 ($C_{py,}$ C_6), 170 ($C_{py,}$ C_4), 165 ($C_{ester,}$ C=O), 153 ($C_{py,}$ C_2), 133 ($C_{ph,}$ $C_{1,4}$), 128,127 ($C_{py,}$ $C_{2,3,5,6}$), 118 (C, CN), 106 ($C_{py,}$ C_3), 104 (C_{py}, C_3), 60 (C, OCH_2), 17 (C, $ArCH_3$) and 13 (C, CH_3). MS at m/z =332 (M^+, 100 %) .

Synthesis of 4-aryl-2-carboxymethylsulfanyl-3-cyano-5-ethoxycarbonyl-6-methylpyridine 3a,b.

To a mixture of 2a,b (10 mmol), chloroacetic acid (2.2 ml, 10 mmol) and sodium acetate trihydrate (3 g, 22 mmol) in ethanol (50 ml) was heated under reflux for 3 h. The precipitate that formed on cooling was filtered, washed with water and recrystallized from ethanol to give pale yellow crystals of 3a,b.

2-Carboxymethylsulfanyl-3-cyano-5-ethoxycarbonyl-6-methyl-4-phenyl pyridine 3a.

Prepared from 2a. Yield: 62 %; m.p: 120 ^{o}C. Anal. Calcd. for $C_{18}H_{16}N_2O_4S$ (356.40): C, 60.66; H, 4.53; N, 7.86 %. Found: C, 60.41; H, 4.48; N, 7.59 %. IR (cm^{-1}) 3400 - 3000 (OH, COOH), 2200 (C≡N), 1724 (C=O groups). ^{1}H NMR (DMSO-d_6) at δ = 9.3 (s,1H, COOH), 7.2 - 7.5 (m, 5H, aromatic protons), 4.1 (q,2H, OCH_2)), 3.8 (s, 2H, SCH_2), 2.6 (s, 3H, CH_3 at C_6) and 1.0 (t, 3H, CH_3 of ester). ^{13}C NMR (DMSO-d_6) at δ =185 ($C_{py,}$ C_6), 176 ($C_{acid,}$ C=O), 167 ($C_{ester,}$ C=O), 162 ($C_{py,}$ C_6), 153 ($C_{py,}$ C_4), 138 ($C_{ph,}$ C_1), 128,126 ($C_{ph,}$ $C_{2,3,4,5,6}$), 120 ($C_{py,}$ C_3), 118 (C, CN), 100 ($C_{py,}$ C_3), 60 (C, OCH_2), 14(C, $ArCH_3$) and 13(C, CH_3). MS at m/z = 355 (M^+-1, 50 %) and 311 (M^+-45, 100 %).

2-Carboxymethylsulfanyl-4-(4-chlorophenyl)-3-cyano-5-ethoxy- carbonyl-6-methylpyridine 3b.

Prepared from 2b. Yield: 64 %; m.p: 170 ^{o}C. Anal. Calcd. for $C_{18}H_{15}ClN_2O_4S$ (390.85): C, 55.32; H,3.87; N, 9.07 %. Found: C, 55.08; H, 3.53; N, 9.23 %. IR (cm^{-1}) 3400 - 3000 (OH, COOH), 2200 (C≡N), 1724 (C=O groups). ^{1}H NMR (DMSO-d_6) at δ = 9.4 (s, 1H, COOH), 7.1 -7.5 (m, 4H, aromatic protons), 4.0 (q, 2H, OCH_2), 3.8 (s, 2H, SCH_2), 2.6 (s, 3H, CH_3 at C_6) and 0.8 (t, 3H, CH_3 of ester). MS at m/z = 391 (M^++1, 20 %) and 64 (M^+-326, 100 %).

Synthesis of 3-amino-4-aryl-2-carboxy-5-ethoxycarbonyl-6-methylthieno[2,3-b]pyridine 4a,b.

Method A

Compounds 3a,b were suspended in sodium ethoxide solution (0.05 g) sodium in 30 ml abs. ethanol) and heated under reflux for 5 min. The solid that formed while hot was collected and recrystallized from ethanol-chloroform mixture to give yellow crystals of 4a,b.

