Synthesis, Isomerization, and Antimicrobial Evaluation of Some IndenothienoPyrimidine Derivatives

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Abstract: 9-Hydroindeno[1′,2′:4,5]thieno[2,3-d]pyrimidin-4-ylhydrazine**(2)**was used as a precursor for preparation of some novel 2-substituted [1,2,4] triazolo[1,5,-c]-9H-indeno [1′,2′:4,5]thieno[3,2-e]pyrimidine derivatives **(5,6,8)**and 9H-indeno[1′,2′,:4,5]thieno[3,2-e]tetrazolo [1,5-c] pyrimidine **(10)**. Furthermore, the preparation of N-substituted-9-H-indeno [1′,2′: 4,5]thieno[2,3-d] pyrimidin-4-yl) amine derivatives**(11-14)** were described. Also, thieno[2,3-d] pyrimidin-4-yl-isothiourea derivatives **15** was obtained from reaction of **1** with thiourea. Selected members of the prepared compounds were screened for antimicrobial activity.
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1. Introduction:

Since resistance to antimicrobial drugs is widespread, there is an increasing need for identification of novel structure lead that may be used in designing new, potent and less toxic antimicrobial agents. Many thienopyrimidine derivatives have been found to posses a wide span of medical activities including antimicrobial activity,[1-6] antiviral,[7-10] antihypertensive,[11]antihistaminic,[12] neurotropic,[13] antidepressant, sedative and analgestic activities.[14,15] Previous observations revealed that the [1,2,4] triazolo[4,3-*c*]pyrimidine derivatives can isomerize under different suitable reaction condition to the thermodynamically more stable [1,2,4]triazolo [1,5-c]pyrimidines.[4,5] This isomerization was reported early by Miller and Rose.[16,17] In continuation of our previous work on thienopyrimidines,[2,7,9] we aimed to synthesize[1,2,4]triazolo[4,3-*c*]pyrimidines and [1,2,4] triazolo [1,5-*c*] pyrimidines not only to study their isomerization, but also to obtain new compounds which are expected to possess notable chemical and biological activities.

2. Experimental

Melting points were recorded on an electrothermal IA 9100 digital melting point apparatus. IR spectra (V_{max} in cm^{-1}) were recorded on a Shimadzu FT-IR 8300 spectrophotometer using KBr pellets technique. ^{1}H-NMR and ^{13}C NMR spectra were recorded using Bruker WM-400 spectrophotometer using DMSO-d_6 as the solvent and TMS as the internal reference (chemist shifts in ppm). The mass spectra were run at 70 eV with a finnigan SSQ7000 spectrophotometer (thermo-insturment system incorporation, USA). The above spectra and elemental analyses were measured at the National Research Center.

Synthesis of N-(Phenyl methylene)indeno[1′,2′:4,5] thieno[2,3-d] pyrmidin-4yl] hydrazine (3).

A solution of compound **2** (2.54 g, 0.01 mol) in ethanol (50 mL) was treated with benzaldehyde (1.06 mL, 0.01 mol) and dropwise of pyridine. The reaction mixture was heated for 15 minutes, cooled, filtered, dried and recrystallized from ethanol to give compound **3**. Yield: 45%, M.P. 211-213°C. ^{1}H-NMR δ 4.0 (s, 2H, CH_2), 4.56 (s, 1H, CH aliphatic) 6.9-7.73 (m, 5H, phenyl), 7.12-7.34 (m, 4H, Ar-H+NH, D_2O exchangeable), 8.04 (d, 1H, J=7Hz, Ar-H), 8.65 (s, 1H, C_2-H). Anal. Calcd. For $C_{20}H_{14}N_4S$ (342.42); C, 70.15; H, 4.12; N, 16.36; S, 9.36%. Found, C, 70.29; H, 4.34; N, 16.57; S, 9.66.

Synthesis of 2-Phenyl-9*H*-indeno [1′,2′:4,5] thieno [3,2-e] [1,2,4] triazolo[1,5-c]pyrmidine (5).

A solution of compound **3** (3.42 g, 0.01 mol) was treated with pyridine drop wise in glacial acetic acid (50 ml) were refluxed for 3h. The reaction mixture was cooled, filtered, dried, and recrystallized from dioxane to give compound **5** . Yield: 40%, M.P. 234-236°C. ^{1}H-NMR δ: 4.01 (s, 2H, CH_2), 7.2-7.59 (m, 5H, phenyl-H), 7.69-7.9 (m, 3H, Ar–H), 8.03 (d, 1H, J= 7Hz, Ar–H), 8.13 (s, 1H, C_5–H), MS.: m/z%=340 (M^+, 5), 82 (100), 156 (16.55) 155 (91.52),

152 (2.43), 87 (2.05), 83(9.16) 70(28.31), Anal. Calcd. For $C_{20}H_{12}N_4S$ (340.40); C, 70.57; H, 3.55; N, 16.65; S, 9.53% Found, C, 70.58; H, 3.56; N, 16.67; S, 9.55%.

