Synthesis of Some Novel Thieno[2,3-c]pyridazines, Pyrimidothienopyridazines and Related Triazolo[1"5":1',6']pyrimido[4',5': 4,5]thieno [2,3-c]pyridazines

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Síntesis de algunas nuevas tieno[2,3-c]piridazinas, pirimidotienopiridazinas y triazolo[1''5'':1',6']pirimido[4',5': 4,5]tieno[2,3-c]piridazinas relacionadas

Síntesi d'algunes noves tieno[2,3-c]piridazines, pirimidotienopiridazines i triazolo[1''5'':1',6']pirimido[4',5': 4,5]tieno[2,3-c]piridazines relacionades

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RESUMEN

Se sintetizan 3,4-dimetiltieno[2,3-*c*]piridazinas 5,6-disubstituidas (5a-d, 6 y 7). El 5-amino-3,4-dimetiltieno[2,3-*c*]piridazina-6-carbonitrilo (5b) se usa como intermedio clave en la síntesis de nuevos derivados de pirimido[4',5':4,5]tieno[2,3-c]piridazina (8-12) y 1,2,4-triazolo[1»,5»:1',6']pirimido[4',5':4,5]tieno[2,3-*c*]piridazina (14, 15).

***Palabras clave:* Tienopiridazina. Pirimidotienopiridazinas. Triazolopirimidotienopiridazinas.**

RESUM

Se sintetitzen 3,4-dimetiltieno[2,3-c]piridazines 5,6-disubstituïdes (5a-d, 6 i 7). El 5-amino-3,4-dimetiltieno[2,3-*c*]piridazina-6-carbonitril (5b) s'empra com a intermedi clau en la síntesi de nous derivats de pirimido[4',5':4,5]tieno[2,3-c]piridazina (8-12) i 1,2,4-triazolo[1»,5»:1',6']pirimido[4',5':4,5]tieno[2,3-c]piridazina (14, 15).

***Mots clau:* Tienopiridazina. Pirimidotienopiridazines. Triazolopirimidotienopiridazines.**

SUMMARY

3,4-Dimethyl-5,6-disubstited-thieno[2,3-*c*]pyridazines (5a-d, 6, and 7) have been synthesized. 5-Amino-3,4-dimethylthieno[2,3-*c*]pyridazine-6-carbonitrile (5b) was used as a key intermediate in the synthesis of novel pyrimido[4',5':4,5]thieno[2,3-c]pyridazine derivatives (8-12) and 1,2,4-triazolo[1»,5»:1',6']pyrimido[4',5':4,5]thieno[2,3-c]pyridazine (14, 15).

***Key words:* Thienopyridazine. Pyrimidothienopyridazines. Triazolopyrimidothienopyridazines.**

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1. INTRODUCTION

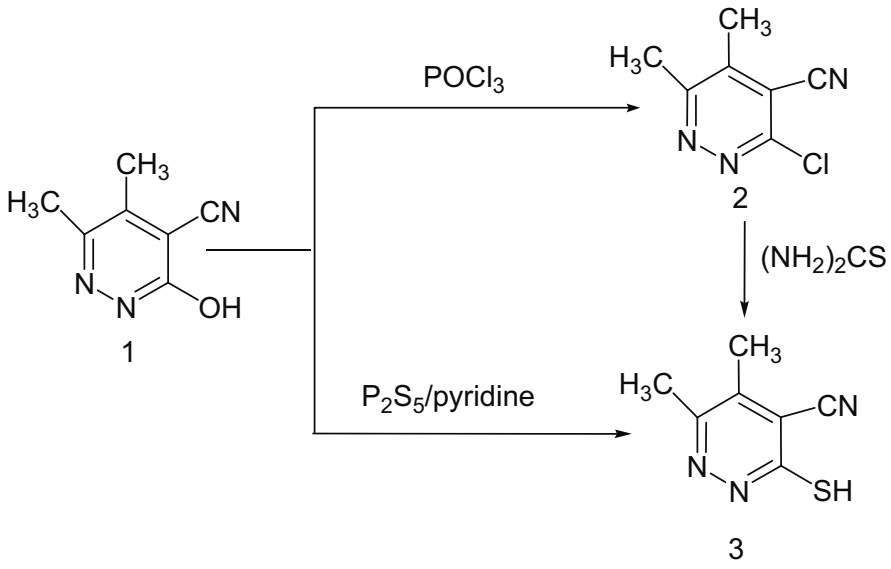
Thienopyridazine derivatives have aroused great interest in recent year because of the range of their biological and pharmacological properties. Thienopyridazine derivatives, for example, have been evaluated pharmacologically and used for potent and selective phosphodiesterase IV inhibitor[1], immunosuppressants[2], antiarrhythmic[3], antibiotic[4], antiasthmatic[5], anti-inflammatory[6], antispasmodic[7], anti-tumor[8], antimicrobials[9], antibacterial[10], antiviral[11], blood platelet aggregation inhibitors[12], and enhanced fibrinolytic activity in intact and spleenectomized rats[13]. In view of the forementioned facts and as a continuation on our previous work on the chemistry o f pyridazine compounds[14-16], we reported here the synthesis of some novel thieno[2,3-*c*] pyridazine, pyrimidothienopyridazin, and related triazolo[1'',5'':1',6']pyrimido[4',5':4,5]thieno[2,3-*c*]pyridazines from 4-cyano-5,6-dimethyl-3-pyridazi-none **1** as starting material.

