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Synthesis of nitrogen heterocycles from ethyl 3-(6-dibenzothiophen-2-yl-pyridazin-3-ylamino)-3-oxopropanoate

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ABSTRACT

An efficient synthesis of nitrogen-containing heterocycles pyrazole, triazole, pyridinone and pyrimidinone derivatives from ethyl 3-(6-dibenzothiophen-2-yl-pyridazin-3-ylamino)-3-oxopropanoate (2) was described. The structures of all products were confirmed and characterized by the elemental analysis and spectroscopic studies (IR, MS, ^{1}H NMR, ^{13}C NMR).

1. Introduction

Nitrogen and sulfur-containing heterocycles have received a great deal of interest in the biological and medicinal sciences and this justifies continuing efforts in the development of new efficient and mild synthetic strategies for their synthesis. Among a large variety of nitrogen containing heterocyclic compounds, pyridazines have received considerable attention because of their pharmacological properties and clinical applications [1-9]. For example, 3-amino-6-aryl-pyridazines were reported to possess anti-inflammatory and analgesic properties [7]. Also, pyridazine derivatives possess antiviral and anticancer [10-12], antituberculosis [13], antihypertensive [14,15] and antimicrobial [16-19] activity. On the other hand, 6-alkoxy-[1,2,4]triazolo[4,3-b]pyridazines have been reported to possess anticonvulsant properties [20].

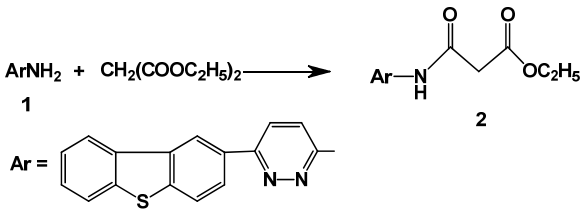
Based on the reported observations and in continuation of our research interest for the synthesis of biologically active heterocycles [21-24], the aim of this study is to design simple route for the synthesis of pyrazoles, triazoles, pyridinones and pyrimidinones derivatives attached to pyridazine moiety.

2. Experimental

2.1. Synthesis

2.1.1. Ethyl 3-(6-dibenzothiophen-2-yl-pyridazin-3-ylamino)-3-oxopropanoate (2)

A mixture of an equimolar amount of aminopyridazine **1** [25] and diethylmalonate (0.01 mol) was heated in an oil bath at 180 °C for 2 hours then left to cool. The product was collected and purified: Yellow, Yield: 80%, (Ethanol) (Scheme 1). M.p.: 176-178 °C. IR (KBr, cm^{-1}): 3390-3280 ν(NH), 2950, 2880 ν(CH_2), 1730, 1685 ν(CO), 1630 ν(C=N). ^{1}H NMR (200 MHz, $CDCl_3$): 1.32 (t, 3H, CH_3), 4.31 (q, 2H, CH_2), 5.40 (s, 2H, CH_2), 8.62 (s, 1H, NH, exchangeable), 6.91-7.96 (m, 9H, Ar-H). ^{13}C NMR (50 MHz, $CDCl_3$): 17.2 (CH_3), 54.3 (CH_2 ester), 47.1 (CH_2), 119.2, 121.3, 121.8, 122.6, 123.1, 123.7, 124.2, 124.6, 126.3, 127.6, 128.1, 132.5, 138.3, 139.1, 148.7, 151.1 (dibenzothiophene and pyridazine carbons), 172.2, 175.4 (2CO). MS (m/z): 391 (M^+). Anal. Calcd. for $C_{21}H_{17}N_3O_3S$: C, 64.43; H, 4.38; N, 10.73. Found: C, 64.28; H, 4.25; N, 10.56 %.