Synthesis of 2-Amino-9*H*-indeno[1′,2′:4,5]thieno [3,2-e] [1,2,4] triazolo[1,5-c]pyrmidine (6).

Compound **2** (2.54 g, 0.01 mol) was dissolved in (50 mL) glacial acetic acid, then potassium thiocyanate (0.97g , 0.01 mol) was added. The reaction mixture was refluxed for 6h, cooled, filtered, washed with water then ethanol, dried and recrystallized from methanol to give compound 6. Yield: 61%, M.P. 231-233°C IR υ: 3329.78, 3229cm^{-1} (NH_2) ^{1}H-NMR δ: 4 (s, 2H, CH_2), 7.2-7.59 (m, 3H, Ar-H), 8.1 (d, 1H, J=7Hz, Ar-H), 8.77 (s, 1H, C_5-H), 9.8 (br, 2H, NH_2), 14.1 (br, H, NH, D_2O exchangeable) MS: m/z% 280(M^+, 35), 256 (19.61); 240 (25.13), 196(41.56), 44(100). Anal. Calcd for $C_{14}H_9N_5S$ (280.32); C, 60.20; H, 3.25; N, 25.07; S, 11.48%. Found, C, 60.21; H, 3.26; N, 25.09; S, 11.50.

Synthesis of 2-N-[thien-2-yl) methyleneamino-9*H*-indeno[1′,2′:4,5] thieno [3,2-e] [1,2,4] triazolo[1,5-c]pyrmidine (7).

A solution of compound **6** (2.81g, 0.01 mol) and 2-thiophene aldhyde (1.12g., 0.01 mol) and drop wise of pipyridine in ethanol (50 ml) was refluxed for 3h. The reaction mixture was cooled, filtered off, dried, and recrystallized from dioxane to give compound **7**. Yield 56%, MP: 212-214°C. IR υ: 1605.4 (C=N) cm^{-1} , ^{1}H-NMR δ: 4.08 (s, 2H, CH_2), 5.2 (s, 1H, aliphatic CH), 7.04-7.3 (m, 3H, thiophene), 7.29-7.31 (m, 3H, Ar-H), 8 (d, 1H, J= 7Hz, Ar-H), 8.19 (s, 1H, C_5-H), MS: m/z% 373 M^+ 6.35), 334(4.04), 313 (1.88), 256(100). Anal. Calcd for $C_{19}H_{11}N_5S_2$ (373.45); C, 61.11; H, 2.97; N, 18.75; S, 17.17%. Found C, 61.32; H, 3.12; N, 18.76; S, 17.31.

Synthesis of 3-Methyl-9H-indeno [1′,2′: 4,5]thieno [3,2-e][1,2,4]triazolo [1,5-c] pyrimidine (8).

Compound **2** (2.54g, 0.01 mol) was heated under reflux in 50 ml acetic acid for 6 h; then the reaction mixture was cooled, filtered, dried and recrstallized from acetone to give compound **8**. yield 57%, M.P. 243-245°C. IR, υ 1612.2 cm^{-1}(C=N). ^{1}H–NMR δ: 2.62 (s, 3H, CH_3), 4.12 (s, 2H, CH_2), 7.22-7.43 (m, 3H, Ar–H), 8.2 (d, 1H, J=7Hz, Ar–H), 8.6 (s, 1H, C_5–H). MS: m/z%= 278 (M^+, 18.38), 289(41.9), 224 (4.11), 198(1.57). Anal. Calcd for $C_{15}H_{10}N_4S$(278.33); C, 64.73; H, 3.62, N; 20.13; S, 11.52%, Found C, 64.84; H, 3.82; N, 20.34; S, 11.73.

Synthesis of 3-Methyl-9*H*-indeno [1′,2′:4,5]thieno [3,2-e][1,2,4]triazolo [4,3-c]pyrimidine (9).

A solution of compound **2** (2.54g, 0.01 mol) in 20 mL triethyl orthoacetate was heated under reflux temperature for 10 h. The reaction mixture was cooled, filtered, dried and the product was recrystllized from ethanol to give compound **9**.