2. RESULTS AND DISCUSSION

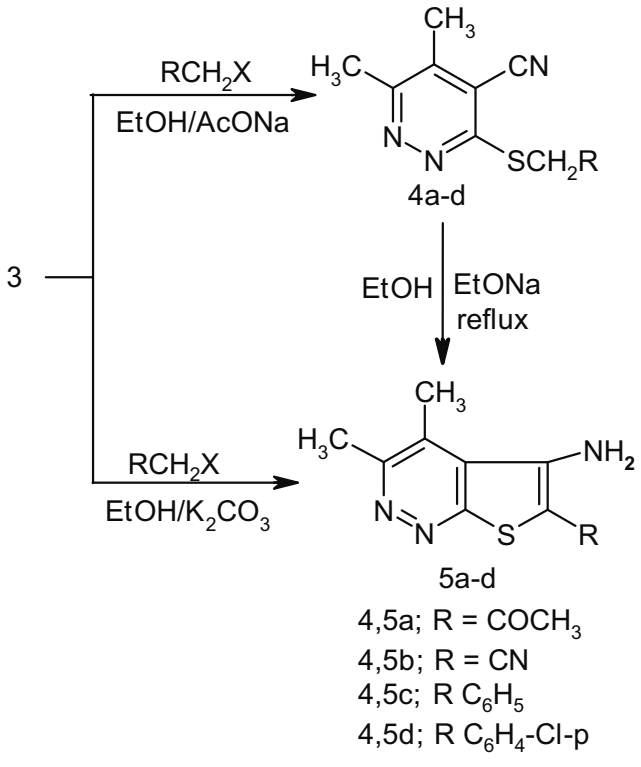
4-Cyano-5,6-dimethylpyridazin-3(2H)-one **1** which was prepared according to literature procedure[16]. The reaction of compound **1** with phosphorus oxychlorid gave the 3-chloropyridazine derivative **2** in quantitative yield 90%. Pyridazinethione **3** was achieved by treating of compound **2** with thiourea in refluxing ethanol (Scheme 1). The structure of pyridazinethione 3 was established by another synthetic route via thionation of pyridazinone **1** with phosphorus pentasulfide under reflex in pyridine.

The alkylation of compound (**3**) with some alkylating agents such as chloroacetone, chloroacetonitrile, phenacyl bromide and *p*-chlorophenacyl bromide in ethanol in the presence of sodium acetate to give the s-alkylated products **4a-d**). Thieno[2,3-*c*]-pyridazines (**5a-d**) were synthesized by ring closure of the intermediates (**4a-d**) in ethanol in presence of sodium ethoxide (Scheme 2). The structure of the new compounds (**4a-d**) was established on the basis of their elemental analysis and spectral date. The IR spectra showed bands at 2200-2220 cm^{-1} (CN). Further support for the foregoing structure of the thieno[2,3-*c*]pyridazines (**5a-d**) was obtained from an alternative one-step synthesis. Thus, when compound **3** was allowed to react with the alkylating agents in the presence of potassium carbonate, products (**5a-d**) were isolated in good yield. The identity of the two products obtained from the different routes was indicated through their m.p.; m.m.p.; TLC and superimposed IR spectra.