Scheme 1

2.1.2. Ethyl 2-(6-dibenzothiophen-2-yl –pyridazin-3-yl carbamoyl)-3-phenylacrylate (3)

Benzaldehyde (0.01 mol) was added to a solution of ester **2** (0.01 mol) in dioxan (30 mL) containing few drops of piperidine. The reaction mixture was heated under reflux for 3 hours then the solvent was removed. The remaining residue was triturated with petroleum ether to give the solid product: Yellow, Yield: 68% (Butanol) (Scheme 2). M.p.: 197-199 °C. IR (KBr, cm^{-1}): 3360-3230 ν(NH), 2940, 2860 ν(CH-aliphatic) 1715, 1670 ν(CO), 1620 ν(C=C). ^{1}H NMR (200 MHz, $CDCl_3$): 1.32 (t, 3H, CH_3), 4.20 (q, 2H, CH_2), 6.62 (s, 1H, C=CH), 8.81 (s,

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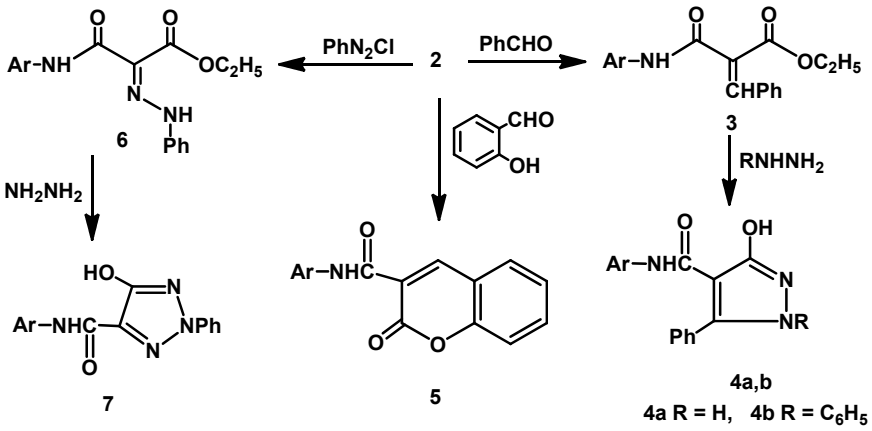


Scheme 2

1H, NH, exchangeable), 6.84-8.02 (m, 14H, ArH). ^{13}C NMR (50 MHz, $CDCl_3$): 16.4 (CH_3), 55.6 (CH_2 ester), 123.6 (*C*=CHPh), 146.2 (C=*C*HPh), 125.6, 127.3, 128.2, 135.5 (phenyl carbons, in addition to dibenzothiophene and pyridazine carbons). MS (m/z): 479 (M^+). Anal. Calcd. for $C_{28}H_{21}N_3O_3S$: C, 70.13; H, 4.41; N, 8.76 . Found: C, 70.27; H, 4.52; N, 8.58 %.

2.1.3. General procedure for the synthesis of 4a,b

A mixture of **3** (0.01 mol) and hydrazine hydrate or phenylhydrazine (0.01 mol) was heated in ethanol (30 mL) under reflux for 3 hours then left to cool. The formed solid product was collected by filtration and recrystallized (Scheme 2).

N-(6-Dibenzothiophen-2-yl–pyridazin-3-yl)-3-hydroxy-5-phenyl-1H-pyrazole-4-carboxamide (**4a**): Yellow, Yield: 81% (Ethanol). M.p.: 180-182 °C. IR (KBr, cm^{-1}): 3490-3240 ν(OH, NH), 1685 ν(CO), 1650 ν(C=N), 1635 ν(C=C). ^{1}H NMR (200 MHz, $CDCl_3$): 8.52, 9.33 (2s, 2H, 2NH, exchangeable), 10.24 (s, 1H, OH), 7.02-7.98 (m, 14H, Ar-H). MS (m/z): 463 (M^+). Anal. Calcd. for $C_{26}H_{17}N_5O_2S$: C, 67.37; H, 3.70; N, 15.11. Found: C, 67.20; H, 3.53; N, 14.85 %.

N-(6-Dibenzothiophen-2-yl–pyridazin-3-yl)-3-hydroxy-1,5-diphenyl-1H-pyrazole-4-carboxamide (**4b**): Yellow, Yield: 74% (Ethanol). M.p.: 186-188 °C. IR (KBr, cm^{-1}): 3460-3255 ν(OH, NH), 1685 ν(CO), 1645 ν(C=N), 1622 ν(C=C). ^{1}H NMR (200 MHz, $CDCl_3$): 8.90 (s, 1H, NH, exchangeable), 10.28 (s, 1H, OH), 7.89-8.10 (m, H, 19Ar-H). MS (m/z): 539 (M^+). Anal. Calcd. for $C_{32}H_{21}N_5O_2S$: C, 71.23; H, 3.92; N, 12.98. Found: C, 71.04; H, 3.64; N, 12.74 %.