Isomerization of compound 9 to 8

A solution of compound **9** (2.78g, 0.01 mol) in ethanol (30mL) in the presence of a few drops of piperidine was heated under reflux temperature for 30 min. the solvent removed under reduced pressure leaving a solid product which was recrystallized from ethanol to give a compound identical in all aspects with compound **8**.

Synthesis of 9*H*-Indeno[1′,2′:4,5]thieno[3,2-e] tetrazolo [1,5-c]pyrmidine (10).

A cooled solution of compound **2** (2.54 g, 0.01 mol) in diluted HCl (20 mL) was treated drop wise with a cooled solution of sodium nitrite (prepared from 1g sodium nitrite dissolved in 15 mL water), then stirred at room temperature for 2h. The separated solid was filtered off, dried, and recrystallized from dioxane to give **10**. Yield : 58%, M.P. 211-213°C: IR υ: 1612.2 cm^{-1} (C=N). ^{1}H-NMR δ: 3.97 (s, 2H, CH_2), 7.12-7.6 (m, 3H, Ar–H), 8.4 (d, 1H, J=7 Hz, Ar-H), 9.4 (s, 1H, C_5-H) MS: m/z% 265(M^+, 6.09), 237 (16.54), 236 (17.94), 63 (100). Anal. Calcd. For $C_{13}H_7N_5S$ (265.29); C, 58.86; H, 2.66; N, 26.4; S, 12.09%. Found : C, 58.87; H, 2.67; N, 26.5; S, 12.11.

Synthesis of 4-N-Substituted (indeno[1′,2′:4,5] thieno[2,3-d] pyrimidine 11-14: General procedure

To a solution of compound **1** (2.58g., 0.01 mol) in ethanol (30 mL), aniline, phenyl hydrazine, aminoacetic acid or ethanol amine (0.01 mol) was added respectively. The reaction mixture was heated for 2-6h. then the formed precipitate was filtered off and recrystallized from ethanol to give compounds **11-14**.

Phenyl (9H-Indeno[1′,2′:4,5]thieno[2,3-d] pyrimidin- 4-yl) amine (11).

Yield after 2h: 81%, M.P. 209-211°C. IR υ: 3438 (NH) cm^{-1}. ^{1}H-NMR δ: 4.1 (s, 2H, CH_2), 7.06-7.17 (m, 5H, phenyl), 7.25-7.83 (m, 3H, Ar–H), 7.85 (d, 1H, J=7Hz, Ar–H), 8.56 (s, 1H, C_2-H) 9.41 (br, 1H, NH, D_2O exchangeable) MS: m/z% 315 (M^+, 12.53), 258 (100), 224 (15.43). Anal. Calcd for $C_{19}H_{13}N_3S$ (315.39); C, 72.36; H, 4.15; N, 13.32; S, 10.17%. Found: C, 72.38; H, 4.17; N, 13.33; S, 10.19.

N-Phenyl-N\'-(9H-indeno[1′,2′:4,5]thieno[2,3-d] pyrimidin-4-yl)hydrazine (12).

Yield after 2h: 83%, M.P. 205-207°C. ^{1}H NMR δ: 3.64 (s, 2H, CH_2), 6.82-6.94 (m, 5H, phenyl), 7.20-7.26 (m, 3H, Ar–H), 7.8 (d, 1H, J = 7Hz, Ar–H), 7.9 (s, 1H, C_2–H), 8.2 (br, 1H-NHNHPh) , 9.42 (br, 1H, NHNHPh), and NH, D_2O exchangeable. Anal Calcd for $C_{19}H_{14}N_4S$ (330.41); C, 69.07; H, 4.27; N, 16.96; S, 9.70. Found, C, 69.10; H, 4.29; N, 16.98, S, 9.72.

N-(9H-Indeno[1′,2′:4,5]thieno[2,3-d]pyrimidin-4-yl) amino acetic acid(13).

Yield after 6h: 51%, M.P. 214-216°C. IR: υ 1713.12 cm^{-1} (C=O), 3443.18 broad (NH, OH). MS: m/z 297.33, (M^+, 20%) 280 (6.7), 225(1.44), 142 (12.100). Anal calad. For $C_{15}H_{11}N_3O_2S$ (297.33); C, 60.59; H, 3.73; N, 14.13 ; S, 10.78%. Found, C 60.60; H, 3.74; N, 14.14; S, 10.80.

