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Research Article

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Synthesis and Characterization of New S-substituted Sulfanypyridines, 3-Aminothieno[2,3-b] Pyridines and 3-(1H-pyrrol-1-yl) Thieno[2,3-b] Pyridines and Related Heterocycles

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ABSTRACT

Abstract Reaction of ethyl (3-cyano-5-ethoxycarbonyl-6-methyl-4-styryl-2-pyridylsulfanyl)acetate with hydrazine hydrate gave a mixture of the corresponding acetohydrazide and diethyl 3-amino-6-methyl-4-styrylthieno [2,3-b] pyridine-2,5-dicarboxylate. The latter compound was reacted with 2,5-dimethoxytetrahydrofuran to give 3-(1H-pyrrol-1-yl)thieno [2,3-b] pyridine. Patially hydrazinolysis of resulted in the formation of 5-ethoxycarbonyl-6-methyl-3-(1H-pyrrol-1-yl)-4-styrylthieno [2,3-b] pyridine-2-carbohydrazide. The acetohydrazide and carbohydrazide 10 were used as precursors for the title compounds by subjecting them to some sequental reactions with different reagents. All new compounds were characterized on the basis of their elemental analyses and spectroscopic data.

Keywords: Acetohydrazide; carbohydrazide; Pyridine; Gonaodotropin; Hetereocyclic

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INTRODUCTION

Pyridine and its derivatives abundantly exist in nature and became interesting targets in 1930 with the importance of niacin for the treatment of dermatitis and dementia. Some pyridines have been reported to exhibit good biological activities and medicinal applications, and numbers of them are in clinical uses. Many thieno [2,3-*b*]pyridines have been synthesized and reported to show versatile biological and pharmacological applications. Some of them proved to possess antiviral, anti-diabetic, antimicrobial, anti-inflammatory, antitumor, anticancer, antiparasitic and neurotropic activities, others are useful as sedatives, gonaodotropin releasing hormone antagonists, anticoagulants, anti-artherosselerotics and as analgesics. In view of the aforementioned facts and as a continuation of our programm towards synthesis of new hetereocyclic compounds with expected biological and medicinal applications, this work was planned to snthesize and explore the synthetic utility of both (3-cyano-5-ethoxycarbonyl-6-methyl-4-styryl-2-

pyridylsulfanyl) acethydrazide and 5-ethoxycarbonyl-6-methyl-3-(1*H*-pyrrol-1-yl)-4-styrylthieno [2,3-*b*]pyridine-2-carbohydrazide hoping to get new compounds with potential pharmacological and biological applications [1].

MATERIALS AND METHODS

The starting compound, ethyl 3-cyano-1,2-dihydro-6-methyl-4-styryl-2-thioxopyridine-5-carboxylate (1) was prepared according to our previous method (Figure 1). Reaction of 1 with ethyl chloroacetate by refluxing in ethanol containing slightly excess amounts of sodium acetate for 30 mins. produced the expected ester, ethyl (3-cyano-5-ethoxycarbonyl-6-methyl-4-styryl-2-pyridylsulfanyl)acetate (2). When the above reaction was repeated again with increasing the reaction time to 3 hours, the product was identified as diethyl 3-amino-6-methyl-4-styrylthieno[2,3-*b*]pyridine-2,5-dicarboxylate (3). However, cyclization of 2 to 3 was achieved by heating in ethanol containing a catalytic quantity of sodium acetate for 2.5 hours (Figure 1).

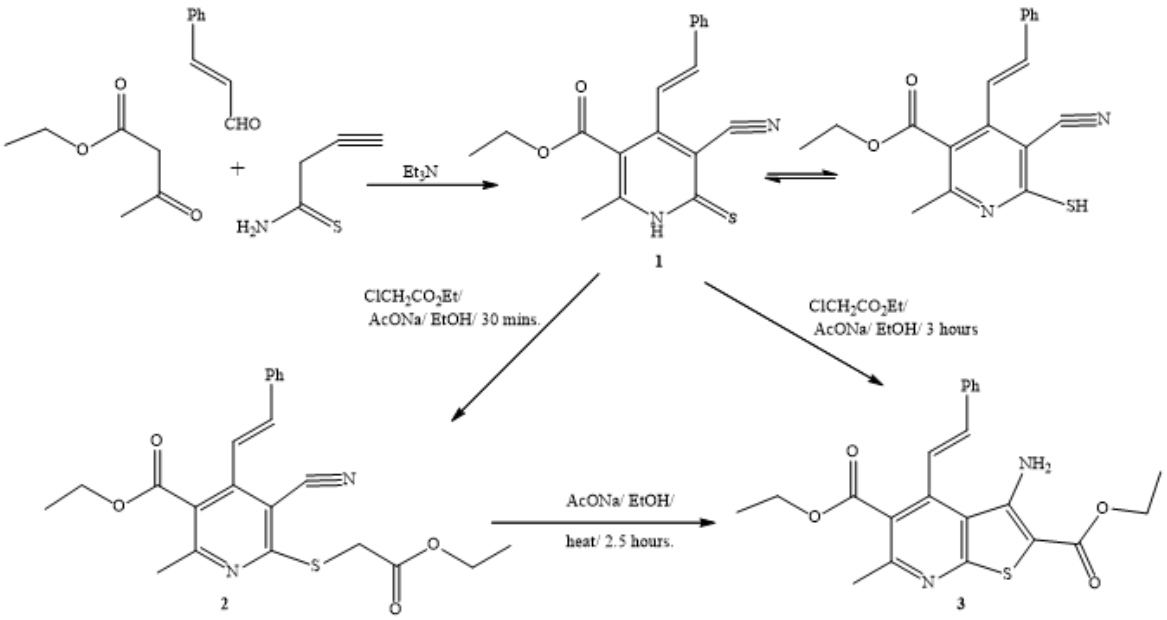

Figure 1: The physical properties of compounds and are in agreement with those reported before.