3-Amino-2-carboxy-5-ethoxy carbonyl-6-methyl-4-phenylthieno[2,3-b]pyridine 4a.

Prepared from 3a. Yield: 54 %; m.p: 260 ^{o}C. Anal. Calcd. for $C_{18}H_{16}N_2O_4S$ (356.40): C, 60.66; H, 4.53; N, 7.86 %. Found: C, 60.83; H, 4.61; N, 7.90 %. IR (cm^{-1}) 3450 (NH_2), 1724 (C=O groups). ^{1}H NMR (DMSO-d_6) at δ = 9.3 (s, 1H, COOH), 7.2 - 7.4 (m, 5H, aromatic protons), 4.2 (s, 2H, NH_2), 3.9 (q, 2H, OCH_2), 2.5 (s, 3H, CH_3 at C_6) and 1.0 (t, 3H, CH_3 of ester). ^{13}C NMR at δ = 185 ($C_{py,}$ C_2), 167 ($C_{ester,}$ C=O), 166 ($C_{acid,}$ C=O),158($C_{py,}$ $C_{2,6}$), 153 ($C_{py,}$ C_4), 141 ($C_{th,}$ $C_{2,3}$), 138 ($C_{ph,}$ C_1), 129 ($C_{ph,}$ $C_{2,3,4,5,6}$), 128 ($C_{py,}$ C_5), 120 ($C_{py,}$ C_3), 60 (C, OCH_2), 14 (C, $ArCH_3$) and 13(C, CH_3). MS at m/z = 356 (M^+, 85 %) and 242 (M^+-114, 100%).

3-Amino-2-carboxy-4-(4-chlorophenyl)-5-ethoxycarbonyl-6-methylthieno[2,3-b]pyridine 4b.

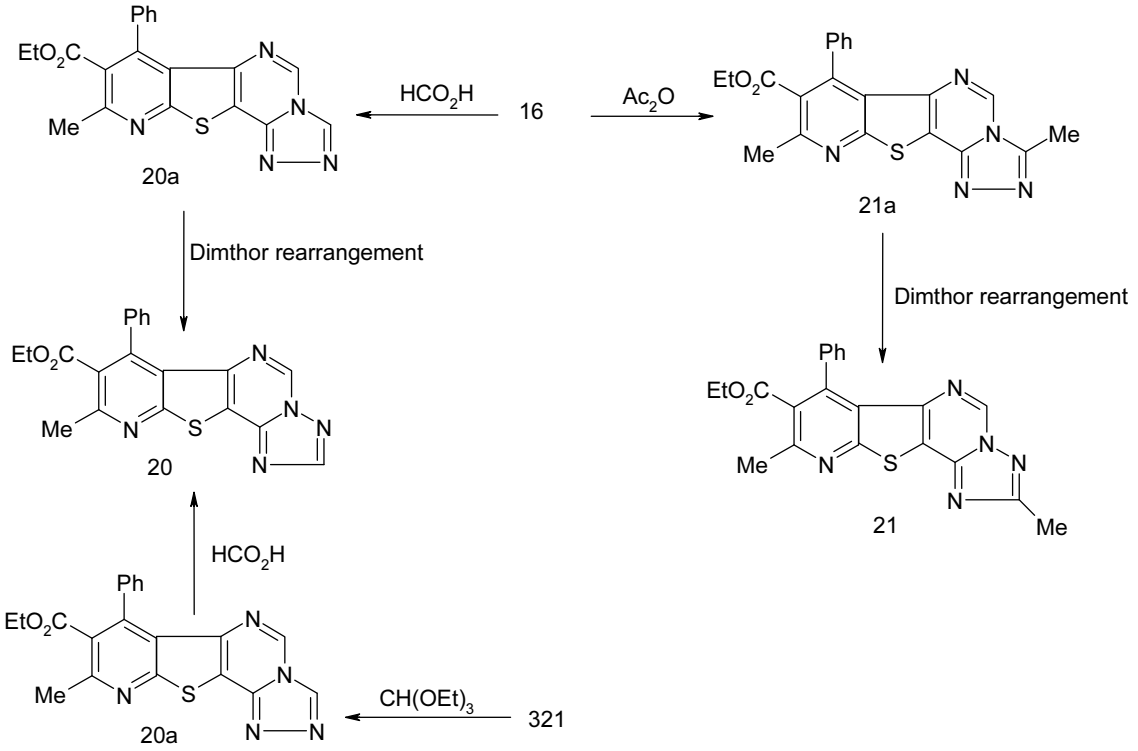
Prepared from 3b. Yield: 75 %; m.p: 290 ^{o}C. Anal. for $C_{18}H_{15}ClN_2O_4S$ (390.84) Calcd.: C, 55.31; H, 3.87; N, 9.07 %. Found: C, 55.50; H, 3.73; N, 9.30 %. The IR at 3450 cm^{-1} for (NH_2), at 1724 cm^{-1} for (C=O groups). The ^{1}H NMR (DMSO-d_6) at δ = 9.3 (s, 1H, COOH), 7.2 - 7.5 (m, 4H, aromatic protons), 4.1 (s, 2H, NH_2), 3.9 (q, 2H, OCH_2), 2.5 (s, 3H, CH_3 at C_6) and 1.0 (t, 3H, CH_3 of ester). MS at m/z = 392 (M^++2, 70 %) and 55 (M^+-335, 100 %).