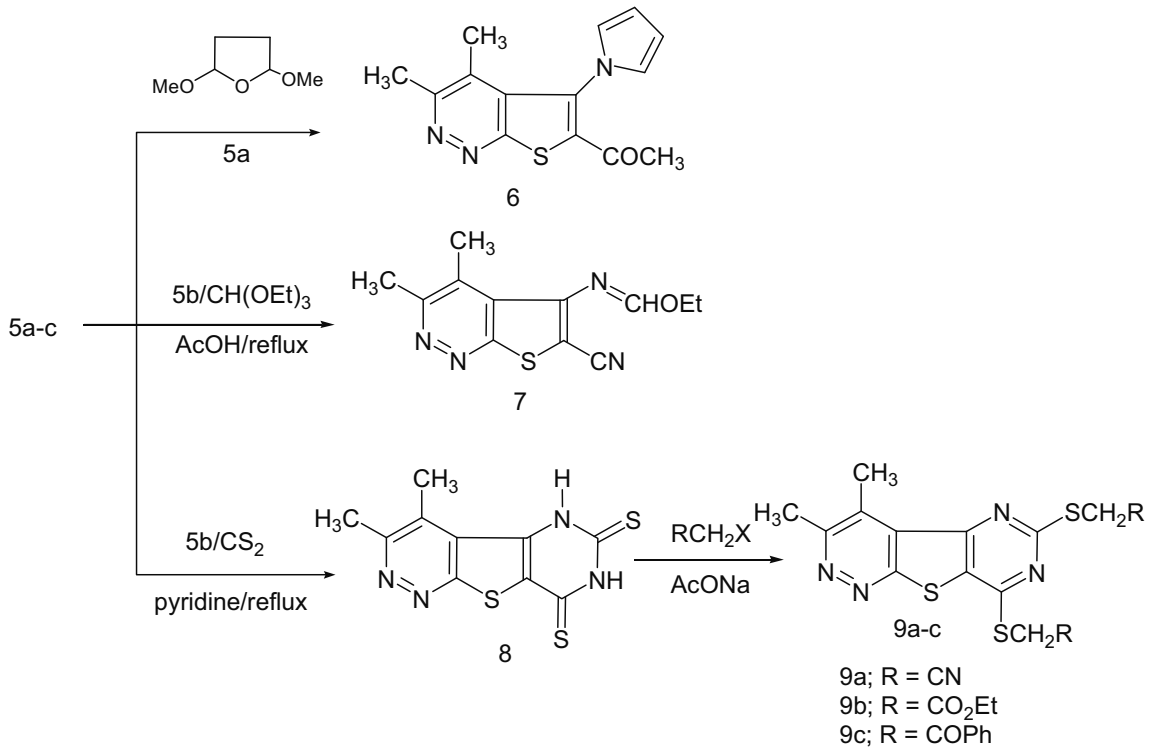
The amino group of compound (**5a**) was converted into the pyrrolyl moiety via the interaction with 2,5-dimethoxytetrahydrofuran in boiling acetic acid to give the pyrrolyl ketone (**6**). Heating of compound (**5b**) with triethyl orthoformate in acetic acid afforded the formaimidate derivative (**7**). The pyrimidothienopyridazine (**8**) was obtained by heating of compound (**5b**) with carbon disulfide in dry pyridine. This dithione was easily reacted with two mole equivalents of alkylating agents such as chloroacetonitrile, eth-



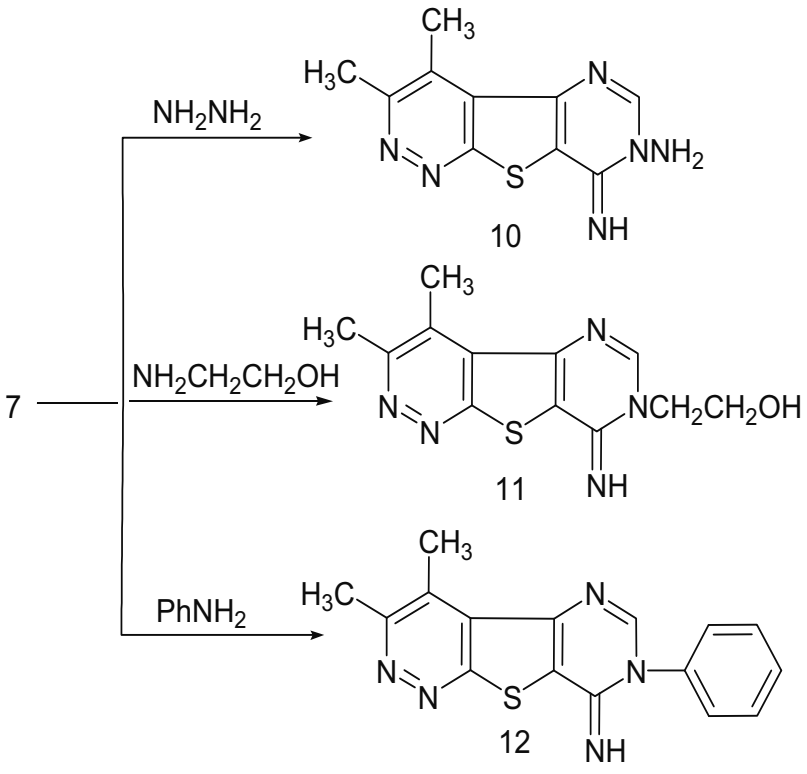
Scheme 1.