IR spectrum of showed characteristic absorption bands at 2219 for (C≡N), at 1748 for (C=O, non conjugated ester) and at 1724 for (C=O, conjugated ester). ^{1}H NMR spectrum (DMSO-d_6) displayed a multiplet at δ 6.60-7.63 (7H: CH=CH and Ar-H's), a multiplet at δ 4.16-4.37 (6H: two OCH_2 and SCH_2), a singlet at δ 2.52 (3H, CH_3 at C-6, overlapped with solvent signal) and a multiplet at δ 1.21-1.27 (6H: two CH_3 of ester groups).

Heating an ethanolic solution of the ester with hydrazine hydrate furnished a mixture of (3-cyano-5-ethoxycarbonyl-6-methyl-4-styryl-2-pyridylsulfanyl)aceto- hydrazide and diethyl 3-amino-6-methyl-4-styrylthieno[2,3-*b*]pyridine-2,5-dicarboxylate.

IR spectrum of 4 showed characteristic absorption bands at 3321, 3210, 3105 for ($NHNH_2$), 3027 for (C-H, aromatic), 2986 for (C-H, aliphatic), 2218 for (C≡N), 1717 for (C=O) and 1651 for (C=O, hydrazide).

^{1}H NMR spectrum of 4 ($CDCl_3$) displayed a singlet at δ 7.92 (1H, NH), a multiplet at δ 7.09-7.52 (7H: CH=CH and Ar-H's), a quartet at δ 4.36-4.41 (2H, OCH_2), a singlet at δ 3.91 (2H, SCH_2), a broad singlet at δ 3.89 (2H, NH_2), a singlet at δ 2.61 (3H, CH_3 at C-6) and a triplet at δ 1.30-1.34 (3H, CH_3 of ester).

^{13}C NMR and Dept 135 spectra of ($CDCl_3$) showed the following peaks: δ 169.90, 167.21, 161.90, 158.89, 148.01, 140.54 (CH), 135.14, 129.72 (CH), 128.93 (CH), 127.42 (CH), 126.70, 124.50, 120.35 (CH), 114.42, 102.95, 62.14 (OCH_2), 31.97 (SCH_2), 23.37 (CH_3 at C-6), 14.14 CH_3 of ester group) which are in agreement with its structure.

Reaction of acetohydrazide with phenyl iso-thiocyanate gave the corresponding thiosemicarbazide derivative. Condensation of acetohydrazide with some aromatic aldehydes or thiophene-2-carboxaldehyde afforded N'-arylidene or (2-thienyl-methylene) (3-cyano-5-ethoxycarbonyl-6-methyl-4-styryl-2-pyridylsulfanyl) aceto-hydrazides 6a-d. Cyclization of 6a-d into the corresponding 3-amino-*N'-(*arylidene or heteroarylidene)-5-ethoxycarbonyl-6-methyl-4-styrylthieno [2,3-*b*]pyridine-2-carbo-hydrazides 7a-d was achieived by heating in ethanol containing catalytic amounts of sodium ethoxide. Treatment of 7a-d with triethyl orthoformate in the presence of acetic anhydride produced 3- arylidene or (2-thienyl-methylene)aminopyridothienopyrimidine-4 (3*H*)-ones 8a-d in high yield [2].

RESULTS AND DISCUSSION

IR spectrum of 5 exhibited three absorption bands in the region 3280 to 3200 characteristic for (NH) groups. Its HNMR spectrum showed three singlet signals at δ values 9.80, 9.19 and 8.40 which equivalent to three (NH) groups beside the other signals. IR spectra of 6a-d showed characteristic absorption bands in the regions 3190 to 3208 for (NH), 2221 to 2224 for (C≡N), 1719 to 1725 for (C=O, ester) and 1655 to 1679 for (C=O, acetohydrazide). Their H NMR spectra showed a singlet at δ value ranged from 10.12 to 11.48 corresponds to (NH) group and a singlet signal at δ value ranged from 4.15 to 4.57 equivalent to SCH_2 group. IR spectra of compounds 7a-d showed characteristic absorption bands in the regions 3450 to 3461, 3303 to 3311, 3215 to 3132 for (NH_2) and (NH) groups, 1716 to 1724 for (C=O, ester) and 1628 to 1640 for (C=O, carbohydrazide). Their ^{1}HNMR spectra exhibited a singlet signal at δ value ranged from 9.51 to 10.85 corresponds to (NH) group and a singlet signal at δ value ranged from 6.74 to 6.93 equivalent to NH_2 group. IR spectra of compounds 8a-d showed characteristic absorption bands in the regions 1705 to 1670 for (C=O, ester) and 1670 to 1687 for (C=O, pyrimidinone). Their H NMR spectra exhibited a singlet at δ value ranged from 9.26 to 9.63 corresponds to (CH) of pyrimidinone moiety. C NMR and Dept 135 spectral data of 6a and 6c and 7b are in accordance with their structures.