2.1.4. N-(6-Dibenzothiophen-2-yl–pyridazin-3-yl)-2-oxo-2H-chromene-3-carbox amide (5)

The same procedures described for the synthesis of compound 3. Yellow, Yield: 82 % (Ethanol) (Scheme 2). M.p. 206-208 °C. IR (KBr, cm^{-1}): 3390-3270 ν(NH), 3020 ν(CH-aromatic), 1710, 1680 ν(CO), 1620 ν(C=C). ^{1}H NMR (200 MHz, $CDCl_3$): 6.92-7.88 (m, 14H, ArH+chromene-H), 8.93 (s, 1H, NH, exchangeable). ^{13} C NMR (50 MHz, $CDCl_3$): 120.2, 123.6, 126.1, 126.9, 127.5, 128.6, 148.3, 150.2, (in addition to dibenzo thiophene and pyridazine carbons), 162.2, 163.4 (2CO). MS (m/z): 449 (M^+); Anal. Calcd. for $C_{26}H_{15}N_3O_3S$: C, 69.48; H, 3.36; N, 9.35. Found: C, 69.25; H, 3.16; N, 9.18 %.

2.1.5. Ethyl 3-(6-dibenzothiophen-2-yl–pyridazin-3-ylamino)-3-oxo-2-(phenylhyda zono)propanoate (6)

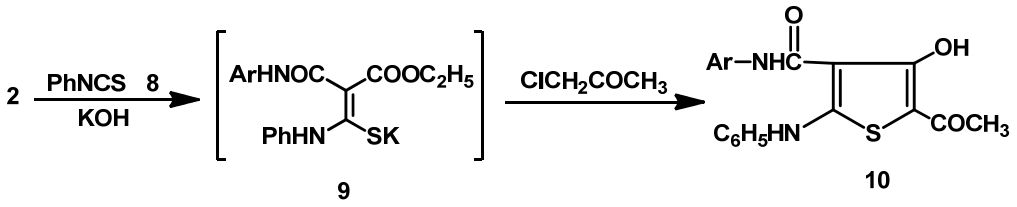
A cold solution of benzene diazonium chloride (0.01 mol) was added to stirred solution of **3** (0.01 mol) in ethanol (30 mL). The reaction mixture was stirred at room temperature for 3 hours and the formed solid product was collected by filtration and washed: Orange, Yield: 78 % (Ethanol) (Scheme 2). M.p.: 170-172 °C. IR (KBr, cm^{-1}): 2930, 2850 ν(CH-aliphatic), 1705, 1685 ν(CO), 3360-3225 ν(NH). ^{1}H NMR (200 MHz, $CDCl_3$): 1.32 (t, 3 H, CH_3), 4.21 (q, 2H, CH_2), 6.83-8.02 (m, 14H, ArH), 8.84, 9.23 (2s, 2H, 2NH, exchangeable). MS (m/z): 495 (M^+). Anal. Calcd. for $C_{27}H_{21}N_5O_3S$: C, 65.44; H, 4.27; N, 14.13. Found: C, 65.32; H, 4.07; N, 13.94 %.

2.1.6. N-(6-Dibenzothiophen-2-yl–pyridazin-3-yl)-5-hydroxy-2-phenyl-2H-1,2,3-triazole-4- carboxamide (7)

A mixture of hydrazone **6** (0.01 mol) and hydrazine hydrate (0.01 mol) in ethanol (30 mL) was heated under reflux for 4 hours. After evaporation of solvent on a vacuum, the solid product was recrystallized: Yellow, Yield 70 % (Acetone) (Scheme 2). M.p.: 180-182 °C. IR (KBr, cm^{-1}): 3480-3255 ν(OH, NH), 1680 ν(CO), 1630 ν(C=N), 1605 ν(C=C). ^{1}H NMR (200 MHz, DMSO-d_6): 6.97-7.94 (m, 14H, ArH), 8.32 (s, 1H, NH, exchangeable), 9.22 (s, 1H, OH, exchangeable). MS (m/z): 464 (M^+). Anal. Calcd. for $C_{25}H_{16}N_6O_2S$: C, 64.64; H, 3.47; N, 18.09. Found: C, 64.42; H, 3.3; N, 17.89 %.