Scheme 2.



Scheme 3.



Scheme 4.

yl chloroacetate, and phenacyl bromide to furnish the S-alkylated (**9a-c**) (Scheme 3).

Ethyl N-(6-cyano-3,4-dimethyl-thieno [2,3-*c*]pyridazine-5-yl)-formaimidate (**7**) was proved to be a versatile starting material for the synthesis of some novel substituted pyrim-ido[4',5':4,5] thieno[2,3-*c*]pyridazine derivatives. Thus, cyclocondensation of compound (**7**) with hydrazine hydrate, ethanol amine and aniline in ethanol at room temperature produced the novel pyrimidothienopyridazine derivatives (**10-12**) (Scheme 4). Reaction of compound (**10**) with acetyl acetone afforded the 3,4,9-trimethyl-1,2,4-triazolo[1''5''1',6']pyrimido[4',5':4,5]thieno[2,3-*c*]pyridazine (**14**) instead of the 3,4, 9,11-tetramethylpyridazino[3''4'':5',4']thieno[2',3':5,4]pyrimido[1,6-*b*]1,2,4-triazepine (**13**). Heating of compound (**10**) with triethyl orthoformate under boiling condition yielded the novel 3,4-dimethyl-1,2,4-triazolo[1''5''1',6']pyrimido[4',5':4,5]thieno[2,3-*c*]-pyridazine (**15**) (Scheme 5).

3. EXPERIMENTAL

All melting points are uncorrected and measured on a Fisher-John apparatus. Elemental analyses were determined on an Elementar Analysensystem GmbH-VarioEL V.3 microanalyzer in the central lab of Assiut University. IR spectra were

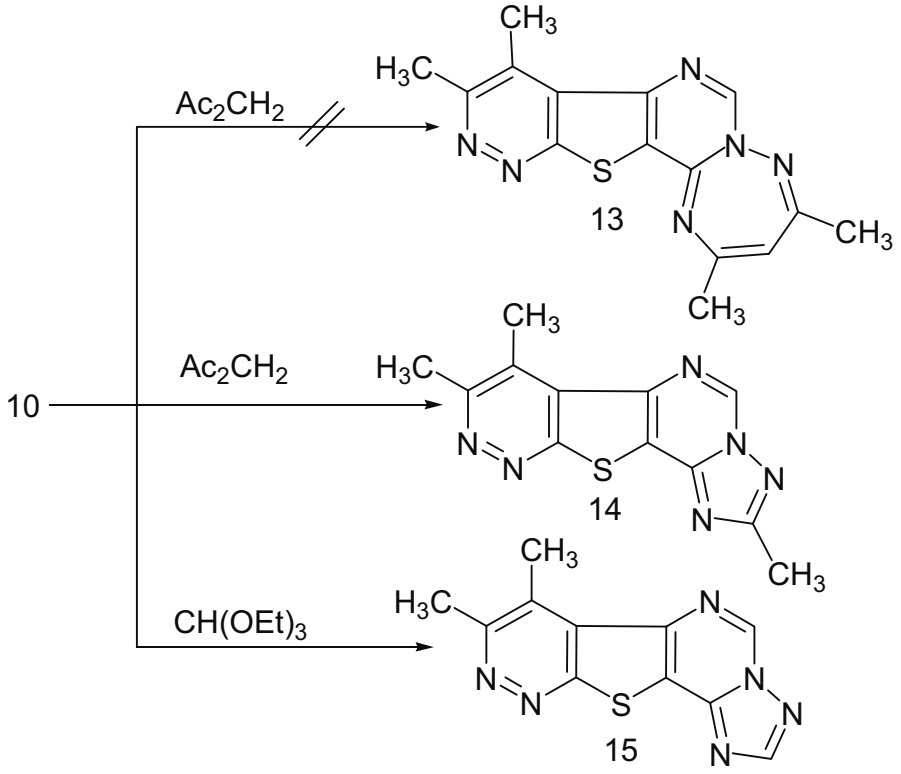
recorded on a Pye-Unicam Sp-100 spectrophotometer using KBr wafer technique. NMR spectra were recorded on a varian EM-390 90 MHz and Joel 400 MHz spectrometers in a suitable deutrated solvent using TMS as internal standard (chemical shifts in ppm). MS spectra were recorded on Jeol JMS-600 apparatus.