Incorporating the pyrrole nucleus into thieno[2,3-*b*]pyridine framework was achieved by reacting compound with 2,5-dimethoxytetrahydrofuran, wherein the pyrrolyl derivative was obtained. Heating compound with hydrazine hydrate in ethanol for two hours resulted in partial hydrazinolysis and formation of 5-ethoxycarbonyl-6-methyl-3-(1*H*-pyrrol-1-yl)-4-styrylthieno [2,3-*b*] pyridine-2-carbohydrazide in high yield. Condensation of carbohydrazide 10 with some aromatic aldehydes by refluxing in ethanol yielded N'-arylidene-5-ethoxycarbonyl-6-methyl-3-(1*H*-pyrrol-1-yl)-4-styryl-thieno [2,3-*b*] pyridine-2-carbohydrazides 11a-c. Diazotisation of carbohydrazide 10 led to the formation of 5-ethoxycarbonyl-6-methyl-3-(1*H*-pyrrol-1-yl)-4-styrylthieno[2,3-*b*]pyridine-2-carbonylazide (12) (Figure 2) [3].

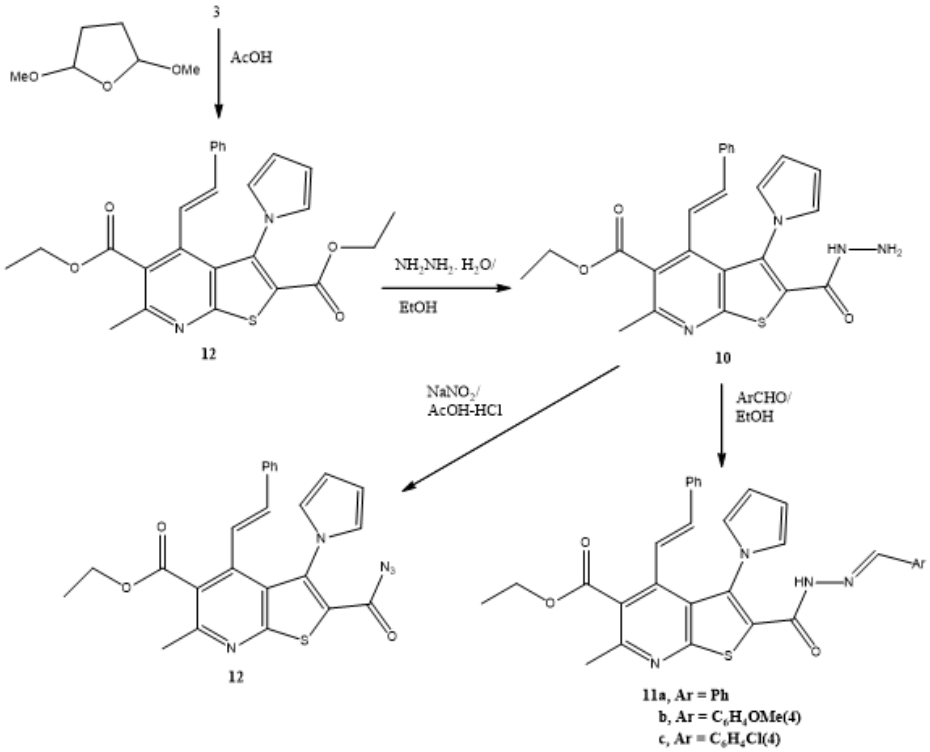

Figure 2: Diazotisation of carbohydrazide 10 led to the formation of 5-ethoxycarbonyl-6-methyl-3-(1H-pyrrol-1-yl)-4-styrylthieno[2,3-b]pyridine-2-carbonylazide

IR spectrum of revealed the disappearance of ν_{NH2}. Its ^{1}H NMR spectrum showed a doublet at δ value ranged from 6.94 to 6.95 for 2CH (pyrrole) and a doublet signal at δ value 6.22 for 2CH (pyrrole). IR spectrum of compound 10 showed absorption bands at 3418, 3334, 3278 for ($NHNH_2$), 1723 for (C=O, ester group attached to pyridine ring) and 1657 for (C=O, carbohydrazide). Its HNMR spectrum showed a singlet at δ 8.06 (NH) and a singlet signal at δ 4.53 (s, 2H, NH_2). IR spectra of compounds 11a-c showed an absorption band in the regions 3290 to 3299 for (NH), 1716-1724 for (C=O, ester) and 1664-1673 for (C=O, carbohydrazide). IR spectrum of compound 12 showed absorption bands at 2142 for (N_3), 1724 for (C=O, ester) and 1691 for (C=O, carbonylazide). MS of compounds 9, 10 and 11b are in agreement with their structures.

Heating carbonylazide 12 in ethanol at reflux temperature for two hours provided a mixture of the corresponding carbamate 14 and the fused pyrazinone 15. This reaction may proceed via Curtius rearrangement of the carbonylazide 13 affording the reactive isocyanate intermediate 13 which underwent *in situ* either reaction with ethanol giving the carbamate 14 or an intramolecular cycloaddition reaction affording pyrazinone 15 respectively. In contrast, heating carbonylazide 12 in an inert solvent such as toluene furnished pyrazinone 15 as a sole product.