Method B

To a suspension of 2a,b (10 mmol) in sodium ethoxide solution (0.35 g sodium in 40 ml abs. ethanol), the chloroacetic acid (10 mmol) was added. The resulting mixture was refluxed for 20 min. The formed yellow precipitate was collected and recrystallized from ethanol-chloroform mixture to give compounds 4a,b (yield 55 - 65 %). These products were identical in all aspects to those described in method A.

Synthesis of 4-aryl-2-chlorocarbonylmethyl sulfanyl-5-ethoxycarbonyl-6-methyl pyridine 5a,b.

To a mixture of 2a,b (10 mmol), chloro acetylchloride (2.2 ml, 10 mmol) and sodium acetate tri hydrate (3 g, 22 mmol) in ethanol 50 ml. The mixture was heated under reflux for 4 h. The precipitate that formed on cooling was filtered, washed with water and recrystallized from ethanol to give pale yellow crystals of compounds 5a,b.



Scheme 4

3-Experimental

The uncorrected melting points were determined on a thermometer 360 ^{o}C. The IR spectrum were recorded on a VAR AM-2000 FT-IR scimitar series. ^{1}H-NMR spectra were recorded with a JEOL ECP400 NMR meter operating at 500 and 200 MHz respectively. ^{13}C-NMR spectra were determined on DEITA-NMR ECP-400 400MHz spectrometer with tetramethylsilane (TMS). Mass spectra were taken on Ionization Mode: EI, 70 eV and checking the homogeneity of the compounds were made by TLC (thin layer chromatography).

Synthesis of 4-aryl-3-cyano-5-ethoxycarbonyl-6-methylpyridine-2-(1*H)*-thiones 2a,b.

To a mixture of 3-aryl-2-cyanothioacrylamide 1a,b (20 mmol), ethyl acetoacetate (2.5 ml, 20 mmol) in ethanol (30 ml), few drops of piperidine were added. The mixture was refluxed for 3 h. and then left to cool. The solid that formed while hot was collected and recrystallized from ethanol to give orange needles crystals of 2a,b.