4-Cyano-5,6-dimethylpyridazine-3(2H)-one (1):

This compound was prepared according to the reported method[16].

3-Chloro-4-cyano-5,6-dimethylpyridazine (2):

A mixture of compound **1** (0.01 mol) and phosphorusoxychloride (30 ml) was heated under for 4 h, then allowed to cool, the cooled reaction mixture was added with stirring to an ice-water the solid product was collected and recrystallized from petroleum ether (60-80°C) as white crystals, in 84% yield, m.p. 80°C. IR: ν = 2210 cm^{-1} (CN). ^{1}H-NMR (DMSO-d_6): δ = 2.4, 2.7 (2 s, 6H, $2CH_3$). Anal. Calcd. for $C_7H_6ClN_3$ (167.60): C, 50.16; H, 3.16; N, 25.07%. Found: C, 50.30; H, 3.27; N, 25.15%.



Scheme 5.

4-Cyano-5,6-dimethylpyridazin-3(2H)-thione (3):

Method A: A mixture of compound **1** (0.01 mole) and phosphorous pentasulfide (mole) in dry pyridine (50 ml) was re fluxed for 4 h. The cold clear solution was poured into ice-water and the solid product obtained was recrystallised from ethanol as yellow crystals in 90% yield, m.p. 212-213°C. IR: ν = 3300 cm^{-1} (NH) and 2200 cm^{-1} (CN). ^{1}H-NMR (DMSO-d_6): δ = 2.33, 2.4 (2s, 6H, $2CH_3$), 12.24 (hump, 1H, NH). Anal. Calcd. for $C_7H_7N_3S$ (165.12): C, 50.89; H, 4.27; N, 25.44; S,19.41%. Found: C, 50.80; H, 4.10; N, 25.50; S, 19.30%.

Method B: A mixture of compound **2** (0.01 mole) and thiourea (0.02 mole) in ethanol (20 ml) was heated under reflux for 4 h, then allowed to cool .The solid product was collected and recrystallized from ethanol as Yellow crystals in 86% yield.

4-Cyano-5,6-dimethyl-3-substituted mercapto-pyridazines (4a-d):

General procedure: A mixture of compound **3** (0.01 mole), alkylating agents (0.01 mole) and sodium acetate (2 g) in ethanol (30 ml) was heated under reflux for 2 h. The perciptated solid which formed on cooling was filtered off, washed with water and recrystallized from ethanol.

4a: Yellow crystals, yield (85%), m.p. 162°C. IR: ν = 2200 cm^{-1}(CN) and 1725 cm^{-1} (CO). ^{1}H-NMR ($CDCl_3$): δ = 2.35, 2.62 (2s, 6H, $2CH_3$), 2.5 (s, 3H, $COCH_3$), 4.2 (s, 2H, SCH_2). Anal. Calcd for $C_{10}H_{11}N_3OS$ (221.28): C, 54.28; H, 5.01; N, 18.99; S, 14.49%. Found: C, 54.20; H, 4.90; N, 19.01; S, 14.52%.

4b: Yellow crystals, yield (75%), m.p. 154°C. IR: ν = 2280 cm^{-1} (CN), 2210 cm^{-1} (CN). ^{1}H-NMR ($CDCl_3$): δ = 2.3, 2.6 (2s, 6H, $2CH_3$), 4.1 (s, 2H, SCH_2). Anal. Calcd for $C_9H_8N_4S$ (204.25): C, 52.92; H, 3.95; N, 27.43; S, 15.70%. Found: C, 52.80; H, 3.80; N, 27.33; S, 15.50 %.

4c: Brown crystals, yield (55%), m.p. 138°C. IR: ν = 2220 cm^{-1} (CN) and 1680 cm^{-1} (CO). ^{1}H-NMR (DMSO-d_6): δ = 2.3, 2.5 (2s, 6H, $2CH_3$), 4.5 (s, 2H, SCH_2), 7.3-7.7 (m, 5H, Ar-H). Anal. Calcd for $C_{15}H_{13}N_3OS$ (283.35): C, 63.58; H, 4.62; N, 14.62, S, 11.32%. Found: C, 63.70; H, 4.57; N, 14.70; S, 11.50%.