IR spectrum of 14 showed absorption bands at 3411 (NH), 1728 for (C=O, ester) and 1669 for (C=O, carbamate). IR spectrum of 15 showed absorption bands at 3243 for (NH), 1719 for (C=O, ester) and 1644 for (C=O, pyrazinone). H NMR spectra of compounds 14 and 15 are in accordance with their structures.

"It is noteworthy that the double bond of the styryl group (2-phenylethenyl group) of all prepared compounds possesses *E*-configuration since we start with *E*-cinnimaldehyde and all entire sequence of reactions took place far away from this double bond. This fact was further suported *via* our previous publication in which the crystal structure of compound 3 was studied and proved the *E*-configuration of the styryl group"

(3-cyano-5-ethoxycarbonyl-6-methyl-4-styryl-2-pyridylsulfanyl)acetohydrazide and 5-ethoxycarbonyl-6-methyl-3-(1*H*-pyrrol-1-yl)-4-styrylthieno[2,3-*b*]pyridine-2-carbo-hydrazide have been synthesized and succefuly used as precursors for synthesizing of other new *S*-substituted sulfanylpyridines, thienopyridines, pyrrolylthienopyridines and pyridothienopyrimidines as well as pyridolthienopyrrolopyrazinone. Full characterization of all these compounds is reported. The new synthesized compounds are interesting for their potential pharmacological and biological applications owing to their incorporation of additional pharmacophores.

Melting points were determined on a Gallan-Kamp apparatus and are uncorrected. The IR spectra were recorded on a Shimadzu 470 IR-spectrophotometer (KBr; ν_{max} in cm^{-1}). The ^{1}H NMR spectra were recorded on a Bruker 400 MHz spectrometer using $CDCl_3$ or DMSO-d_6 as a solvent and tetramethylsilane (TMS) as internal reference. ^{13}C NMR and Dept 135 spectra were recorded on on a Bruker 100 MHz spectrometer using $CDCl_3$ or DMSO-d_6 as a solvent and tetramethylsilane (TMS) as internal reference. Coupling constants (J values) are given in hertz(Hz). Elemental analyses were performed on Perkin Elmer 2400 LS Series CHN/O analyzer. MS analyses were performed on a Thermo Scientific single quadrupole mass spectrometer Model: ISQ 7000.

A mixture of 1 (6.48 g, 20 mmol), ethyl chloroacetate (2.2 ml, 20 mmol) and sodium acetate trihydrate (3.0 g, 22 mmol) in ethanol (70 ml) was refluxed for 30 mins. The solid that formed after dilution with water (30 ml) was filtered off and crystallized from methanol as fine colorless crystals of 2. Yield: 7.00 g (85%); m. p.: 70-71 °C. Anal. Calcd. For $C_{22}H_{22}N_2O_4S$ (410.13): C, 64.37; H, 5.40; N, 6.82%. Found: C, 64.12; H, 5.34; N, 6.91%.

A mixture of 2 (2.05 g, 5 mmol) and sodium acetate trihydrate (0.14 g, 1 mmol) in ethanol (25 ml) was heated under reflux for for 2.5 hours. The product that formed after cooling was filtered off, washed with water and crystallized from ethanol to give compound 3; yield: 1.90 g (93%); m. p.: 116-117 °C (Lit. 116-117 °C) [4].

A mixture of **1** (3.24 g, 10 mmol), ethyl chloroacetate (1.1 ml, 10 mmol) and sodium acetate trihydrate (1.50 g, 11 mmol) in ethanol (25 ml) was refluxed for 3 hours. The product that obtained upon recrystallization was identical to that described above in all aspects.

A mixture of ester 2 (4.10 g, 10 mmol) and hydrazine hydrate (0.5 ml, 10 mmol) in ethanol (40 ml) was refluxed for 10 mins. The white sold which formed while hot was filtered off and crystallized from dioxane as white needles. This product was assigned as (3-cyano-5-ethoxycarbonyl-6-methyl-4-styryl-2-pyridylsulfanyl)acet-hydrazide (4). Yield: 1.10 g (28 %); m. p.: 222-223°C. Anal. Calcd. For $C_{20}H_{20}N_4O_3S$ (396.13): C, 60.59; H, 5.08; N, 14.13%. Found: C, 60.84; H, 5.11; N, 14.00%.

The filtrate of the above crude product was allowed to cool whereby a yellow fine needles formed. It was filtered off and recrystallized from ethanol. This compound was identified as diethyl 3-amino-6-methyl-4-styrylthieno[2,3-*b*]pyridine-2,5-dicarboxylate (**3)**. Yield: 2.05 g (50%).

A mixture of **4** (1.98 g, 5 mmol) and phenyl *iso*-thiocyanate (0.70 ml) in ethanol (30 ml) was refluxed for one hour. The white product was filtered off and crystallized from dioxane to give needle crystals of **5**. Yield: 2.13 g (80%); m. p.: 287-288 °C. IR (cm^{-1}): 3280, 3143 (3 NH), 3002 (CH, aromatic), 2224 (C≡N), 1719 (C=O, ester), 1678 (C=O, amide). ^{1}H NMR (DMSO-d_6): δ 9.80 (s, 1H, NH), 9.19 (s, 1H, NH), 8.40 (s, 1H, NH), 7.10-8.10 (m, 12H: CH=CH and Ar-H's), 4.36 (q, 2H, OCH_2), 4.13 (s, 2H, SCH_2), 2.58 (s, 3H, CH_3 at C-6), 1.30-1.33 (t, 3H, CH_3 of ester). Anal. Calcd. For $C_{27}H_{25}N_5O_3S_2$ (531.14): C, 61.00; H, 4.74; N, 13.17 %. Found: C, 61.35; H, 4.78; N, 13.04 %.