2-(9H-Indeno[1′,2′:4,5]thieno[2,3,-d]pyrimidin-4-yl amino)-4-ethanol (14)

Yield after 3h: 86%, M.P. 207-209°C. ^{1}H-NMR δ: 3.66 (t, 2H, J = 8.0, $CH_2\underline{CH_2}OH$), 3.73 (t, 2H, J = 8.0, $CH_2\underline{CH_2}OH$), 4.0 (s, 2H, CH_2), 5.0 (s, 1H, OH, D_2O exchangeable), 6.78 (br, 1H, NH, D_2O exchangeable), 7.26-7.85 (m, 3H, Ar-H), 7.93 (s, 1H, J=7 Hz, Ar–H), 8.39 (s, 1H, C_2H).^{13}C NMR δ: 37(1C, indeno C), 44.06 (1C, aliphatic NH$\underline{C}$), 60.27 (1C, aliphatic $\underline{C}H_2O$) 115-125.7 (6C, phenyl), 121-127 (6C, Ar–C), 141.8-146.99 (4C, thiophene), 153.3 (1C, C_2 pyrimidine), 157.97 (1C, pyrimidine $\underline{C}$NHNH) Anal. Calcd. For $C_{15}H_{13}N_3OS$ (283.25); C, 63.58; H, 4.62; N, 14.83; S, 11.32%. Found, C, 63.59; H, 4.64; N, 14.84; S, 11.34.

Synthesis of 2-(9H-Indeno[1′,2′:4,5]thieno[2,3-d] pyrimidin-4-yl) isothiourea (15).

A mixture of compound **1** (2.58g, 0.01 mol), thiourea (0.76g, 0.01), sodium hydroxide (0.4g, 0.01 mol) in 30 ml ethanol was stirred at room temperature for 4h. The reaction mixture was filtered dried and recrystallized from methanol to give compound **15**. yield 82%, M.P. 204-206°C. ^{1}H NMR δ: 4.13 (s, 2H, CH_2), 7.29 (br, 2H, NH_2, S_2O exchangeable), 7.34-7.83 (m, 3H, Ar-H), 8.1 (s, 1H, J = 7 Hz, Ar-H), 8.8 (s, 1H, C_2-H) 10.8 (br, 1H, NH, D_2O exchangeable). Anal. Calcd for $C_{14}H_{10}N_4S_2$ (298.39); C, 56.35; H, 3.38; N, 18.78; S, 21.49%. Found C, 56.36; H, H 3.39; N, 18.79; S, 21.51.

Agar Diffusion Medium:

A suspension of the organisms were added to sterile nutrient agar media at 45 °C and the mixture was transferred to sterile petri dishes and allowed to solidify. Holes of 10 mm in diameter were made using a cork borer.) An amount of 0.l ml of the synthesized compounds was poured inside the holes. A hole filled with DMSO was also used as control. The plates were left for 1 hour at room temperature as a period of pre-incubation diffusion to minimize the effects to variation in time between the applications of the different solutions. The plates were then incubated at 37°C for 24 hours and observed for antibacterial activity. The diameters of zone of inhibition were measured and compared with that of the standard, the values were tabulated. Ciprofloxacin (50 µg/ml) and Ketoconazole (50 µg/ml) were used as standard for antibacterial and antifungal activity respectively. The observed zone of inhibition is presented in Table (1).

Minimum Inhibitory Concentration:

Minimum Inhibitory Concentration (MIC) of the tested compounds were determined by agar streak dilution method. 68mg/ml stock solution of the synthesized compounds were made using DMSO as the solvent. From this stock solution, the following concentrations (0.17; 0.34; 0.68; 0.85 and 1.7 mg/ml) of the solutions of the tested compounds were mixed with the known quantities of molten sterile agar media aseptically. About 20 ml of the media containing the tested compound was dispensed into each sterile Petri dish. Then the media were allowed to get solidified. Microorganisms were then streaked one by one on the agar plates aseptically. After streaking alphe-plates were incubated at) 37°C for 24 h/48 h. for bacterial and fungus activity respectively. Then the plates were observed for the growth of microorganisms. The lowest concentration of the synthesized compounds inhibiting the growth of the given bacteria/fungus was considered as minimum inhibitory concentration (MIC) of the test compounds against that bacteria or fungi on the plate is presented in Table (2).