4d: Yellow crystals, yield (55%), m.p. 176°C. IR: ν = 2220 cm^{-1} (CN) and 1675 cm^{-1} (CO). ^{1}H-NMR (DMSO-d_6): δ = 2.3, 2.5 (2s, 6H, $2CH_3$), 4.32 (s, 2H, SCH_2), 7.3, 7.5 (2d, 4H, Ar-H). Anal. Calcd for $C_{15}H_{12}ClN_3OS$ (317.79): C, 56.69; H, 3.81; N, 13.22; S, 10.09%. Found: C, 56.80; H, 4.00; N, 13.12; S, 10.30%.

5-Amino-3,4-dimethyl-6-R-thieno[2,3-*c*]pyridazines(5a-d): General procedure:

Method A: To a suspension of **3** (0.01 mol) and anhydrous potassium carbonate was added (0.02 mol) in ethanol (50 ml), the respective halocompound (0.012 mol). The resulting mixture was heated for 3 h, and then left to cool. The preciptate that formed was filtered thoroughly with water, and recrystallized from ethanol.

Method B: A sample of compound **4** (0.01 mol) in sodium ethoxide (0.23 Na/30 ml ethanol)was heated under reflux for 2 h, then allowed to cool.The solid product was collected by filtration, washed with water and recrystallized to give (**5a-d**).

5a: Orange crystals, yield 87%, m.p. 240°C. IR: ν = 3380, 3250 cm^{-1} (NH_2) and 1590 cm^{-1} (CO). ^{1}H-NMR ($CDCl_3$): δ = 2.55, 2.9 (2s, 6H, $2CH_3$); 3.3 (s, 3H, $COCH_3$); 7.45 (s, 2H, NH_2). Anal. Calcd for $C_{10}H_{11}N_3OS$ (221.28): C, 54.28; H, 5.01;

N, 18.99; S, 14.49%. Found: C, 54.72; H, 5.20; N, 19.02; S, 14.40%.

5b: Yellow crystals, yield (75%), m.p. 240°C. IR: ν = 3400, 3320 cm^{-1} (NH_2) and 2200 cm^{-1} (CN). ^{1}H-NMR (DMSO-d_6): δ = 2.77, 3.3 (2s, 6H, $2CH_3$), 6.20 (broad, 2H, NH_2). Anal.Calcd for $C_9H_8N_4S$ (204.25): C, 52.92; H, 3.95; N, 27.43, S, 15.70%. Found: C, 52.80; H, 3.80; N, 27.33; S, 15.50%.

5c: Orange crystals yield (92%), m.p. 310°C. IR: ν = 3400, 3290 cm^{-1} (NH_2), 1585 cm^{-1} (CO). ^{1}H-NMR (DMSO-d_6): δ = 2.32, 2.8 (2s, 6H, $2CH_3$), 4.95 (s, 2H, NH_2), 7.1-7.6 (m, 5H, Ar-H). Anal. Calcd for $C_{15}H_{13}N_3OS$ (283.35): C, 63.58; H, 4.62; N, 14.62, S, 11.32%. Found: C, 63.70; H, 4.72; N, 14.70; S, 11.50%.

5d: Orange crystals yield (83%), m.p. 310°C. IR: ν = 3400, 3290 cm^{-1} (NH_2) and 1590 cm^{-1} (CO). ^{1}H-NMR (DMSO-d_6): δ = 2.32, 2.8 (2s, 6H, $2CH_3$), 5.9 (s, 2H, NH_2), 7.2, 7.5 (2d, 4H, Ar-H). Anal.Calcd for $C_{15}H_{12}ClN_3OS$ (317.79): C, 56.69; H, 3.81; N, 13.22; S, 10.09%. Found: C, 56.52; H, 3.90; N, 13.15; S, 10.33%.

