SYNTHESIS, REACTIONS AND SPECTRAL CHARACTERIZATION OF NOVEL THIENOPYRAZOLE DERIVATIVES

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4-Amino-3-methyl-1-phenyl-*1H*-thieno[2,3-*c*]pyrazole-5-carboxamide has been synthesized by an innovative method. The aminoamide derivative was gently refluxed with chloroacetyl chloride under neat conditions followed by neutralization with sodium carbonate solution to afford the chloromethyl pyrimidinone compound. The chloromethyl pyrimidinone derivative was converted to the thiol derivative by the reaction with thiourea in ethanol. The thiol compound was alkylated with α-halocompounds such as ethyl chloroacetate, chloroacetone, phenacyl bromide and 2-chloro-4,6-dimethylnicotinonitrile to afford the corresponding S-alkylated compounds. The chemical structures of the newly synthesized compounds were elucidated on the basis of elemental and spectral analyses containing FT-IR, ^{1}H-NMR, and mass spectroscopy.

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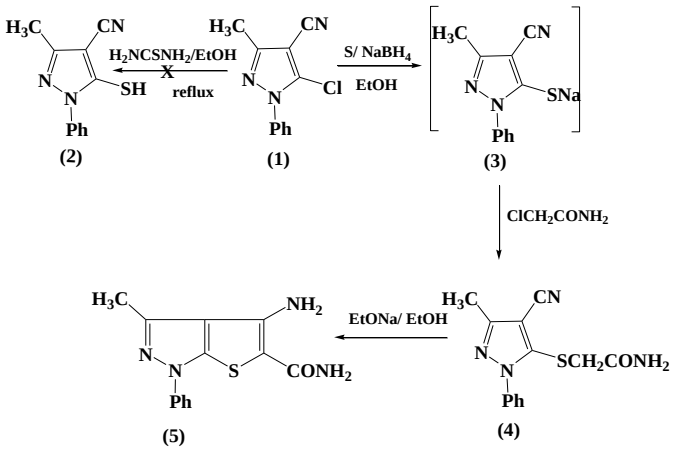
INTRODUCTION

Many of pyrazoles and related compounds are known to possess biological activity.[1-6] Thieno[3,4-*c*]pyrazoles are a class of biologically active compounds, currently employed in the field of medicinal chemistry owing to their remarkable anti-inflammatory,[7,8] analgesic and antithrombotic activities, also for the treatment of cardiovascular or cerebrovascular diseases, and hyperglycemia.[9] Thieno[3,2-*c*]pyrazoles are used in the treatment of hypertension and glaucoma.[10] Thieno[2,3-*c*]pyrazoles on the other hand, represent a class of heterocyclic compounds which have antifungal, antibacterial and anti-inflammatory activities.[11-21]