2.1.7. 5-Acetyl-N-(6-dibenzothiophen-2-yl–pyridazin-3-yl)-4-hydroxy-2-(phenylamino) thiophene-3-carboxamide (10)

Phenyl isothiocyanate (0.01 mol) was added to a solution of **2** (0.01 mol) in dimethylformamide (30 mL) containing potassium hydroxide (0.01 mol). The reaction mixture was stirred at room temperature overnight. Then chloroacetone (0.01 mol) was added to the reaction mixture and all was stirred at room temperature overnight. The mixture was poured into crushed ice and hydrochloric acid. The precipitated solid was collected by filtration, washed and dried: Yellow, Yield: 62 % (Ethanol) (Scheme 3). M.p.: 175-177 °C. IR (KBr, cm^{-1}): 3420-3270 ν(OH, NH), 1690, 1675 ν(CO), 1630 ν(C=C). ^{1}H NMR (200 MHz, $CDCl_3$): 2.30 (s, 3H, CH_3), 7.06-7.94 (m, 14H, Ar-H), 8.41, 8.83 (2s, 2H, 2NH, exchangeable), 10.26 (s, 1H, OH, exchangeable). ^{13}C NMR (50 MHz, $CDCl_3$): 20.4 (CH_3), 114.5, 118.2, 127.1, 142.1 (phenyl carbons), 125.3, 135.2, 148.5, 151.1 (thiophene carbons), 118.6, 121.1, 121.5, 122.2, 122.8, 123.2, 124.1, 124.8, 125.4, 127.3, 128.5, 131.2, 136.6, 138.2, 146.3, 150.4 (dibenzothiophene and pyridazine carbons), 178.5, 182.2 (2CO). MS (m/z): 536 (M^+). Anal. Calcd. for $C_{29}H_{20}N_4O_3S_2$: C, 64.91; H, 3.76; N, 10.44. Found: C, 64.80; H, 3.64; N, 10.32 %.



Scheme 3

2.1.8. General procedure for the synthesis of 11a,b

A mixture of ester **2** (0.01 mol) and urea or thiourea (0.01 mol) was heated in ethanol (30 mL) containing sodium ethoxide under reflux for 6 hours then left to cool. The reaction mixture was poured into cold water and the formed solid product was collected by filtration, washed, dried and recrystallized (Scheme 4).

6-(6-Dibenzothiophen-2-yl–pyridazin-3-ylamino)pyrimidine-2,4(3H,5H)-dione (**11a**): Yellow, Yield: 77 % (Butanol). M.p.: 210-212 °C. IR (KBr, cm^{-1}): 3440-3250 ν(OH, NH), 1682, 1665 ν(CO), 1610 ν(C=N). ^{1}H NMR (200 MHz, $CDCl_3$): 3.21 (s, 2H, CH_2), 6.84-8.01 (m, 9H, Ar-H), 8.33, 9.81 (2s, 2H, 2NH, exchangeable). Anal. Calcd. for $C_{20}H_{13}N_5O_2S$: C, 62.00; H, 3.38; N, 18.08. Found: C, 61.82; H, 3.16; N, 17.88 %.

6-(6-Dibenzothiophen-2-yl–pyridazin-3-ylamino)-2-thioxo-2,3-dihydropyrimidine-4(5H)-one (**11b**): Yellow, Yield: 71 % (Butanol). M.p.: 195-197 °C. IR (KBr, cm^{-1}): 3420-3180 ν(OH, NH), 1680 ν(CO), 1625 ν(C=N). ^{1}H NMR (200 MHz, $CDCl_3$): 2.92 (s, 2H, CH_2), 7.16-7.94 (m, 9H, Ar-H), 8.52, 9.80 (2s, 2H, 2NH, exchangeable). Anal. Calcd. for $C_{20}H_{13}N_5OS_2$: C, 59.54; H, 3.25; N, 17.36. Found: C, 59.19; H, 3.11; N, 17.20 %.

2.1.9. General procedure for the synthesis of pyrimidines (12a-d)

A cold solution of aryl diazonium chloride (0.01 mol) namely benzene diazonium chloride or 4-methxybenzene diazonium chloride was added to stirred solution of pyrimidines **11a**,**b** (0.01 mol) in ethanol (30 mL) and sodium acetate. The reaction mixture was stirred at room temperature for 3 hours and the formed solid product was collected by filtration, washed, dried and crystallized from proper solvent (Scheme 4).