A mixture of acetohydrazide **4** (3.96 g, 10 mmol) and the appropirate aldehyde (11 mmol) in ethanol (40 ml) was refluxed for 3 h. The precipitated product was filtered off and recrystallized from dioxane to give white crystals of **6a-d**.

It was obtained from **4** and benzaldehyde. Yield: 4.11 g (85%); m. p.: 161-162 °C. IR (cm^{-1}): 3192 (NH), 3002 (CH, aromatic), 2877 (CH, aliphatic), 2222 (C≡N), 1724 (C=O, ester), 1659 (C=O, hydrazide). ^{1}H NMR ($CDCl_3$): δ 10.43 (s, 1H, NH), 8.12 (s, 1H, N=CH), 7.02-7.86 (m, 12H: CH=CH and Ar-H's), 4.29 (s, 2H, SCH_2), 4.31-4.35 (q, 2H, OCH_2), 2.48 (s, 3H, CH_3 at C-6), 1.28-1.30 (t, 3H, CH_3 of ester). ^{13}C NMR and Dept 135 ($CDCl_3$): 170.69, 166.85, 164.54, 161.99, 158.60, 148.83 (CH), 147.53, 144.95 (CH), 140.67 (CH), 135.35, 133.54, 130.37 (CH), 129.67 (CH), 128.80 (CH), 127.41 (CH), 123.75, 120.31 (CH), 114.45, 102.38, 62.07 (OCH_2), 32.21 (SCH_2), 23.49 (CH_3 at C-6), 14.14 (CH_3 of ester group). Anal. Calcd. For $C_{27}H_{24}N_4O_3S$ (484.15): C, 66.92; H, 4.99; N, 11.56%. Found: C, 66.78; H, 4.73; N, 11.39%.

It was obtained from **4** and 4-methoxybenzaldehyde. Yield: 4.62 g (90 %); m. p.: 195-196 °C. IR (cm^{-1}): 3190 (NH), 3001 (CH, aromatic), 2224 (C≡N), 1722 (C=O, ester), 1655 (C=O, hydrazide). ^{1}H NMR (DMSO-d6): δ 11.48 (s, 1H, NH), 8.00 (s, 1H, N=CH), 7.00-7.63 (m, 11H: CH=CH and Ar-H's), 4.15-4.59 (m, 4H: OCH_2 and SCH_2), 3.82 (s, 3H, OCH_3), 2.51 (s, 3H, CH_3 at C-6), 1.23-1.26 (t, 3H, CH_3 of ester). Anal. Calcd. for $C_{28}H_{26}N_4O_4S$ (514.17): C, 65.35; H, 5.09; N, 10.89%. Found: C,65.15; H, 5.22; N, 10.64%.

It was obtained from 4 and 4-chlorobenzaldehyde. Yield: 4.71 g (91 %); m. p.: 200-202 °C. IR (cm^{-1}): 3208 (NH), 3000 (CH, aromatic), 2985 (CH, aliphatic), 2221 (C≡N), 1719 (C=O, ester), 1659 (C=O, hydrazide). ^{1}H NMR ($CDCl_3$): δ 11.36 (s, 1H, NH), 8.21 (s, 1H, N=CH), 7.11-7.96 (m, 11H: CH=CH and Ar-H's), 4.57 (s, 2H, SCH_2), 4.32-4.36 (q, 2H, OCH_2), 2.52 (s, 3H, CH_3 at C-6), 1.30-1.33 (t, 3H, CH_3 of ester). ^{13}C NMR and Dept 135 ($CDCl_3$): δ 169.66, 167.01, 162.71, 158.47, 147.33, 146.79, 142.69, 139.58, 135.88, 135.17, 132.69, 129.59, 128.83, 128.14, 127.22, 123.56, 120.67, 114.81, 102.17, 61.97(OCH_2), 32.86 (SCH_2), 23.40 (CH_3 at C-6), 14.02 (CH_3 of ester). Anal. Calcd. for $C_{27}H_{23}ClN_4O_3S$ (518.12): C, 62.48; H, 4.47; N, 10.79%. Found: C, 62.71; H, 4.44; N, 10.84%.

It was obtained from 4 and thiophene-2-carboxaldehyde. Yield: 4.30 g (88 %); m. p.: 210-211 °C. IR (cm^{-1}): 3198 (NH), 3084, 3027 (CH, aromatic), 2981, 2883 (CH, aliphatic), 2223 (C≡N), 1725 (C=O, ester), 1664 (C=O, acetohydrazide).^{1}H NMR ($CDCl_3$): δ 10.12 (s, 1H, NH), 7.12-7.62 (m, 11H: CH=CH, N=CH, thiophene-H and Ar-H's), 4.34-4.36 (q, 2H, OCH_2), 4.23 (s, 2H, SCH_2), δ 2.51 (s, 3H, CH_3), 1.24-1.26 (t, 3H, CH_3 of ester). Anal. Calcd. for $C_{25}H_{22}N_4O_3S_2$ (490.11): C, 61.21; H, 4.52; N, 11.42%. Found C, 61.00; H, 4.39; N, 11.61%.