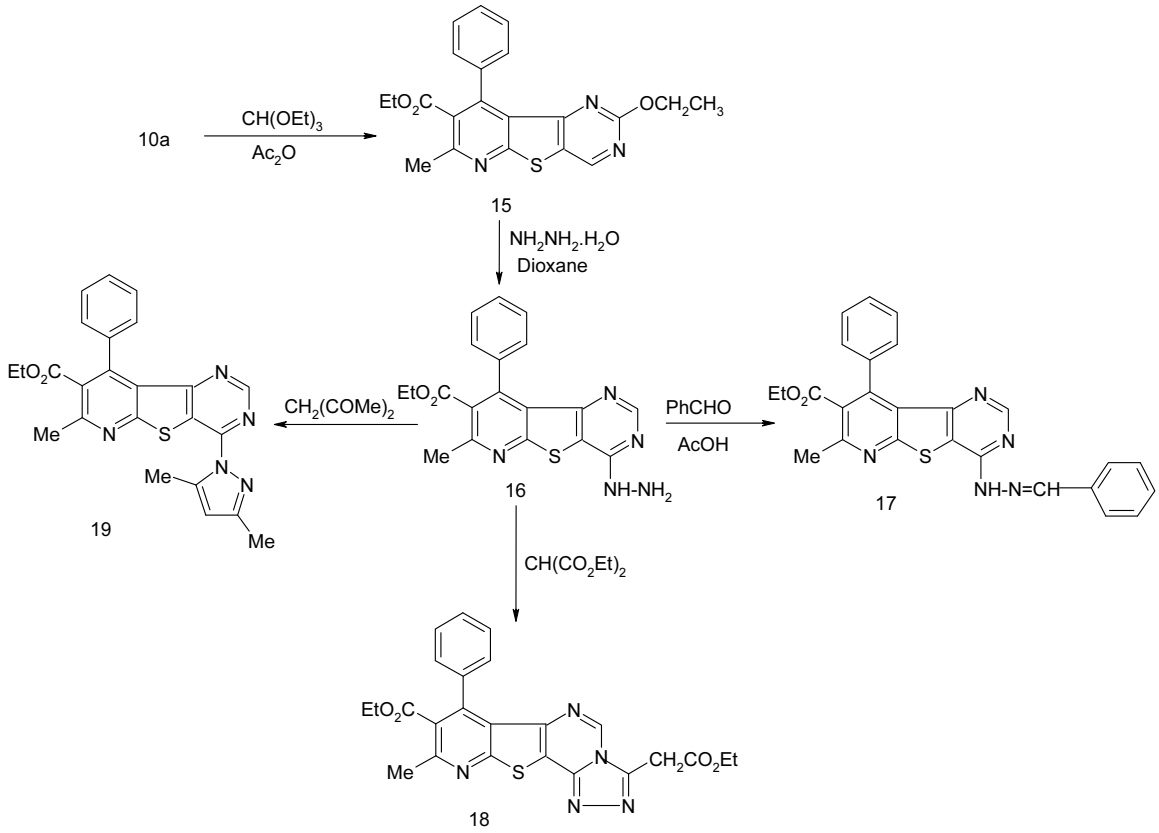
3-Cyano-5-ethoxycarbonyl-6-methyl-4-phenyl pyridine-2-(1*H)*-thiones 2a.

Prepared from 1a. Yield: 63.8 %; m.p: 238 ^{o}C. Anal. Calcd. for $C_{16}H_{14}N_2O_2S$ (298.37): C, 64.41; H, 4.73; N, 9.38 %. Found: C, 64.33; H,4.55; N, 9.48; % . IR (cm^{-1}) 3320 (NH), 3050 (=CH $_{aromatic}$), 2925 (CH $_{aliphatic}$), 2233 (C≡N), 1719 (C=O of ester) and 1620 (C=C $_{aromatic}$). ^{1}H NMR ($CDCl_3$) at δ 7.2 -7.6 (m, (5H, aromatic protons), 4.0 (q, 2H, OCH_2), 2.8 (s 1H, NH), 2.7 (s 3H, CH_3 at C_6) and 0.8 (t, 3H, CH_3 of ester). ^{13}C NMR ($CDCl_3$) at δ = 185 ($C_{py,}$ C_6), 170 ($C_{py,}$ C_4), 165 ($C_{ester,}$ C=O),153 ($C_{py,}$ C_2), 134 ($C_{ph,}$ C_1), 128,127,126 ($C_{ph,}$ $C_{2,3,4,5,6}$), 118 (C, CN), 106 ($C_{py,}$ C_3), 104 ($C_{py,}$ C_5), 60 (C, OCH_2), 17 (C, $ArCH_3$) and 13 (C, CH_3). MS at m/z = 298 (M^+,100 %).