6-(6-Dibenzothiophen-2-yl–pyridazin-3-ylamino)-5-(phenylhydrazono)pyrimidine-2,4(3H,5H)-dione (**12a**): yellow, Yield: 74 % (Ethanol). M.p.: 191-193 °C. IR (KBr, cm^{-1}): 3435-3220 ν(OH, NH) 1675, 1665 ν(CO), 1620 ν(C=N). ^{1}H NMR (200 MHz, $CDCl_3$): 5.32, 7.21, 10.41 (3s, 3H, 3NH, exchangeable), 6.74-7.93 (m, 14H, Ar-H). MS (m/z): 491 (M^+). Anal. Calcd. for $C_{26}H_{17}N_7O_2S$: C, 63.53; H, 3.49; N, 19.95. Found: C, 63.40; H, 3.28; N, 19.71 %.

6-(6-Dibenzothiophen-2-yl–pyridazin-3-ylamino)-5-(4-methoxyphenyl) hydrazonopyrimidine-2,4(3H,5H)-dione (**12b**): Yellow, Yield: 77 % (Ethanol). M.p.: 211-213 °C. IR (KBr, cm^{-1}): 3460-3235 ν(OH, NH), 1670, 1665 ν(CO), 1630 ν(C=N). ^{1}H NMR (200 MHz, $CDCl_3$): 3.55 (s, 3H, OCH_3), 7.44, 8.23, 9.82 (3s, 3H, 3NH, exchangeable) 6.91-8.03 (m, 13H, Ar-H). MS (m/z): 521 (M^+). Anal. Calcd. for $C_{27}H_{19}N_7O_3S$: C, 62.18; H, 3.67; N, 8.80. Found: C, 61.88; H, 3.50; N, 8.62 %.

6-(6-Dibenzothiophen-2-yl–pyridazin-3-ylamino)-5-phenyl hydrazono-2-thioxo-2,3-dihydropyrimidine-4(5H)-one (**12c**): Yellow, Yield: 69 % (Ethanol). M.p.: 217-219 °C. IR (KBr, cm^{-1}): 3410-3210 ν(NH) 1680, 1668 ν(CO), 1620 ν(C=N). ^{1}H NMR (200 MHz, $CDCl_3$): 5.63, 9.28, 9.92 (3s, 3H, 3NH, exchangeable) 7.10-8.04 (m, 14H, Ar-H). MS (m/z): 507 (M^+). Anal. Calcd. for $C_{27}H_{17}N_7OS_2$: C, 61.52; H, 3.38; N, 19.32. Found: C, 61.37; H, 3.25; N, 19.21 %.

6-(6-Dibenzothiophen-2-yl–pyridazin-3-ylamino)-5-(4-methoxyphenyl)hydrazono-2-thioxo-2,3-dihydropyrimidine-4(5H)-one (**12d**): Yellow, Yield: 80 % (Ethanol). M.p.: 184-186 °C. IR (KBr, cm^{-1}): 3420-3190 ν(OH, NH), 1682, 1670 ν(CO), 1626 ν(C=N). ^{1}H NMR (200 MHz, $CDCl_3$): 3.33 (s, 3H, OCH_3), 8.33, 8.94, 10.40 (3s, 3H, 3NH, exchangeable) 6.83-7.94 (m, 13H, Ar-H). MS (m/z): 537 (M^+). Anal. Calcd. for $C_{27}H_{19}N_7O_2S_2$: C, 60.32; H, 3.56; N, 18.24. Found: C, 60.24; H, 3.42; N, 18.11 %.