To a suspension of 6a-d (5 mmol) in ethanol (25 ml), an ethanolic sodium ethoxide solution (0.15 g of sodium in 40 ml of absolute ethanol) was added . The resulting mixture was refluxed for 10 mins. The precipitated solid was filtered off and recrystallized from dimethylsulfoxide to give 7a-d.

It was synthesized by using 6a. Yield: 2.32 g (92 %); m. p.: 280-282 °C. IR (cm^{-1}): 3461, 3303, 3150 (NH_2, NH), 2929 (C-H, aliphatic), 1716 (C=O, ester), 1634 (C=O, carbohydrazide). ^{1}H NMR (DMSO-d_6): δ 10.85 (s, 1H, NH), 7.22-7.98 (m, 13H: N=CH, CH=CH and Ar-H's), 6.91 (s, 2H, NH_2), 4.32-4.36 (q, 2H, OCH_2), 2.56 (s, 3H, CH_3 at C-6), 1.26-1.29 (t, 3H, CH_3 of ester). Anal. Calcd. For $C_{27}H_{24}N_4O_3S$ (484.16): C, 66.92; H, 4.99; N, 11.56%. Found: C, 67.08; H, 4.74; N, 11.33%.

It was synthesized by using 6b.Yield: 2.43 g (95 %); m. p.: 248-250 °C. IR (cm^{-1}): 3457, 3300, 3153 (NH_2, NH), 2929 (CH, aliphatic), 1716 (C=O, ester), 1632 (C=O, hydrazide). ^{1}H NMR (DMSO-d_6): δ 9.91 (s, 1H, NH), 6.90-7.80 (m, 12H: N=CH, CH=CH and Ar-H's), 6.84 (s, 2H, NH_2), 4.30-4.34 (q, 2H, OCH_2), 3.83 (s, 3H, OCH_3), 2.64 (s, 3H, CH_3 at C-6), 1.25-1.28 (t, 3H, CH_3 of ester). ^{13}C NMR and Dept 135 (DMSO-d_6): δ 170.28, 168.41, 167.20, 162.74, 161.14, 156.00, 144.23, 141.52, 139.67, 137.88, 135.33, 129.60, 128.88, 127.38, 126.53, 125.51, 121.56, 120.78, 114.16, 95.86, 62.01 (OCH_2), 55.34 (OCH_3), 23.44 (CH_3 at C-6), 14.24 (CH_3 of ester). Anal. Calcd. For $C_{28}H_{26}N_4O_4S$ (514.17): C,65.35; H, 5.09; N, 10.89%. Found: C,65.15; H, 5.00; N, 10.72%.

It was synthesized by using 6c. Yield: 2.48 g (95 %); m. p.: 285-287 °C. IR (cm^{-1}): 3450, 3311, 3215 (NH_2, NH), 2929 (CH, aliphatic), 1720 (C=O, ester), 1640 (C=O, carbohydrazide).^{1}H NMR ($CDCl_3$): δ 10.56 (s, 1H, NH), 7.10-8.06 (m, 12H: N=CH, CH=CH and Ar-H's), 6.93 (s, 2H, NH_2), 4.34-4.38 (q, 2H, OCH_2), 2.57 (s, 3H, CH_3 at C-6), 1.28-1.31 (t, 3H, CH_3 of ester). Anal. Calcd. for $C_{27}H_{23}ClN_4O_3S$ (519.02): C, 62.48; H, 4.47; N, 10.79%. Found: C, 62.16; H, 4.49; N, 10.62%.

It was synthesized by using 6d. Yield: 2.15 g (87 %); m. p.: 280-281 °C. IR (cm^{-1}): 3452, 3304, 3132 (NH_2, NH), 3060, 3023 (CH, aromatic), 2957, 2923 (CH, aliphatic), 1724 (C=O, ester), 1628 (C=O, carbohydrazide).^{1}H NMR ($CDCl_3$): ^{1}H NMR (DMSO-d_6): δ 9.51 (s, 1H, NH), 7.74-7.78 (d, 1H, CH=C), 7.33-7.68 (m, 9H: N=CH, thiophene-H and Ar-H's), 6.80-6. 84 (d, 1H, C=CH), 6.74 (s, 2H, NH_2), 4.26-4.29 (q, 2H, OCH_2), 2.60 (s, 3H, CH_3 at C-6), 1.18-1.20 (t, 3H, CH_3 of ester). Anal. Calcd. for $C_{25}H_{22}N_4O_3S_2$ (490.11): C, 61.21; H, 4.52; N, 11.42%. Found C, 61.33; H, 4.46; N, 11.50%.

A mixture of 7a-d (2 mmol) and $HC(OEt)_3$(5 ml) in acetic anhydride (10 ml) was refluxed for 4 h. The precipitated solid was filtered off and crystallized from isopropanol as white crystals of 8a-d.

Obtained from 7a. Yield: 0.83 g (84%); m. p.: 180-182 °C. IR(cm^{-1}): 2973 (CH, aliphatic), 1705 (C=O, ester), 1670 (C=O, pyrimidinone). ^{1}H NMR (DMSO-d_6): δ 10.00 (s, 1H, pyrimidinone-H), 9.60 (s, 1H, N=CH), 7.24-8.04 (m, 12H: N=CH, CH=CH and Ar-H's), 4.31-4.35 (q, 2H, OCH_2), 2.57 (s, 3H, CH_3 at C-6), 1.23-1.2 (t, 3H, CH_3 of ester). Anal. Calcd. For $C_{28}H_{22}N_4O_3S$ (494.14): C, 68.00; H, 4.48; N, 11.33%. Found: C, 67.82; H, 4.47; N, 11.19 %.