6-Acetyl-3,4-dimethyl-5-(1-pyrryl)thieno[2,3-*c*] pyridazine (6)

A mixture of compound **5a** (0.01 mol) and 2,5-dimethoxytetrahydrofuran (0.01 mol) in glacial acetic acid (30 ml) was heated under reflux for 2 h. The solid product was collected and recrystallized from acetic acid as yellow crystals in 78% yield, m.p. 288°C. IR: ν = 1655 cm^{-1} (CO). ^{1}H-NMR ($CDCl_3$): δ = 2.2 ,2.35 (2s, 6H, $2CH_3$), 3.1 (s, 3H, $COCH_3$), 6.8 (m, 2H, CH Pyrrole); 6.9 (m, 2H, CH Pyrrole). Anal. Calcd for $C_{14}H_{13}N_3OS$ (271.34): C, 61.97; H, 4.83; N, 15.49, S, 11.82%. Found: C, 61.70; H, 4.92; N, 15.70; S, 11.90%.

6-Cyano-3,4-dimethyl-5-ethoxymethylene amino thieno[2,3-*c*]pyridazine (7):

A mixture of compound **5b** (0.01 mol) and triethylortho formate (4 ml) in acetic acid (20 ml) was refluxed for 3 h. After cooling the solid product was collected and recrystallized from ethanol to give white crystals in 81% yield, m.p. 162°C. IR: ν = 2980 cm^{-1} (CH-aliphatic), 2220 cm^{-1} (CN), 1620 cm^{-1} (C = N). ^{1}H-NMR ($CDCl_3$): δ = 1.2-1.6 (t, 3H, CH_3), 2.5, 2.7 (2s, 6H, $2CH_3$), 4.1-4.5 (q, 2H, OCH_2) 8.2 (s, 1H, N = CH). Anal. Calcd. for $C_{12}H_{12}N_4OS$ (260.31): C, 55.36; H, 4.65; N, 21.52; S, 12.32%. Found: C, 55.50; H, 4.70; N, 21.32; S, 12.30%.

3,4-Dimethyl-5,6,7,8-tetrahydro-6,8-dithioxopyrimido [4',5':4,5]thieno[2,3-*c*]pyridazine (8):

A mixture of compound **5b** (0.01 mol), carbon disulphide (10 ml) in dry pyridine (30 ml) was heated on water bath for 12 h. After cooling ,the precipitate was filtered and recrystallized from pyridine as yellow crystals, yield 80%, m.p. 300°C. IR: ν = 3150 cm^{-1} (NH), 1150 cm^{-1} (C = S). ^{1}H-NMR (DMSO-d_6): δ = 3.32, 3.6 (2s, 6H, $2CH_3$). Anal. Calcd. for $C_{10}H_8N_4S_3$ (280.38): C, 42.83; H, 2.88; N, 19.98; S, 3.45%. Found: C, 42.63; H, 3.00; N, 20.01; S, 3.65%.

Alkylation of 3,4-Dimethyl-5,6,7,8-tetrahydro-6,8-dithioxopyrimido[4',5':4,5]-thieno[2,3-*c*]pyridazine (8). Formation of (9a-d) General procedure:

To a solution of **8** (0.001 mol) in ethanol (30 ml), sodium acetate (0.0022 mol) and halocompounds (0.0025 mol) was refluxed for 3 h. After cooling the solid product was collected and recrystallized from the proper solvent to give **9a-d**.

9a: Yellow crystals, yield (60%), m.p. 154 °C. IR: ν = 2220 cm^{-1} (CN), 2920 cm^{-1} (CHaliph). ^{1}H-NMR (CF_3CO_2D): δ = 3.2, 3.5 (2s, 6H, $2CH_3$), 4.26, 4.46 (2s, 4H, $2CH_2$). Anal.Calcd for $C_{14}H_{10}N_6S_3$ (358.64): C, 46.91; H, 2.81; N, 23.45, S, 26.83%. Found: C, 46.70; H, 2.72; N, 23.60; S, 27.10%.

9b: Yellow crystals, yield (50%), m.p. 138 °C. IR: ν = 1730 cm^{-1} (CO ester). ^{1}H-NMR (CF_3CO_2D): δ = 1.5 (t, 6H, $2CH_3$), 3.2, 3.5 (2s, $2CH_3$), 4.2 (s, 4H, $2SCH_2$), 4.43 (q, 4H, $2OCH_2$). Anal. Calcd for $C_{18}H_{20}N_4O_4S_3$ (452.56): C, 47.77; H, 4.45; N, 12.83, S, 21.25%. Found: C, 47.70; H, 4.62; N, 12.50; S, 21.50%.

9c: Yellow crystals, yield (50%), m.p. 170 °C. IR: ν = 1680 cm^{-1} (CO). Anal. Calcd for $C_{26}H_{20}N_4O_2S_3$ (516.64): C, 60.44; H, 3.90; N, 10.84; S, 18.62%. Found: C, 60.50; H, 4.12; N, 11.02; S, 18.94%.