2.1.10. General procedure for the synthesis of pyrimidines (13a-d)

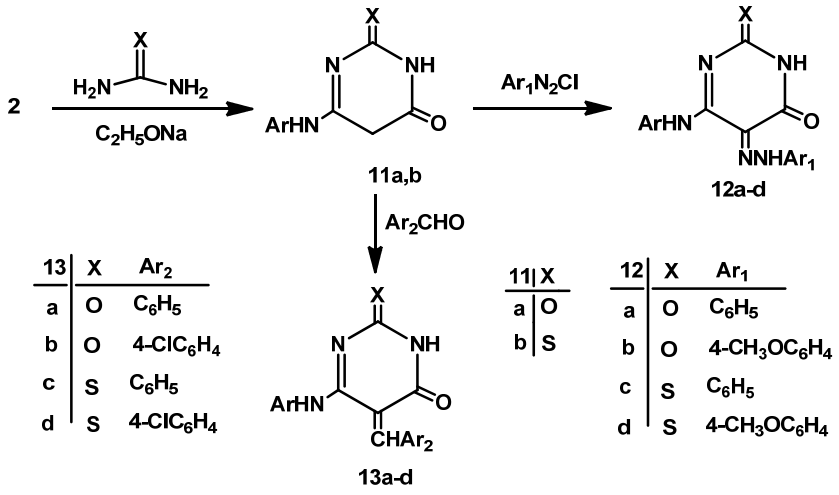
A mixture of pyrimidine **11a**,**b** (0.01 mol) and aromatic aldehydes, e.g. benzaldehyde and 4-chlorobenzaldahyde (0.01 mol) was heated in ethanol (30 mL) under reflux for 6 hours then left to cool. The solid product was collected by filtration and recrystallized from proper solvent (Scheme 4).

5-Benzylidene-6-(6-dibenzothiophen-2-yl–pyridazin-3-ylamino)pyrimidine-2,4 (3H,5H)-dione (**13a**): Yellow, Yield: 85 % (Ethanol). M.p.: 188-190 °C. IR (KBr, cm^{-1}): 3415-3140 ν(OH, NH) 1675, 1667 ν(CO), 1620 ν(C=N), 1605 ν(C=C). ^{1}H NMR (200 MHz, $CDCl_3$): 8.34, 10.13 (2s, 2H, 2NH, exchangeable), 6.91-7.93 (m, 15H, Ar-H and CH=C). MS (m/z): 475 (M^+). Anal. Calcd. for $C_{27}H_{17}N_5O_2S$: C, 68.20; H, 3.60; N, 14.73. Found: C, 68.03; H, 3.48; N, 14.57 %.

5-(4-Chlorobenzylidene)-6-(6-dibenzothiophen-2-yl–pyridazin-3-ylamino)pyrimidine-2,4(3H,5H)-dione (**13b**): Yellow Yield: 87 % (Ethanol). M.p.: 167-169 °C. IR (KBr, cm^{-1}): 3400-3175 ν(OH, NH), 1681, 1668 ν(CO), 1625 ν(C=N),1616 ν(C=C). ^{1}H NMR (200 MHz, $CDCl_3$): 9.24, 10.61 (2s, 2H, 2NH, exchangeable), 7.10-8.22 (m, 14H, Ar-H and CH=C). Anal. Calcd. for $C_{27}H_{16}ClN_5O_2S$: C, 63.59; H, 3.16; N, 13.73. Found: C, 63.43; H, 3.06; N, 13.57 %.

5-Benzylidene-6-(6-dibenzothiophen-2-yl–pyridazin-3-yl amino)-2-thioxo-2,3-dihydropyrimidine-4(5H)-one (**13c**): Yellow, Yield: 78 % (Ethanol). M.p.: 182-184 °C. IR (KBr, cm^{-1}): 3480-3160 ν(OH, NH), 1680, 1665 ν(CO), 1625 ν(C=N), 1612 ν(C=C). ^{1}H NMR (200 MHz, $CDCl_3$): 8.51, 9.87 (2s, 2H, 2NH, exchangeable), 6.84-7.92 (m, 15H, Ar-H and CH=C). Anal. Calcd. for $C_{27}H_{17}N_5O_2S$: C, 65.97; H, 3.49; N, 14.25. Found: C, 65.75; H, 3.33; N 14.11 %.

5-(4-Chlorobenzylidene)-6-(6-dibenzothiophen-2-yl–pyridazin-3-ylamino)-2-thioxo-2,3-dihydropyrimidine-4(5H)-one (**13d**): yellow, Yield: 81 % (Ethanol). M.p.: 202-204 °C. IR (KBr, cm^{-1}): 3455-3215 ν(OH, NH), 1675, 1662 ν(CO), 1625 ν(C=N), 1610 ν(C=C). ^{1}H NMR (200 MHz, $CDCl_3$): 9.37, 10.21 (2s, 2H, 2NH, exchangeable), 6.90-8.11(m, 14H, Ar-H and CH=C). Anal. Calcd. for $C_{27}H_{16}ClN_5O_2S$: C, 61.65; H, 3.07; N, 13.31. Found: C, 61.71; H, 3.16; N, 13.19 %.