Obtained from 7b. Yield: 0.92 g (88%); m. p.: 188-190 °C. IR (cm^{-1}): 2977 (CH, aliphatic), 1719 (C=O, ester), 1678 (C=O, pyrimidinone).). ^{1}H NMR (DMSO-d_6): δ 9.46 (s, 1H, pyrimidinone-H), 9.22 (s, 1H, N=CH), 6.87-7.92 (m, 11H: CH=CH and Ar-H's), 4.31-4.34 (q, 2H, OCH_2), 3.81 (s, 3H, OCH_3), 2.66 (s, 3H, CH_3 at C-6), 1.24-1.27 (t, 3H, CH_3 of ester). Anal. Calcd. For $C_{29}H_{24}N_4O_4S$ (524.15): C, 66.40; H, 4.61; N, 10.68%. Found: C, 66.59; H, 4.73; N, 10.52%.

Obtained from 7c. Yield: 0.93 g (88%); m. p.: 220-222 °C. IR (cm^{-1}): 3021 (CH, aromatic), 2981 (CH, aliphatic), 1721 (C=O, ester), 1687 (C=O, pyrimidinone).^{1}H NMR (DMSO-d_6): δ 9.75 (s, 1H, CH pyrimidinone), 9.50 (s, 1H, N=CH), 6.55-8.07 (m, 11H: CH=CH and Ar-H's), 4.00.4.04 (q, 2H, OCH_2), 2.74 (s, 3H, CH_3 at C-6), 1.16-1.19 (t, 3H, CH_3 of ester). Anal. Calcd. for $C_{28}H_{21}ClN_4O_3S$ (528.10): C, 63.57; H, 4.00; N, 10.59 %. Found: C, 63.42; H, 4.12; N, 10.43%.

Obtained from 7d. Yield: 0.95 g (95 %); m. p.: 202-204 °C. IR (cm^{-1}): 3063,3025 (CH, aromatic), 2983, 2933 (CH, aliphatic), 1720 (C=O, ester), 1673 (C=O, pyrimidinone).^{1}H NMR ($CDCl_3$): δ 8.45-8.49 (d, *J = 16 Hz*, 1H, CH=C), 8.26 (s, 1H, CH pyrimidinone), 7.28-7.60 (m, 9H: N=CH, thiophene-H and Ar-H's), 7.07-7.11 (d, *J = 16 Hz*, 1H, C=CH), 4.41 (q, 2H, OCH_2), 2.77 (s, 3H, CH_3 at C-6), 1.26-1.35 (t, 3H, CH_3 of ester). Anal. Calcd. for $C_{26}H_{20}N_4O_3S_2$ (500.10): C, 62.38; H, 4.03; N, 11.19%. Found: C, 62.21; H, 4.06; N, 11.00%.

A mixture of ester 4 (3.96 g, 10 mmol) and 2,5-dimethoxytetrahydrofuran (1.84 ml, 14 mmol) in glacial acetic acid (30 ml) was refluxed for 3 h. The precipitate that formed was filtered off and recrystallized from ethanol to give colorless needles of 9. Yield: 4.15 g (90%); m.p.: 127-128 °C. IR (cm^{-1}): 3094, 3061, 3024 (C-H, aromatic), 2991, 2900 (C-H, aliphatic), 1722 (C=O, attached to pyridine ring), 1694 (C=O, attached to thiophene ring). ^{1}H NMR (DMSO-*d_6*): δ 7.30-7.33 (m, 3H, Ar-H's), 7.16-7.18 (m, 2H, Ar-H's); 6.94-6.95 (d, 2H, pyrrole-H), 6.69-6.73 (d, 1H, CH=C); 6.20-6.23 (m, 3H: C=CH and Pyrrole-H); 4.25-4.29 (q, 2H, OCH_2), 4.13-4.17 (q, 2H, OCH_2), 2.50 (s, 3H,

CH_3 at C-6), 1.15-1.18 (t, 3H, CH_3 of ester); 1.19-1.22 (t, 3H, CH_3 of ester). MS:) at m/z 460 (M^+, 15 %), 415 (M^{+-}- OEt, 100%). Anal. Calcd. for $C_{26}H_{24}N_2O_4S$ (460.15): C, 67.81; H, 5.25; N, 6.08%. Found: C, 67.59; H, 5.27; N, 6.00%

A mixture of ester 9 (2.30 g, 5 mmol) and hydrazine hydrate (0.5 ml, 10 mmol) in ethanol (40 ml) was refluxed for 3 h. The solid that formed was filtered off and crystallized from dioxane as white needles of 10. Yield: 2.06 g (92%); m.p.: 230-231 °C. IR (cm^{-1}): 3418, 3334, 3278 ($NHNH_2$), 2996, 2899 (C-H, aliphatic), 1723 (C=O, ester), 1657 (C=O, carbohydrazide). ^{1}H NMR (DMSO-d_6): δ 8.06 (s, 1H, NH), 6.19-7.33(11H: CH=CH, pyrrole-H, Ar-H's), 4.53 (s, 2H, NH_2), 4.26-4.29 (q, 2H, OCH_2), 2.62 (s, 3H, CH_3 at C-6), 1.15-1.18 (t, 3H, CH_3 of ester). MS: m/z 446 (M^+, 30 %) ,401 (M^{+-}-OEt, 100%), 415 (M^{+-}- $NHNH_2$, 80%). Anal. Calcd. for $C_{24}H_{22}N_4O_3S$ (446.14): C, 64.56; H, 4.97; N,12.55 %. Found: C, 64.71; H, 4.87; N,12.32 % [5].