3. Results and Discussion

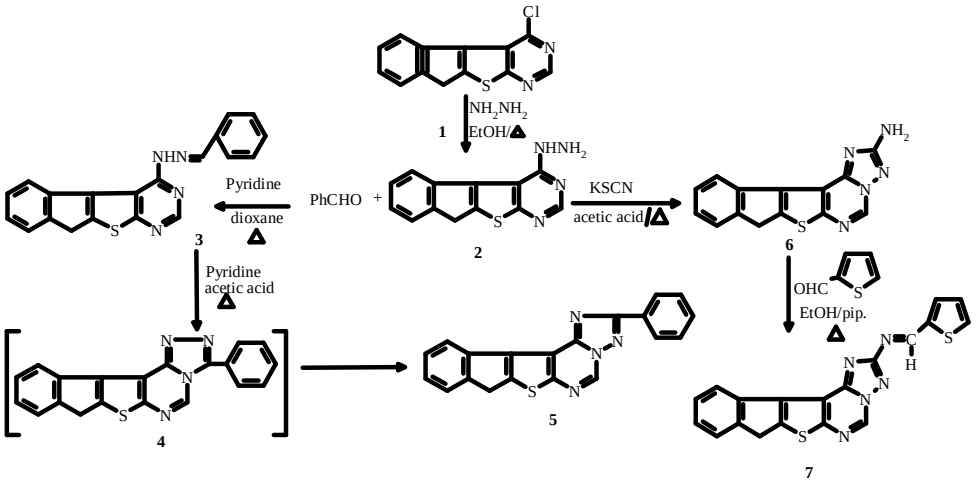
Chemistry

Indeno[1',2':4,5]thieno[2,3-d]pyrimidin-4-yl hydrazine **(2)**, as key compound for this study and for further syntheses of other fused heterocyclic compounds, was previously synthesized by Hegab *et al.*[(5)]. Through the reaction of 4-chloroindeno [1',2':4,5] thieno[2,3-d]pyrmidine **(1)** with hydrazine hydrate in ethanol under reflux temperature. Condensation of hydrazino derivative **2** with benzaldehyde in the presence of few drops of pyridine took place by heating under reflux in ethanol where the corresponding hydrazone **3** was produced. Attempts to cyclize the latter compound to its corresponding 2-phenyl [1,2,4] triazolo[1, 5-c] pyrimidine derivative **5** by refluxing with pyridine in glacial acetic acid took place presumably via the isomerization of intermediate [1,2,4] triazolo[4,3-*c*]

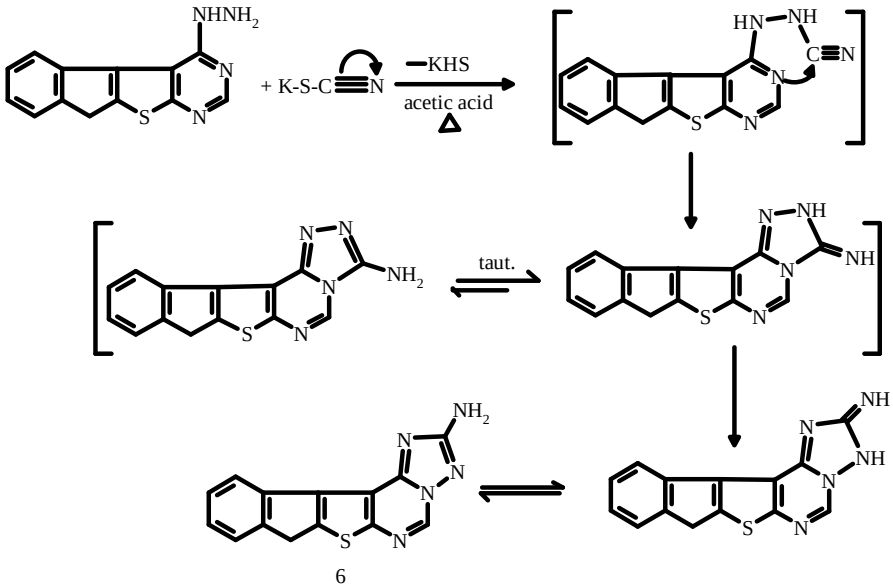
pyrimidine **4** according to dimroth-type rearrangement.[18] The structures of compounds **3** & **5** (Scheme 1) were confirmed on the basis of their elemental and spectral data. The ^{1}H NMR spectrum of product **5** showed the absence of the signals for N=CHPh and NH protons which appeared in the spectrum **3** at δ 4.56 & 7.12 ppm, respectively. Moreover, the C_5-H proton of product **5** which appeared at δ 8.13 favors its structure over structure **4** since the C_5-H proton of **4** is more deshilded and would have appeared at a higher value.

4-Hydrazino derivative **2** reacted with potassium thiocyanate in boiling acetic acid to give 2-aminoindeno[1',2':4,5]thieno[3,2-e] triazolo[1,5-c] pyrimidine **(6)** (scheme 1). The reaction may be accomplished via the intermediates as shown in the considered mechanism (Scheme 2).