Scheme 4

2.1.11. General procedure for the synthesis of pyridines (14a,b)

To a solution of ester **2** (0.01 mol) in dimethylformamide (30 mL) containing triethylamine (few drops), either malononitrile or ethyl cyanoacetate (0.01 mol) was added. After heating of the reaction mixture for 6 hours and cooling, the mixture was poured into crushed ice and hydrochloric acid. The precipitated product was collected by filtration, washed and dried (Scheme 5).

Ethyl 4,6-diamino-1-(6-dibenzothiophen-2-yl-pyridazin-3-yl)-2-oxo-1,2-dihydropyridine-3-carboxylate (**14a**): Yellow, Yield: 63 % (Ethanol). M.p.: 195-197 °C. IR (KBr, cm^{-1}): 3390-3180 ν(NH_2), 3050 ν(CH-aromatic), 1705, 1680 ν(CO), 1620 ν(C=C). ^{1}H NMR (200 MHz, $CDCl_3$): 1.31 (t, 3H, CH_3), 4.23 (q, 2H, CH_2), 6.92-7.87 (m, 9H, Ar-H), 7.11 (s, 1H, pyridine H), 8.44, 8.93 (2s, 4H, $2NH_2$, exchangeable). MS (m/z): 457 (M^+). Anal. Calcd. for $C_{24}H_{19}N_5O_3S$: C, 63.01; H, 4.19; N, 15.31. Found: C, 62.88; H, 4.05; N, 15.15 %.

Ethyl 4-amino-1-(6-dibenzothiophen-2-yl-pyridazin-3-yl)-6-hydroxy-2-oxo-1,2-dihydropyridine-3-carboxylate (**14b**): Yellow, Yield: 65 % (Ethanol). M.p.: 186-188 °C. IR (KBr, cm^{-1}): 3520-3310 ν(OH, NH_2), 3040 ν(CH-aromatic), 1700, 1683 ν(CO), 1626 ν(C=C). ^{1}H NMR (200 MHz, $CDCl_3$): 1.29 (t, 3H, CH_3), 4.31(q, 2H, CH_2), 6.98-7.92 (m, 9H, Ar-H), 6.91 (s, 1H, pyridine H), 6.33 (s, 2H, NH_2, exchangeable), 9.82 (s, 1H, OH). Anal. Calcd. for $C_{24}H_{18}N_4O_4S$: C, 62.87; H, 3.96; N, 12.22. Found: C, 62.33; H, 3.85; N, 12.11 %.

2.1.12. Ethyl 6-amino-5-cyano-1-(6-dibenzothiophen-2-yl-pyridazin-3-yl)-2-oxo-4-phenyl-1,2-dihydro pyridine-3-carboxylate (15)

The same procedures described for the synthesis of compounds **14a**,**b**. Yellow, Yield: 68 % (Ethanol) (Scheme 5). M.p.: 201-203 °C. IR (KBr, cm^{-1}): 3385-3190 ν(NH_2), 3040 ν(CH-aromatic), 2220 ν(C≡N), 1705, 1685 ν(CO), 1630 ν(C=C). ^{1}H NMR (200 MHz, $CDCl_3$): 1.31 (t, 3H, CH_3), 4.32 (q, 2H, CH_2), 6.80-7.93 (m, 14H, Ar-H), 8.34 (s, 2H, NH_2, exchangeable). Anal. Calcd. for $C_{31}H_{21}N_5O_3S$: C, 68.49; H, 3.89; N, 12.88. Found: C, 68.36; H, 3.81; N, 12.73 %.

2.2. Instrumentation

Melting points of the prepared products are uncorrected. All reactions were monitored by thin layer chromatography (TLC) carried out on 0.2 mm silica gel 60 F254 (Merck) plates. IR spectra in KBr were recorded using a Perkin-Elmer 298 spectrophotometer. ^{1}H- and ^{13}C NMR spectra were obtained using a Varian Gemini 200 MHz and 50 MHz instrument. The solvent used for NMR analysis was $CDCl_3$, unless stated otherwise. Mass spectra were obtained using a Shimadzu GCMS-QP 1000 EX mass spectrometer.