A mixture of 10 (0.89 g, 2 mmol) and the respective aromatic or heterocyclic aldehyde (2 mmol) in ethanol (25 ml) was refluxed for 2 h. The precipitate that formed while hot was filtered off and recrystallized from dioxane to give white crystals of 11a-c.

It was prepared by using benzaldehyde. Yield: 1.00 g (93 %); m. p.: 258-259 °C. IR (cm^{-1}): 3292 (NH), 3058, 3027 (CH, aromatic), 2981 (CH, aliphatic), 1716 (C=O, ester), 1664 (C=O, carbohydrazide). ^{1}H NMR (DMSO-d_6): δ 7.15-7.30 (m, 11H :N=CH and Ar-H's); 6.90-6.92 (d, 2H, pyrrole-H), 6.70-6.73 (d, 1H, CH=C); 6.20-6.24 (m, 3H: C=CH and Pyrrole-H); 4.26-4.30 (q, 2H, OCH_2); 2.60 (s, 3H, CH_3 at C-6), 1.12-1.15(t, 3H, CH_3 of ester). Anal. Calcd. For $C_{31}H_{26}N_4O_3S$ (534.17): C, 69.64; H, 4.90; N,10.48%. Found: C, 69.33; H, 4.88; N,10.30%.

It was prepared by using 4-methoxybenzaldehyde. Yield: 1.00 g (88 %); m. p.: 224-225 °C. IR (cm^{-1}): 3299 (NH), 3061 (CH, aromatic), 2986, 2927, 2836 (CH, aliphatic), 1719 (C=O, ester), 1669 (C=O, carbohydrazide). MS: m/z 564 **(**M^+, 20%**)**; 134 (100%). Anal. Calcd. For $C_{32}H_{28}N_4O_4S$ (564.18): C,68.07; H, 5.00; N, 9.92%. Found: C,68.00; H, 5.09; N, 9.82%.

It was obtained by using 4-chlorobenzaldehyde. Yield: 1.02 g (89 %); m. p.: 254-255 °C. IR (cm^{-1}): 3290 (NH), 3061 (CH, aromatic), 2986, 2904 (CH, aliphatic), 1724(C=O, ester), 1673 (C=O, carbohydrazide). Anal. Calcd. for $C_{31}H_{25}ClN_4O_3S$ (568.13): C, 65.43; H, 4.43; N, 9.85%. Found: C, 65.70; H, 4.44; N, 9.63%.

To a cold solution of compound 4 (3.96 g, 10 mmol) in glacial acetic acid (30 ml), a cold solution of sodium nitrite (0.69 g; 10 mmol in 2 ml water) was added dropwise with stirring. After the completion of addition, stirring was continued fpr 1 hour at room temperature. The solid that formed was collected by filtration, washed abudantly with cold water and air dired. It was applied in the next steps without purification; m.p. :; Yield: 4.10 g (89%); m.p.: 140-141°C (dec.). IR (cm^{-1}): 2982 (CH, aliphatic), 2142 (N_3), 1724 (C=O, ester), 1691(C=O, carbonylazide).

CONCLUSION

Compound 12 (0.91 g, 2 mmol) in ethanol (30 ml) was refluxed for 3 h. The precipitate that formed while hot was filtered off and recrystallized from dioxane as pale yellow needles. This product was assigned as 9-ethoxycarbonyl-8-methyl-10-styrylpyrido[3',2':4,5]lthieno[2,3-e]pyrrolo[1,2-a]pyrazine-4(5*H*)-one (15); yield: 0.20 g (24%); m. p.: 264-265 °C. IR (cm^{-1}): 3243 (NH), 2999, 2974 (C-H, aliphatic), 1719(C=O, ester), 1644 (C=O, pyrazineone). ^{1}H NMR (DMSO-d_6): δ 6.20-7.00 (m, 11H: CH=CH, pyrrole-H, Ar-H's), 4.48-4.52 (q, 2H, OCH_2), 2.71 (s, 3H, CH_3), 1.15-1.18 (t, 3H, CH_3 of ester). Anal. Calcd. for $C_{24}H_{19}N_3O_3S$ (429.11): C, 67.12; H, 4.46; N, 9.78 %. Found: C, 67.39; H, 4.48; N, 9.91%.

The filtrate of the above crude product was allowed to cool whereby a yellowih white crystals precipitated. They were filtered off and recrystallized from ethanol. This compound was identified as ethyl 5-ethoxycarbonyl-6-methyl-3-(1*H*-pyrrol-1-yl)-4-styrylthieno[2,3-b]pyridine-2-carbamate (14); yield: 0.34 g (36%). m. p.: 183-184 °C. IR (cm^{-1}): 3411 (NH), 3025 (CH, aromatic), 2976, 2930 (CH, aliphatic), 1728 (C=O, ester), 1669 (C=O, carbamate). Anal. Calcd. for $C_{26}H_{25}N_3O_4S$ (475.16): C, 65.67; H, 5.30; N, 8.84%. Found: C, 65.60; H, 5.38; N, 8.71%.

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