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New route for the synthesis of thieno[2, 3- d]pyrimidine derivatives

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Abstract: Condensation of ethylthioglycolate with 2,4-dichloro-6-phenylpyrimidine-5-carbonitrile afforded ethyl 5-amino-2-chloro-4-phenylthieno[2,3-d]pyrimidine-6-carboxylate in alkalineethanol. Chlorine atom of the latter compound was easily replaced by secondary amines in ethanol to achieve a new group of ethyl5-amino -4-phenylthieno[2,3-d]pyrimidine-6-carboxylate derivatives.

Keywords: Ethylthioglycolate, 2,4-Dichloro-6-phenylpyrimidine-5-carbonitrile, Ethyl-5-amino-2-chloro-4-phenylthieno[2,3-d]pyrimidine-6-carboxylate, Substitution, Cyclocondensation.

Introduction

Pyrimidine and thienopyrimidine derivatives have fascinated a great magnitude of interest containing to their medicinal activities [1–4]. Pyrimidine derivatives and heterocyclic annelatedpyrimidines continue to attract great interest belong to the wide variety of interestingbiological activities observed for these compounds, such as anticancer [4], antiviral [5],antitumor [6] and anti-inflammatory [7-8]. Also, the fastgrowthin the literature concerning with the preparation and biological activity of the thienopyrimidinederivatives encouraged us to synthesize new derivatives of fused pyrimidine, thienopyrimidine derivatives.

Results and Discussion

Despite of the most previous reports on the literature which startedthe preparation of this class of heterocycles from the thiophen derivatives, our route starts from pyrimidine by the cyclocondensation Reactionof 2, 4-dichloro-6-phenylpyrimidine-5-carbonitrile **1** with ethylthioglycolate**2** as shown in Scheme **1**.

This condensation carries out through two stag including: a) nucleophilic substitution of the thiol moiety of ethylthioglycolate**2**over the number 4 position of 2,4-dichloro-6-phenylpyrimidine-5-carbonitrile**1**;b) alkaline condensation of active methylene with the neighbor nitrilmoiety.Replacement of the chlorine atom of ethyl 5-amino-2-chloro-4-phenylthieno[2,3-d]pyrimidine-6-carboxylate**3** with amines in boiling ethanol afforded the 2, 5 diamino derivatives**4a-d**of this heterocyclic ring system.The structural assignment of compounds **3**&**4a-d** based upon the spectral and microanalytical data. The IR spectrum of compound **3** did not show a sharp band around 2200- 2400 cm^{-1} belonging to stretching vibration of nitrile group of precursor **1** but showed bands on 1720 and 3300 & 3450 cm^{-1} concerning to carbonyl and amine moieties of product **3** respectively. More proof came from ^{1}HNMR spectrum of compound **3**, whichshowed signals at 1.2, 4.2, 4.5 (removable with D_2O) and 7.3- 7.6 ppm due to CH_3, OCH_2, NH_2 and aromatic protons. Further proof came from mass

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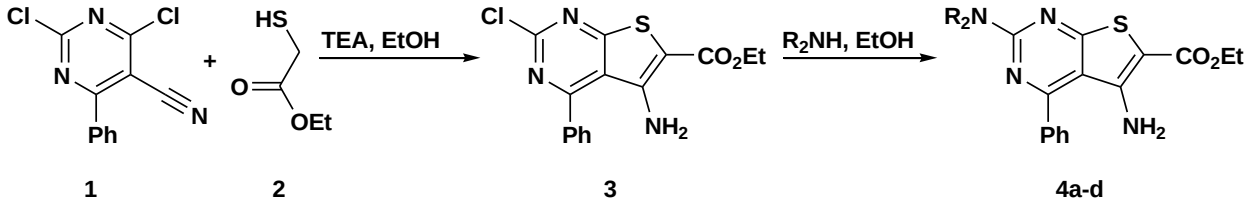
spectrum of compound **3**, which showed two signals at m/e= 333 & 335 with the 3 to 1 ratio, confirming the existence of a chlorine atom on the molecule.