4-(4-Chlorophenyl)-3-cyano-5-ethoxycarbonyl-6-methylpyridine-2-(1*H)*-thione 2b.

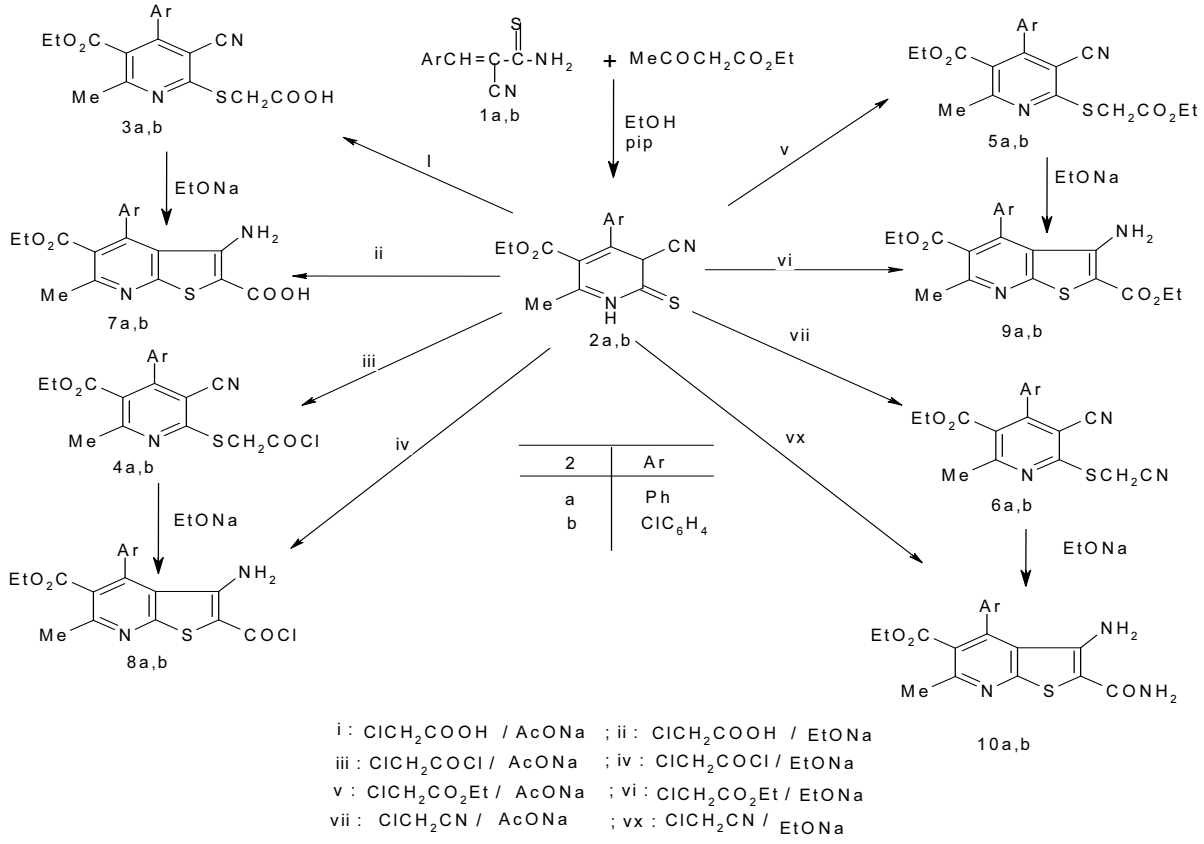
Prepared from 1b. Yield: 67.8 %; m.p: 215 ^{o}C. Anal. Calcd.for $C_{16}H_{13}ClN_2O_2S$ (332.81): C, 57.74; H, 3.94 ; N, 8.42 %. Found: C, 57.28; H, 3.66; N, 8.25%. IR (cm^{-1}) 3320 (NH), 3050 (=CH $_{aromatic}$), 2925 (CH $_{aliphatic}$), 2233 (C≡N), 1719 (C=O of ester)