RESULT AND DISCUSSION

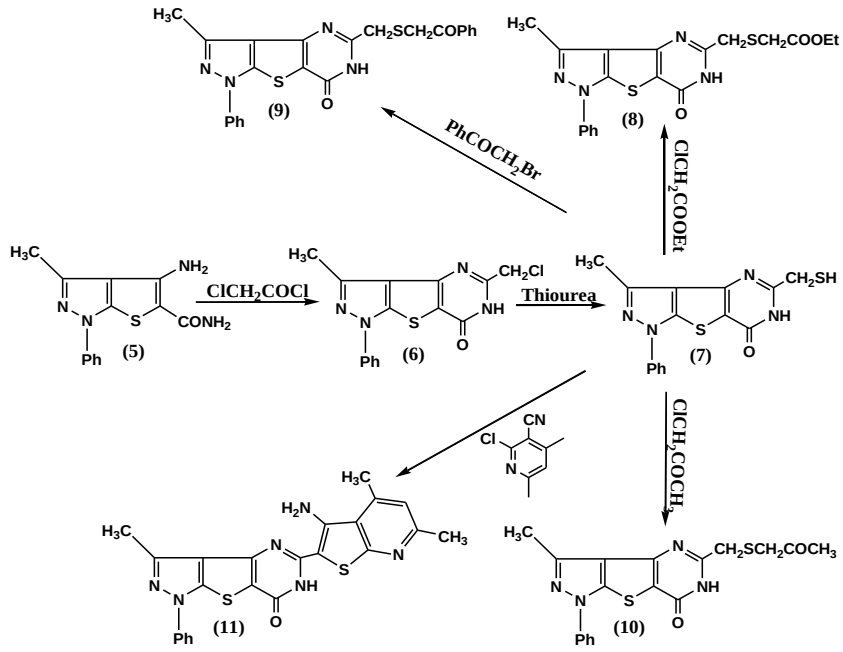
4-Amino-3-methyl-1-phenyl-*1H*-thieno[2,3-*c*]pyrazole-5-carboxamide was synthesized by an innovative method according to literature procedure.[19-21] All attempts to displace the chloride ion by the thiol group in the previously prepared 5-chloro-3-methyl-1-phenyl-*1H*-pyrazole-4-carbonitrile compound **(1)** by the reaction of thiourea in ethanol and with other moieties to obtain 5-mercapto-*N*-phenylpyrazole-4-carbonitrile **(2)** failed, giving the chloropyrazole carbonitrile starting material **(1)**. The previous results forced us to search for another method to prepare the target amino thienopyrazole carboxamide compound **(5)**. The desired results were achieved by the reaction of elemental sulfur with chloropyrazole in the presence of sodiumborohydride to give the non-isolated sulfanyl sodium salt **(3)** which underwent an *in situ* reaction with chloroacetamide to afford the pyrazole sulfanyl acetamide derivative **(4)**. The latter compound underwent Thorpe-Zeigler cyclization on heating in ethanolic sodium ethoxide solution yielding the amino thienopyrazole carboxamide **(5)** (Scheme 1). The chemical structure of compound **(5)** was elucidated on the basis of elemental and spectral data. IR spectrum of compound **(5)** revealed appearance of absorption band at 3400, 3305, 3190 cm^{-1} due to two NH_2 group. ^{1}H NMR spectrum showed two singlet signals at δ 2.60, 6.90 and 7.00 ppm characteristic for CH_3 and NH_2 groups respectively. ^{13}C NMR spectrum displayed signals at 15.2 and 169.80 ppm attributed to CH_3 and $CONH_2$ groups respectively.



Scheme 1. Synthesis of aminoamide derivative of thienopyrazole.

Heating the amino carboxamide compound **(5)** with chloroacetyl chloride on a water bath under neat conditions followed by neutralization with diluted sodium carbonate solution afforded the chloromethylpyrazolo-thienopyrimidinone **(6)**. The latter compound was characterized on the basis of elemental and spectral analysis. IR spectrum revealed the disappearance of absorption bands for NH_2 groups in the amino amide compound **(5)** and appearance of a broad absorption band at 3480-3300 cm^{-1} for NH group. ^{1}H NMR spectrum showed singlet signal at δ 4.60 ppm for CH_2 group and singlet signal at 10.60 ppm for NH pyrimidine.

5-(Chloromethyl)-3-methyl-1-phenyl-*1H*-pyrazolo[4',3':4,5]-thieno[3,2-*d*]pyrimidin-7(*6H*)-one **(6)** was converted into corresponding 5-(mercaptomethyl)-3-methyl-1-phenyl-*1H*-pyrazolo[4',3':4,5]thieno[3,2-*d*] pyrimidin-7(*6H*)-one **(7)** by refluxing with thiourea followed by treatment with sodium hydroxide and then acidification with HCl. Mercapto-methylpyrazolothienopyrimidine **(7)** was alkylated using α-halogenated compounds namely, ethyl chloroacetate, phenacyl bromide and chloroacetone to give S-alkylated mercaptomethylpyrazolothienopyrimidine derivatives respectively (**8-10**) (Scheme 2). While the reaction with 2-chloro-4,6-dimethylnicotinonitrile, afforded thienopyridinyl of pyrazolothienopyrimidine compound **(11)**. The structure of compound **(7)** was confirmed using elemental and spectral data. IR spectrum revealed absorption bands at 3428 cm^{-1} characteristic of the NH group and 1655 cm^{-1} for CO group. ^{1}H NMR spectrum of the thiol derivative **(7)** in DMSO-d_6 displayed singlet signals at δ: 3.70 ppm for CH_2, at 1.20 ppm for SH group and at 3.90 ppm attributed to NH group.



Scheme 2. Synthesis and reactions of mercaptomethylpyrimidothienopyrazole derivative.