1 **2** **3** **4a-d**

R_2NH= a: Morpholin, b: Piperidin, c: 1-Methylpiperazin, d: Pyrrolidin

Scheme 1: Conversion of 2, 4-dichloro-6-phenylpyrimidine-5-carbonitrile to thieno[2,3-d]pyrimidine derivatives.

^{1}HNMR spectra of compounds **4a-d** showed the signals belonging to the methylens (and methyl) moieties of the substituted amine group. This result amplified by the lack of the chlorine isotopic effect in the mass spectra of compounds **4a-d**. Elemental analysisof all compounds have no significant difference with the calculated values.

Experimental

The melting points were recorded on an Electrothermal type 9100 melting point apparatus. The IR spectra were obtained on a 4300 Shimadzu Spectrometer. ^{1}H NMR (300 MHz) spectra of products were carried out on Bruker Avance spectrometer in Chloroform-d ($CDCl_3$) with tetramethylsilane (TMS) as an internal standard. The mass spectra were scanned on a Varian Mat CH-7 instrument at 70 eV. Elemental analysis was obtained on a Thermo Finnigan Flash EA microanalyzer. The reaction progress of the reactions and purity of all prepared compounds was monitored by TLC using chloroform as mobile phase.

Ethyl 5-amino-2-chloro-4-phenylthieno[2,3-d]pyrimidine-6-carboxylate 3:

2,4-Dichloro-6-phenylpyrimidine-5-carbonitrile**1** (2.49 gr, 10 mmol), ethylthioglycolate**2** (1.25 gr, 10 mmol) and triethylamine (2ml) dissolved in ethanol (25 ml) and stirred for 30 minutes. Then the reaction mixture heated under reflux condition for 8 hours, poured into the water (25 ml) and kept overnight. The precipitant was filtered off and dried on 80 °C to obtain Ethyl 5-amino-2-chloro-4-phenylthieno[2,3-d]pyrimidine-6-carboxylate **3**.

Yield 2.66 g (80%), white powder, mp182-183 °C°C.IR spectrum, ν, cm^{-1}: 1635 (C=O), 3250& 3400 (NH_2); ^{1}H NMR spectrum, δ, ppm: 1.2 (t, 3H, CH_3), 4.2 (q, 2H, OCH_2), 4.5 (broad, 2H, NH_2) and 7.3-7.6(5H, m, H Ph); Mass spectrum, *m*/*z* (*I*rel, %): 333 $[M]^+$ (65), 335 $[M+2]^+$(23). Elemental Analysis; Found: C, 53.73; H, 3.75; N, 12.64; S, 9.44. Calculated for $C_{15}H_{12}ClN_3O_2S$: C, 53.97; H, 3.62; N, 12.59; S, 9.61.

General procedure for the reaction of ethyl 5-amino-2-chloro-4-phenylthieno[2,3-d]pyrimidine-6-carboxylatewith amines:

Ethyl 5-amino-2-chloro-4-phenylthieno[2,3-d]pyrimidine-6-carboxylate **3**(0.334 gr, 1 mmol) and appropriate amine (2 mmol) dissolved in ethanol (5 ml) and heated under reflux condition for 6 hours, poured into the water (5 ml) and kept overnight.The precipitant was filtered off and dried on 80 °C to obtain compounds **4a-d**.