On the other hand, condensation of 10a with tri ethylorthoformate in the presence of acetic anhydride gave 2-ethoxypyridothienopyrimidine derivative 15. When the latter compound was allowed to react with hydrazine hydrate the 4-hydrazinopyridothieno-pyrimidine derivative 16 was obtained. The hydrazino 16 serves as a converting point of departure to other pyridothienopyrimidine derivative. Thus, its condensation with benzaldehyde gave pyridothienopyrimidine derivative 17. Also, the compound 16 underwent a cyclocondensation with acetylacetone to furnish the dimethylpyrido thienopyrimidine derivative 18. Heating of compound 16 with diethylmalonate under neat conditions, triazolopyridothienopyrimidine 19 was obtained in high yield. (Scheme 3).

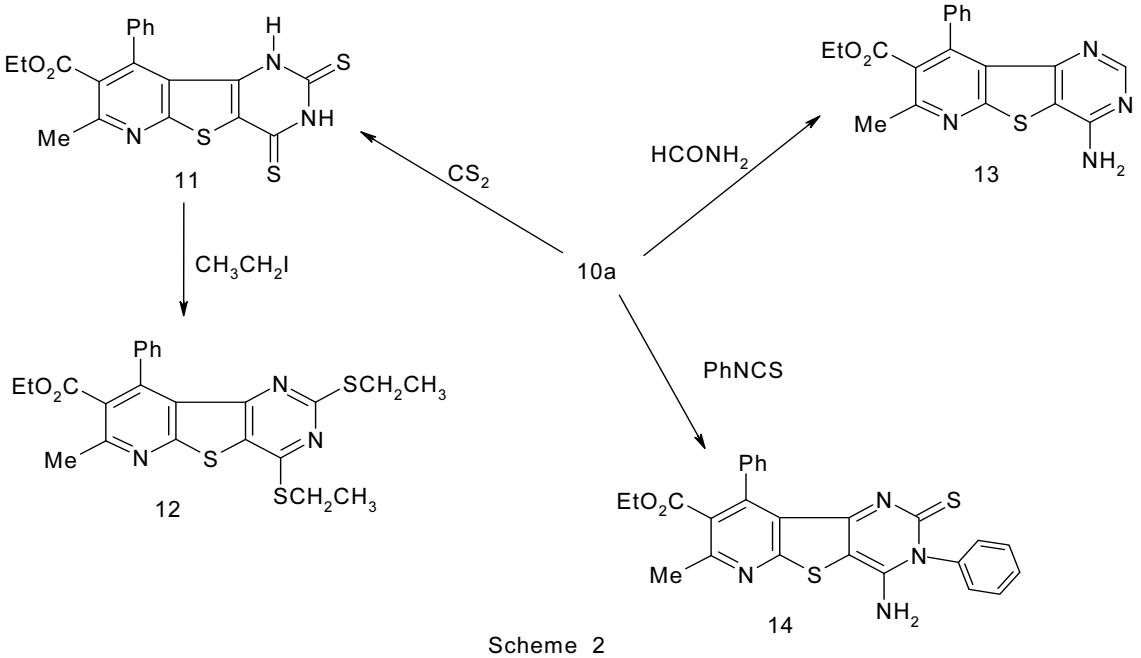


Scheme 3

Heating 16 with formic acid, the product was identified as [1,2,4]triazolopyridothienopyrimidine derivative 20 rather than the expected isomer 20a. In the same manner, the reaction of 16 with acetic anhydride led to formation of methyl[1,2,4] triazolopyridothienopyrimidine derivative 21 rather than the other one 21a. From thermodynamic point of view, the compound 20 and 21 seem to be stable than the corresponding isomer 20a and 21a. The mechanism of the latter reaction may be involved firstly the usual formation of compounds 20a and 21a which underwent Dimroth rearrangement to give the most stable isomer 20 and 21under the applied reaction condition. Heating of compound 16 with in triethylorthoformate resulted in triazolopyridothieno pyrimidine derivative 20a. This proposed mechanism was supported by the fact that the conversion of 20a into 20 was achieved upon heating with formic acid. (Scheme 4).