3. Results and discussion

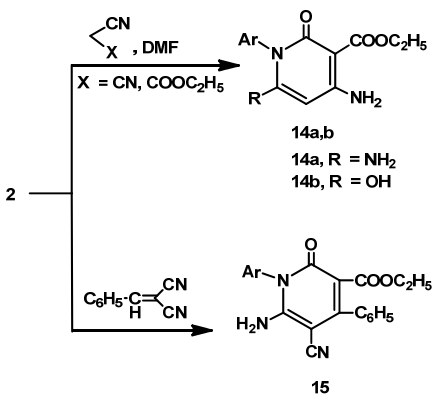
Schemes 1-5 show the synthetic pathways to prepare the target compounds **2**-**15**. The key substrate ester **2** was synthesized from the reaction of aminopyridazine derivative [25] **1** and diethyl malonate (Scheme 1). The IR spectrum of compound **2** showed two strong absorption bands at 1730 and 1685 cm^{-1} assigned to ester and amide carbonyl groups respectively. Another band was revealed at 3380-3280 cm^{-1} characterized for amide NH. ^{1}H NMR spectrum displayed also a triplet signal at 1.3 ppm assigned for CH_3 group, a quartet signal at 4.3 ppm due to CH_2 and signal at 8.8 ppm (D_2O exchangeable) due to NH proton. Furthermore, ^{13}C NMR spectrum of compound **2** displayed signals at 172.2 and 175.4 corresponding to two CO respectively.

The reactivity of the ester **2** towards some reagents with the aim of the synthesis of novel five membered heterocycles was investigated.

Thus, the reaction of compound **2** with aromatic aldehydes *viz* benzaldehyde afforded ethyl 2-(6-dibenzothiophen-2-yl-pyridazin-3-ylcarbamoyl)-3-phenylacrylate (**3**). Cyclization of **3** by hydrazine hydrate or phenylhydrazine to pyrazole derivatives **4a**,**b** was achieved by refluxing in ethanol. The structures of the products were assigned on the basis of their spectral data and elemental analysis. On the other hand, the reaction of compound **2** with salicyldehyde furnished chromene derivative **5**. Treatment of compound **2** with benzene diazonium chloride afforded the hydrazone derivative **6**, which in turn reacted with hydrazine hydrate to give 1,2,3-triazole derivative **7** (Scheme 2).

On the other hand, the reaction of compound **2** with phenyl isothiocyanate **8** in dimethylformamide solution afforded the intermediate **9**. Cyclization of the latter by chloroacetone gave thiophene derivative **10** (Scheme 3).

Also, the reactivity of ester **2** for the synthesis of six membered heterocycles was depicted. Thus, the reaction of ester **2** with urea and/or thiourea in ethanolic sodium ethoxide solution afforded pyrimidinones **11a**,**b**.



Scheme 5

IR spectra displayed absorption band at 3375-3250 cm^{-1} corresponding to NH group. Treatment of pyrimidinones **11a**,**b** with aryl diazonium chloride or aromatic aldehydes result in the formation of pyrimidinone **12a-d** and **13a-d**, respectively (Scheme 4).

The reaction of compound 2 with active methylene reagents *viz* malononitrile and ethyl cyanoacetate in dimethylformamide containing triethyl amine afforded pyridinone derivatives **14a**,**b**, respectively (Scheme 5). Similarly, the reaction of **2** with α-cyanocinnamonitrile furnished ethyl 6-amino-5-cyano-1-(6-dibenzothiophen-2-yl-pyridazin-3-yl)-2-oxo-4-phenyl-1,2-dihydropyridine-3-carboxylate (**15**).

4. Conclusion

In the present paper we describe the reaction of ethyl 3-(6-dibenzothiophen-2-yl-pyridazin-3-ylamino)-3-oxopropanoate with various reagents providing novel five and six membered heterocycle derivatives attached to pyridazine and dibenzothiophene moieties. The structures of all products were confirmed by the elemental analysis and spectroscopic studies.

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