Meanwhile, condensation of 2-amino derivatives **(6)** with thiophene-2-aldhyde in the presence of few drops of piperidine in ethanol gave the corresponding schiff's base **(7)** (Scheme 1), the spectral data of compounds **6** & **7** are in agreement with assigned structures. Their IR spectra showed the absence of the presences of absorption band for NH_2 group at 3329 & 3229cm^{-1} and presence of aliphatic CH signal at δ 5.2 ppm in their ^{1}H-NMR spectrum of compound **7**.



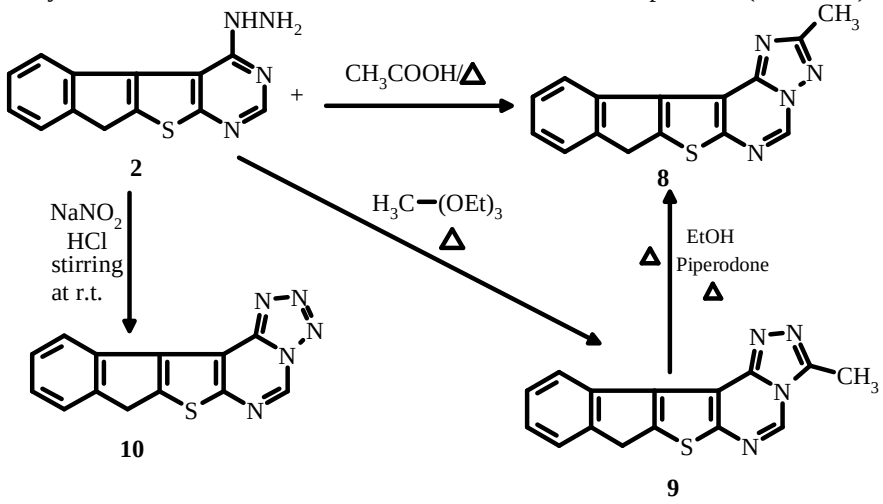
Scheme (1)



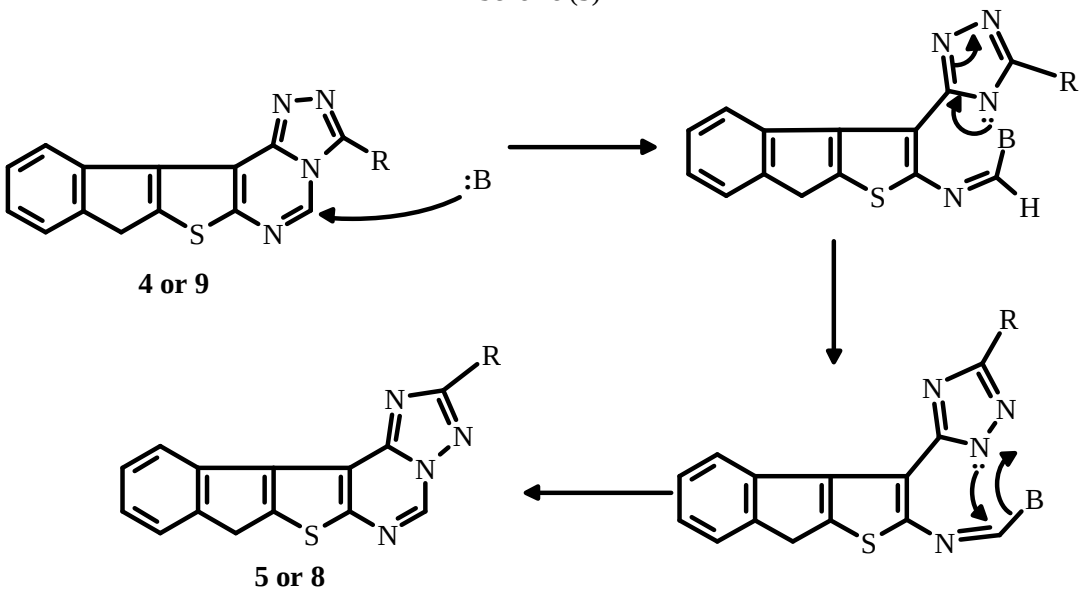
Scheme (2)

Many reports[4,19] have described the synthesis of [l,2,4]triazolo[4,3-c]pyrimidine derivatives and [l,2,4]triazolo[l,5-c]pyrimidine fused to different nitrogen containing heterocyclic moieties. In the meantime, the synthesis of [l,2,4]triazolo[4,3-c]pyrimidine derivatives and [l,2,4] triazolo[l,5-c]pyrimidine derivatives fused to a thiophene moiety have attracted the attention of many investigators.[20-23] Actually, previous observations revealed that thieno[2,3-e] [l,2,4] triazolo [4,3-c]pyrimidines can isomerize under different suitable reaction conditions to the more stable thieno[3,2-e][l,2,4]triazolo[l,5-clpyrimidines[4,5]. Nevertheless, this pattern of isomerization appears to have been overlooked by some workers[21,24].