Scheme 1



Scheme 2

*JKAU: Sci., **Vol 28. . No. (**2) pp: 53 - 64 (1437 A.H / 2016 A.D.)*
DOI:10.4197/Sci.28-6

Synthesis and Reaction of Some New Thienopyridine and Thienopyrimidine Derivatives

Eman Ali Thabet , Fathia Mohammad Qasem Qaid . Abdullah A. Abdalkarim Alshera`a ,

Department of Chemistry, Faculty of Applied Science, Taiz University, Yemen.
E. mail: fethiyemohammed@gmail.com

ABSTRACT*:*4-aryl-3-cyano-5-ethoxycarbonyl-6-methylpyridine-2-(1H)-thiones 2a,b were synthesized. They were reacted with some halocompounds such as chloroacetoacetic acid, chloroacetylcholoride, ethyl chloroacetate or chloroacetonitrile to yield the corresponding 2-substituted cyanothiopyridine 3a,b, 4a,b, 5a,b and 6a,b. Upon treatment of these compounds with sodium ethoxide in ethanol, they underwent intermolecular Thorpe-Ziegler cyclization to furnish 3-amino-4-aryl-2-substitutedthieno[2,3-b]pyridine 7a,b, 8a,b, 9a,b and 10a,b. Compounds 10a,b underwent some reaction to yield pyrido[3',2':4,5]thieno[2,3-e]pyridines

I.Introduction

Pyridines have attained considerable interests due to their wide range of applications in medicine such as anti-inflammatory, antitumor, anti mycobacterial, antifungal and antiviral activates [1-4]. Similarly, thienopyridine and pyridothienopyrimidine derivatives are characterized by a very broad area of biological activities such as antiallergic [5], antiatheroscletotic[6], antibacterial[7,9], anticancer [10], antiviral[11,12], antihypertensive [13,14], antidepressant[15], antihistaminic[[16], antimicrobial and heurotropic activities[17-22]. In view of these reports and in continuation with the previous work, we have herein, synthesize new derivatives thienopyridine and pyrido[3',2':4,5] thieno[2,3-e]pyridines, which are expected to have biological activities.

2-Result and Discussion:-

The starting 4-aryl-3-cyano-5-ethoxycarbonyl-6-methylpyridine-2-(1*H)*-thione derivatives 2a,b were successfully synthesized by cyclo condensation of 3-aryl-2-cyanothio acrylamide 1a,b with ethyl acetoacetate in refluxing ethanol containing catalytic amount of piperidine. Compounds 2a,b were used as starting materials in the synthesis of the larger heterocyclic. The reaction of 2a,b with some halo compounds namely; chloroacetoacetic acid, chloroacetyl choloride, ethyl chloroacetate and chloroacetonitrile in refluxing ethanol in the presence of sodium acetate trihydrate as a basic catalyst afforded 2-substituted methylthio-4-aryl-3-cyano-5-ethoxy carbonylmethylpyridine 3a,b, 4a,b, 5a,b and 6a,b. The latter thieonpyridine derivatives were also prepared *via* direct reaction of 2a,b with the respective halo compounds in the presence of sodium ethoxide as a basic catalyst. (Scheme 1).

The reaction of 10a,b with carbon disulfide in hot pyridine gave dithioxopyrimidine derivative 11 which in turn, reacted with ethyliodide to produce 2,4-disubstitutedthiopyrimidine 12. Heating of compound 10a with formamide at reflux temperature afforded 4-amino-8-ethoxycarbonyl-7-methyl-9-phenylpyrido[3',2':4,5] thieno[3,2-e]pyrimidine (13). When compound 10a was allowed to react with phenylisothiocyanate in pyridine, the 4-amino-3,9-diphenyl-8-ethoxy carbonyl-7-methyl-2-thioxo pyrido [3`,2`:4,5]thieno[3,2-e]pyrimidine (14) was obtained**.** (Scheme 2).