7-Amino-8-imino-3,4-dimethylpyrimido[4',5':4,5] thieno[2,3-*c*] pyridazine (10):

A mixture of **7** (0.001 mol)and hydrazine hydrate (0.001 mol) in ethanol (30 ml) was stirred at room temperature for 6 hours. The product obtained was filtered off and recrystallized from dioxan to afford 10 as white crystals in 76% yield, m.p. 262°C. IR: ν = 3300, 3200, 3080 cm^{-1} (NH_2, NH). ^{1}H-NMR (DMSO-d_6): δ = 2.87, 3.4 (2s, 6H, $2CH_3$), 5.5 (s, 2H, NH_2), 7.6 (s, 1H, NH). Anal. Calcd for $C_{10}H_{10}N_6S$ (246.29): C, 48.76; H, 4.09; N, 34.13, S, 13.02%. Found: C, 48.70; H, 4.22; N, 34.31; S, 13.20%.

7-Ethanol-8-imino-3,4-dimethylpyrimido[4',5':4,5]thieno [2,3-*c*] pyridazine (11):

To a solution of **7** (0.001 mol) in ethanol (20 ml), ethanolamine (0.001 mol) was added and the mixture was refluxed for 3 h. After cooling the solid product was collected and recrystallized from methanol to give white crystals in 56% yield, m.p. 250°C. IR: ν = 3320 cm^{-1} (NH), 3450 cm^{-1} (OH). Anal. Calcd for $C_{12}H_{13}N_5OS$ (275.32): C, 52.35; H, 4.76; N, 25.44, S, 11.65%. Found:C, 52.62; H, 4.72; N, 25.70; S, 11.75%.

8-Imino-3,4-dimethyl-7-phenyl-pyrimido[4',5':4,5]thieno [2,3-*c*]pyridazine (12):

A mixture of **7** (0.001 mol) and aniline (2 ml) in ethanol (20 ml) was refluxed for 3 h. The solid product was filtered off and recrystallized from methanol to give white crystals, yield (54%), m.p. 255°C. IR: ν = 3300 cm^{-1} (NH). ^{1}H-NMR (DMSO-d_6): δ = 2.86, 3.3 (2s, 6H, $2CH_3$), 7.2-7.8 (m, 5H, Ar-H), 9.6 (s, 1H, NH). Anal. Calcd for $C_{16}H_{13}N_5S$ (307.38): C, 62.52; H, 4.26; N, 22.78, S, 10.43%. Found: C, 62.70; H, 4.52; N, 22.70; S, 10.50%.

3,4,9-Trimethyl-1,2,4triazolo[1''5''1',6']pyrimido[4',5':4,5] thieno[2,3-*c*]pyridazine (14):

A sample of compound **7** (001 mol) and acetyl acetone (6 ml) was refluxed for 3 h. After cooling the solid product obtained was filtered off and recrystallized from ethanol to give 14 as white crystals in 70% yield, m.p. 320°C. IR: ν = 1610 cm^{-1} (C = N). ^{1}H-NMR (CF_3CO_2D): δ =2.8, 3.2, 3.5 (3s, $3CH_3$), 9.6 (s, 1H, CH pyrimidine). Anal. Calcd for $C_{12}H_{10}N_6S$ (270.31): C, 53.32; H, 3.73; N, 31.09, S, 11.86%. Found: C, 53.63; H, 3.92; N, 31.35; S, 12.01%.

3,4-Dimethyl-1,2,4-triazolo[1''5'':1',6']pyrimido[4',5':4,5] thieno[2,3-*c*]pyridazine (15):

A mixture of **7** (0.001 mol) was refluxed in triethyl orthoformate (5 ml) for 4 h. The solid product obtained after cooling was filtered off and recrystallized from ethanol /DMF to give 15 as grey crystals in 65% yield, m.p. >300°C. IR: ν = 1610 cm^{-1} (C = N) ^{1}H-NMR (DMSO-d_6): δ = 2.85, 3.30 (2s, 6H, $2CH_3$), 7.5 (s, 1H, CH pyrimidine), 9.5 (s, 1H, triazole). Anal. Calcd. for $C_{11}H_8N_6S$ (256.29): C, 51.55; H, 3.15; N, 32.79, S, 12.51%. Found: C, 51.95; H, 3.35; N, 33.09, S, 12.50%.

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