In this investigation, when compound **2** was heated under reflux temperature in acetic acid, it afforded[1,2,4]triazolo[1,5-c]pyrimidine derivative **(8)** probably via the intermediacy of its isomer[1,2,4]triazolo[4,3-*c*] pyrimidine (**9)** which was not isolated in this reaction, but underwent a Dimroth-type rearrangement[18] under the conditions of the reaction. Compound **9** was reported previously by Hegab *et al.*[4] through the reaction of compound **2** with triethyl orthoacetate under reflux temperature, it afforded [1,2,4]triazolo[4,3-*c*]pyrimidine **(9)** which was converted into the more stable its isomer **(8)** by heating in ethanolic piperidine which presmably involves a sequence of ring opening and ring closure reactions as depicted in (Scheme 4).



Scheme (3)

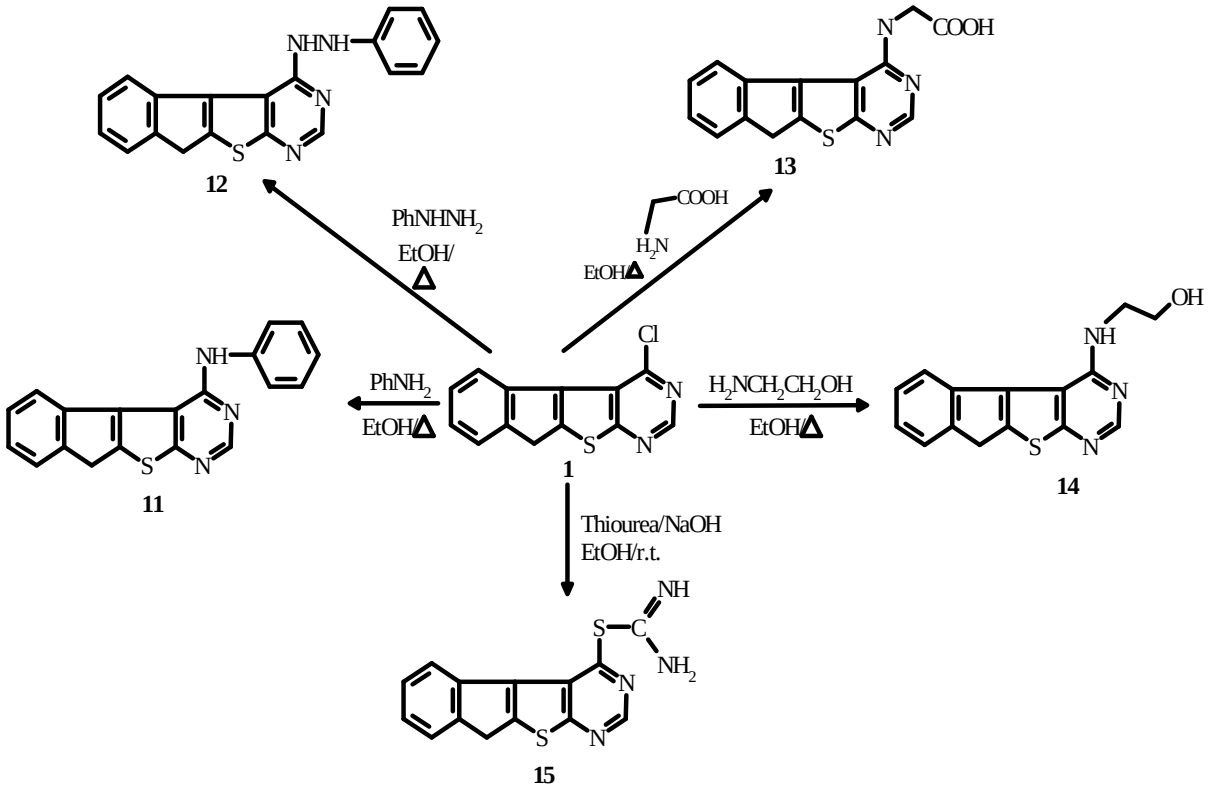


Scheme (4). Rearrangement of compounds **4** and **9** to **5** or **8**

Heterocyclic azides, especially azidomethines, can exist in equilibrium with their tetrazolo tautomers and this equilibrium affected by many factors: pH, temperature, the nature of the substituents around the (C=N) and the used solvent.[25,26] This equilibrium can be shifted in either direction by controlling these factors, and the IR spectroscopy is helpful in revealing which form is predominant, since the azido structure can show a characteristic band in the region υ2220-2320cm^{-1}. Thus, nitrosation of the hydrazino group of compound **2** afforded indeno[1',2':4,5] thieno [3,2-e] tetrazolo [1,5-*c*] pyrimidine **(10).** Analytical and spectral data are in agreement with the proposed structure, IR spectrum did not show absorption frequency indicative for the azido group (cf. Exp.).

Also, the reactivity of chloropyrimidine **1**[5] towards N-nucleophiles, namely, aniline, phenyl hydrazine, ethanol amine in absolute ethanol was investigated which yielded the respective substituted amine derivatives **11-14**. (Scheme 5). The structures of the latter compounds were confirmed on the basis of their elemental analysis and spectral data. The IR spectra of the compounds showed absorption bands characteristic for NH group and ^{1}H-NMR spectrum of compound **14** as an example, revealed signals at δ: 3.66 (t, 2H, J = 8.0 Hz, $\underline{CH_2}CH_2OH$), 