Experimental

All melting points were uncorrected and recorded on a Gallen Kamp electric melting point apparatus. The elemental analyses were carried out at the Micro Analytical Center of Chemistry Department- Assiut University.

The FT-IR spectra were recorded using potassium bromide disks on a FT-IR 8201 PC Shimadzu. ^{1}H NMR and ^{13}C NMR spectra were obtained on a Bruker (^{1}H NMR: 400 and 300 MHz, ^{13}C NMR: 100 and 75 MHz) spectrometers in $CDCl_3$ and DMSO-d_6 using Me_4Si as internal standard and chemical shifts are expressed as ppm. Mass spectra were measured on a Jeol-JMS 600 and Shimadzu Qp-2010 plus spectrometer at the Micro Analytical Center –Cairo University- Giza.

All reactions were monitored by TLC on silica gel coated aluminum sheets (Silica Gel 60 F254, Merck). Compounds **(1)**, **(4),** and **(5)** were prepared according to literature procedure[22-27] with m.p. 120-122 °C, 144-146 °C and 214-216 °C, respectively.

Synthesis of 3-methyl-1-phenyl-5-sulfanylacetamidopyrazole-4-carbonitrile (4)

Sodium borohydride (4 g, 0.105 mol) was added to a suspension of finely powered sulfur (4 g, 0.125 mol) in absolute ethanol (60 ml), kept in an ice bath, in small portions till all sulfur powder dissolved, then chlorocyanopyrazole **(1)** (10 g, 46 mmol) was added to the reaction mixture with stirring in an ice bath for 1 h. The reaction mixture was refluxed for 4 h followed by cooling. Then, the chloroacetamide (4.30 g, 46 mmol) was added to the mixture. The reaction mixture was left overnight with stirring. The solid precipitate which is formed was filtered off, dried, and recrystallized from ethanol as white crystals in (10 g, 80 %). m.p. 144–146 °C. IR (KBr): 3450, 3300 (NH_2), 3050 (CH aromatic), 2920, 2850 (CH aliphatic), 2220 (CN), 1660 (CO amide), 1590 (C=N) cm^{-1}. ^{1}H NMR (400 MHz, DMSO-d_6): δ = 2.35 (s, 3H, CH_3), 3.30 (s, 2H, CH_2), 7.15 (s, 2H, NH_2), 7.30–7.70 (m, 5H, ArH). Anal. Calcd. for $C_{13}H_{12}N_4OS$: C, 57.34; H, 4.44; N, 20.57; S, 11.77, Found: C, 57.26; H, 4.50; N, 20.60; S, 12.00.

Synthesis of 4-Amino-3-methyl-1-phenyl-*1H*-thieno[2,3-*c*]pyrazole-5-carboxamide (5)

To a solution of acetamido-pyrazole carbonitrile compound (**4**) (4 g, 16 mmol) in absolute ethanol (20 ml), sodium ethoxide solution (2.5 ml) was added. The mixture was gently refluxed for 10 min. The solid precipitate which separated out during reflux was filtered off, dried, and recrystallized from the mixture of ethanol–dioxane 2:1 as white crystals in (2.80 g, 70 %). m.p. 214-216 ºC. IR (KBr): 3400, 3305, 3190 (NH_2), 3050 (CH aromatic), 2910 (CH aliphatic), 1635 (CO amide), 1580 (C=N) cm^{-1}. ^1H NMR (DMSO-d_6): δ = 2.60 (s, 3H, CH_3), 6.90 (s, 2H, NH_2 amide), 7.00 (s, 2H, NH_2), 7.30-7.70 (m, 5H, ArH). ^{13}C NMR (100 MHz, DMSO-d_6): 15.2 (CH_3 pyrazole), 109.3, 121.5, 145.4, 145.4, 149.9 (C), 124.4, 128.2, 129.8, 133.1 (Ph pyrazole), 169.8 ($CONH_2$). EI-MS: m/z 272.14 [M^+]. Anal. Calcd. for $C_{13}H_{12}N_4OS$: C, 57.34; H, 4.44; N, 20.57; S, 11.77. Found: C, 57.44; H, 4.55; N, 20.47; S, 11.65.