Ethyl 5-amino-2-(morpholin-4-yl)-4-phenylthieno[2,3-d]pyrimidine-6-carboxylate 4a:

Yield 0.290 g (75%), white powder, mp142-144 °C.IR spectrum, ν, cm^{-1}: 1640 (C=O), 3200& 3400 (NH_2); ^{1}H NMR spectrum, δ, ppm: 1.15 (t, 3H, CH_3), 3.6 (m, 8H, $O(CH_2)_2$& $N(CH_2)_2$), 4.13 (q, 2H, OCH_2), 4.5 (broad, 2H, NH_2) and 7.3- 7.6 (5H, m, H Ph); Mass spectrum, *m*/*z* (*I*rel, %): 384 $[M]^+$ (28). Elemental Analysis; Found:C, 59.17; H, 5.43; N, 14.73; S, 8.14; Calculated for $C_{19}H_{20}N_4O_3S$:C, 59.36; H, 5.24; N, 14.57; S, 8.34.

Ethyl 5-amino-4-phenyl-2-(piperidin-1-yl)thieno[2,3-d]pyrimidine-6-carboxylate 4b:

Yield 0.305 g (80%), white powder, mp138-140°C.IR spectrum, ν, cm^{-1}: 1645 (C=O), 3280& 3420 (NH_2); ^{1}H NMR spectrum, δ, ppm: 1.15 (t, 3H, CH_3),1.3-1.65 (m, 6H, $CH_2CH_2CH_2$), 3.6 (t, 4H, $N(CH_2)_2$), 4.13 (q, 2H, OCH_2), 4.5 (broad, 2H, NH_2) and 7.3- 7.6 (5H, m, H Ph); Mass spectrum, *m*/*z* (*I*rel,

%): 382 $[M]^+$; Elemental Analysis; Found:C, 62.65; H, 5.89; N, 14.48; S, 8.19; Calculated for $C_{20}H_{22}N_4O_2S$:C, 62.80; H, 5.80; N, 14.65; S, 8.38.

Ethyl 5-amino-2-(4-methylpiperazin-1-yl)4-phenyl-thieno[2,3-d]pyrimidine-6-carboxylate 4c:

Yield 0.260 g (65%), white powder, mp101-103 °C.IR spectrum, ν, cm^{-1}: 1635 (C=O), 3280& 3400 (NH_2); ^{1}H NMR spectrum, δ, ppm: 1.16 (t, 3H, CH_3), 1.9 (m, 7H, $CH_3N(CH_2)_2$), 3.5 (t, 4H, $N(CH_2)_2$), 4.12 (q, 2H, OCH_2), 4.5 (broad, 2H, NH_2) and 7.3- 7.6 (5H, m, H Ph); Mass spectrum, *m/z* (*I*rel, %): 397 $[M]^+$ (40); Elemental Analysis; Found:C, 60.65; H, 5.92; N, 17.45; S, 7.88; Calculated for $C_{20}H_{23}N_5O_2S$:C, 60.43; H, 5.83; N, 17.62; S, 8.07.

Ethyl 5-amino-4-phenyl-2-(pyrrolidin-1-yl)thieno[2,3-d]pyrimidine-6-carboxylate 4d:

Yield 0.295 g (80%), white powder, mp130-132 °C.IR spectrum, ν, cm^{-1}: 1635 (C=O), 3250& 3400 (NH_2); ^{1}H NMR spectrum, δ, ppm: 1.15 (t, 3H, CH_3), 1.65 (t, 4H, CH_2CH_2), 3.6 (t, 4H, $N(CH_2)_2$), 4.13 (q, 2H, OCH_2), 4.5 (broad, 2H, NH_2) and 7.3- 7.6 (5H, m, H Ph); Mass spectrum, *m/z* (*I*rel, %): 368 $[M]^+$ (25); Elemental Analysis; Found:C, 61.76; H, 5.33;N, 15.36; S, 8.51; Calculated for $C_{19}H_{20}N_4O_2S$:C, 61.94; H, 5.47; N, 15.21; S, 8.70

Conclusion

In conclusion, sequential reaction of 2,4-dichloro-6-phenylpyrimidine-5-carbonitrile with ethylthioglycolate and amines is a general and efficient rout to thieno[2, 3- d]pyrimidine derivatives.

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