3.73 (t, 2H, J = 8.0 Hz, $CH_2\underline{CH_2}OH$), 4.0 (s, 2H, CH_2), 5.0 (s, 1H, OH, D_2O exchangeable), 6.78 (br, 1H, NH, D_2O exchangeable), 7.26-7.85 (m, 3H, Ar-H), 7.93 (d, 1H, J = 7 Hz, Ar-H), 8.39 (s, 1H, C_2-H) ^{13}C NMR δ: 37 (1C, indeno CH_2), 44.06 (1C, aliphatic NHC), 60.27 (1C, aliphatic CH_2O), 115-125.7 (6C, phenyl), 121-127 (6C, Ar-C), 141.8-146.99 (4C, thiophene), 153.3 (1C, C_2 pyrimidine), 157.97 (1C, pyrimidine $\underline{C}$NHNH).

On the other hand, when a mixture of compound **1**, thiourea and sodium hydroxide in ethanol was stirred at room temperature[5], it gave isothiourean-4-yl indeno [1',2' : 4,5] thieno[2,3-d]pyrimidine **(15)** (scheme 5)



Scheme (5)

Antimicrobial activity:

The antibacterial activity of the synthesized compounds was tested against *Escherichia coli* NRRL B-210 (Gram -ve bacteria), *Bacillus subtilis* NRRL B-543 (Gram +ve bacteria), *Staphylococcus aureus* NRRL B-313 using nutrient agar medium. The antifiingal activity of the compounds was tested against *Candida albicans* NRRL Y-477 using Sabouraud dextrose agar medium. The results are summarized in Table 1 & 2.

Table (1): Inhibition zone in mm as a criterion of antibacterial and antifungal activities of the newly synthesized compounds

Compound No.	Minimum inhibitory concentration in mg/ml			
	Gram positive bacterial		Gram negative bacteria	Fungi
	Bacllus subtilis	*Staphyococcus aureus*	*Escherichia coli*	*Candida albicans*
2	25	22	22	22
3	23	22	21	23
5	18	21	22	22
6	13	-ve	-ve	-ve
7	17	23	13	-ve
8	23	21	23	25
10	22	23	16	25
11	13	17	-ve	12
12	17	18	-ve	17
13	25	25	25	25
14	12	20	21	-ve
15	25	25	25	25
Reference drugs				
Ciprofloxaxine (µg/ml)	23	23	25	-ve
Ketaconazole(µg/ml)	-ve	-ve	-ve	23

Table (2): MIC in mg/ml of the newly synthesized compounds

Compound No.	Minimum inhibitory concentration in mg/ml			
	Gram positive bacterial		Gram negative bacteria	Fungi
	Bacllus subtilis	*Staphyococcus aureus*	*Escherichia coli*	*Candida albicans*
2	1.25	0.625	0.625	
3	0.625	0.625	0.625	
5	0.625	0.625	0.625	
6	0.625	0.625	0.625	
7	1.25	1.25	1.25	
12	1.25	1.25	1.25	
14	1.25	1.25	1.25	
Reference drugs				
Ciprofloxaxine (µg/ml)	0.12	0.15	0.01	--
Ketaconazole(µg/ml)	--	--	--	0.03

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