Synthesis of 5-chloromethyl-3-methyl-1-phenyl-pyrimido-[4',5':4,5]thieno[2,3-*c*]pyrazol-7(*6H*)-one (6)

A mixture of compound (**5**) (4.00 g, 15 mmol) and an excess of chloroacetyl chloride (8 ml, 70 mmol) was heated on water bath for 3 h, then poured into cold water (100 ml), neutralized with sodium carbonate solution (10 %) to just alkaline. The solid product was filtered off, dried and recrystallized from dioxane as pale yellow crystals (3.8 g, 78%). m.p. 304-306 ºC. IR (KBr): 3480-3300 (NH), 3050 cm^{-1} (CH aromatic), 2920, 2850 cm^{-1} (CH aliphatic), 1645 cm^{-1} (CO amide) cm^{-1}. ^1H NMR (DMSO-d_6): δ = 2.60 (s, 3H, CH_3), 4.60 (s, 2H, CH_2), 7.20-7.90 (m, 5H, ArH), 10.60 (s, 1H, NH). Anal. Calcd. for $C_{15}H_{11}ClN_4OS$: C, 54.46; H, 3.35; Cl, 10.72; N, 16.94; S, 9.69. Found: C, 54.69; H, 3.50; Cl, 10.50; N, 17.00; S, 9.50.

Synthesis of 5-(mercaptomethyl)-3-methyl-1-phenyl-*1H*-pyrazolo[4',3':4,5]thieno[3,2-*d*]pyrimidin-7(*6H*)-one (7)

A mixture of compound (**6**) (1.89 g, 5.75 mmol) and thiourea (1.30 g, 0.01 mol) in ethanol was refluxed for 2 h. The yellow precipitate which obtained on heating, was filtered off and dissolved in sodium hydroxide (5 %), then acidified with (0.01 N) HCl until acidic. The solid product was collected as faint yellow crystals (1.37 g, 73%). m.p>360 ºC. IR (KBr): 3428 (NH), 1655 (CO), 2923, 2853 (CH aliphatic) and 1594 (C=N) cm^{-1}. ^1H NMR (DMSO-d_6): δ = 1.20 (s, 1H, SH), 2.50 (s, 3H, CH_3), 3.70 (s, 2H, CH_2), 3.90 (s, 1H, NH), 7.20-7.70 (m, 5H, ArH) ppm. EI-MS: m/z 328 [M^+]. Anal. Calcd. for $C_{15}H_{12}N_4OS_2$: C; 54.86; H, 3.68; N, 17.06; O, 4.87; S, 19.52. Found: C; 54.74; H, 3.75; N, 17.13; S, 19.44.

Synthesis of ethyl-2-(((3-methyl-7-oxo-1-phenyl-6,7-dihydro-*1H*-pyrazolo[4',3':4,5]thieno[3,2-*d*]pyrimidin-5-yl)methyl)thio)-acetate (8)

A mixture of compound (**7**) (1.60 g, 3.87 mmol), ethyl chloroacetate (0.47 ml, 3.87 mmol) and sodium acetate (0.7 g, 8.5 mmol), were refluxed in ethanol (20 ml) for 3hrs. then allowed to cool. The solid product was collected and recrystalized from ethanol as yellowish white crystals (1.30 g, 65 %), m.p. 190-192 ºC. IR (KBr): 3435 (NH), 2923, 2852 cm^{-1} (CH aliphatic), 1663, 1727 cm^{-1} (2CO) and 1595 cm^{-1} (C=N). ^1H NMR (DMSO-d_6): δ= 1.20 (t, 3H, CH_3), 2.60 (s, 3H, CH_3 pyrazole), 3.60 (s, 2H, CH_2-S), 3.70 (s, 2H, -SCH_2) 3.90 (q, 2H, CH_2 ester), 7.40-7.80 (m, 5H, ArH) and 12.80 (s, 1H, NH). Anal. Calcd. for $C_{19}H_{18}N_4O_3S_2$: C; 55.06; H, 4.38; N, 13.52; O, 11.58; S, 15.47. Found: C; 55.18; H, 4.30; N, 13.41; S, 15.39.

Synthesis of 3-methyl-5-(((2-oxo-2-phenylethyl)thio)methyl)-1-phenyl-*1H*-pyrazolo[4',3':4,5]thieno[3,2-*d*]pyrimidin-7(*6H*)-one (9)

A mixture of the mercapto compound (**7**) (0.86 g, 1.93 mmol), phenacyl bromide (0.38 ml, 1.90 mmol) and sodium acetate (0.40 g, 4.87 mmol), were refluxed in ethanol (20 ml) for 3 h. The solid precipitate was formed during reflux was collected, dried and recrystallized from dioxane as yellow crystals (0.47 g, 40%). m.p. 215-217 ºC. IR (KBr) 3435 (NH), 2924, 2853 (CH aliphatic), 1660, 1675 (2CO) and 1595 (C=N) cm^{-1}. ^1H NMR (DMSO-d_6): δ= 2.30 (s, 3H, CH_3 pyrazole), 3.70 (s, 2H, CH_2-S), 4.40 (s, 2H, S-CH_2), 7.30-8.00 (m, 10H, 2ArH) and 12.80 (s, 1H, NH). Anal. Calcd. for $C_{23}H_{18}N_4O_2S_2$(446.54): C; 61.86; H, 4.06; N, 12.55; O, 7.17; S, 14.36%. Found: C; 61.77; H, 4.15; N, 12.41; S, 14.45%.

Synthesis of 3-methyl-5-(((2-oxopropyl)thio)methyl)-1-phenyl-*1H*-pyrazolo[4',3':4,5]thieno[3,2-*d*]pyrimidin-7(*6H*)-one (10)

A mixture of compound (**7**) (1.49 g, 3.87 mmol), chloroacetone (0.47 ml, 3.87 mmol) and sodium acetate (0.7 g, 8.5 mmol), were refluxed in ethanol (20 ml) for 3 h then the mixture was allowed to cool. The solid product formed on cooling was collected and recrystalized from ethanol as a pale yellow crystals (1.34 g, 77 %). m.p. 178-180 ºC. IR: (KBr): 3420 (NH), 2920, 2850 (CH aliphatic), 1680, 1665 (2CO) and 1595 (C=N) cm^{-1}. ^1H NMR (DMSO-d_6): δ= 2.50 (s, 3H, CH_3 pyrazole), 2.60 (s, 3H, $COCH_3$), 3.70 (s, 2H, CH_2-S), 3.90 (s, 2H, S-CH_2), 7.30-7.80 (m, 5H, ArH) and 12.80 (s, 1H, NH). EI-MS: m/z 384 [M^+]. Anal. Calcd. for $C_{18}H_{16}N_4O_2S_2$: C; 56.23; H, 4.19; N, 14.57; O, 8.32; S, 16.68. Found: C; 56.18; H, 4.30; N, 14.41; S, 16.59.

Synthesis of 5-(3-amino-4,6-dimethylthieno[2,3-*b*]pyridine-2-yl)-3-methyl-1-phenyl-*1H*-pyrazolo[4',3':4,5]thieno[3,2-*d*]pyrimidin-7(*6H*)-one (11)

A mixture of the mercapto compound (**7**) (1.77 g, 3.87 mmol), 2-chloro-4,6-dimethylnicotinonitrile (0.64 g, 3.87 mmol) and sodium acetate (0.7 g, 8.5 mmol), were refluxed in ethanol (20 ml) for 3h and then allowed to cool. The solid product was collected and recrystalized from ethanol as yellowish white crystals (1.55 g, 63 %). m.p. 290-292 ºC. IR (KBr): 3415, 3400 (NH, NH_2), 3028 (CH aromatic), 2931 (CH aliphatic), 1678 (CO) and 1595 (C=N) cm^{-1}. ^1H NMR (DMSO-d_6): δ= 2.50 (s, 3H, CH_3 pyrazole), 3.30 (s, 3H, CH_3 pyridine), 4.00 (s, 3H, CH_3 pyridine), 6.10 (s, 2H, NH_2), 7.20-7.40 (m, 5H, ArH), 7.80 (s, 1H, CH pyridine) and 12.80 (s, 1H, NH). Anal. Calcd. for $C_{23}H_{18}N_6OS_2$: C; 60.24; H, 3.96; N, 18.33; O, 3.49; S, 13.98 . Found: C; 60.18; H, 4.10; N, 18.41; S, 13.85.

CONCLUSION

The aim of this work is to synthesize some new bi-functionally substituted thieno[2,3-*c*] pyrazole compounds which were subjected to react with different reagents to synthesize new heterocyclic rings fused or attached to thienopyrazole system namely: pyrimidinone and thien[2,3-*b*]pyridinyl compounds.

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