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Synthesis of Some New Thieno [2, 3-d] pyrimidines

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4-IMINO-3N- (substituted) -5-(thiophen-2-yl) -3,4,dihydro-thieno [2,3-d] pyrimidine-2(1H) (2) was used as precursor for the preparation of some novel 1-(2,3-dihydro-3-methyl-5-(thiophen-2-yl)-2-thioxothieno[2,3-d] pyrimidine – 4 (1H)-ylidene) -3-methyl or phenylthiourea (3a,b) and also for the preparation of 2-Hydrazinyl -3-methyl-5- (thiophen-2-yl)- thieno [2,3-d] pyrimidin-4(3H-imine) (5) which was reacted with methyl and phenylisothiocyanat at room temp. to give compounds 6a,b. Also, 5 was reacted with methylisothiocyanate, and / or formic acid to give the triazolopyrimidines 7 and 8. Also, 5 was reacted with nitrous acid to give the 2-azido thienopyrimidine 9.

Keywords: Thienopyrimidine, Triazolopyrimidines and Azido thienopyrimidine .

Fused pyrimidines still attract considerable attention of researchers in different countries because of their great practical uses, primarily, due to a very wide spectrum of their biological activities [(1)]. Thienopyrimidines occupy a special position among these compounds because they are valued not only for their rich and varied chemistry, but also for many important biological properties such as antitumor [(2)] antiviral [(3)], antibiotic [(4)], as potential anti-HIV agents [(5)], against HSV-I [(6, 7)], analgesic and CNS depressant activity [(8, 9)]. Other thieno [2,3-d] pyrimidines have been reported as potential anti-inflammatory agents[(10)]. Also, some aminothienopyrimidine and thienotriazolo pyrimidine derivatives have been reported for their significant anticonvulsant activity [(11)]. Thus in view of these observations and as continuation of our previous work on the synthesis of organic compounds have biological interest [(12-16)], we synthesize some newer thienopyrimidine derivatives for their expected biological activity.

Results and Discussion

Upon treating 2-amino-4-(thiophen-2-yl)thiophene-3-carbonitrile (1) with methylisothiocyanate in pyridine under reflux (3hr), afforded the corresponding 4-imino-3N-(substituted)-5-(thiophen-2-yl)-3,4,dihydro-thieno[2,3-d]pyrimidine-2(1H) (2) . When 2 was heated under reflux with methyl and / or phenyl isothiocyanates in dry benzene, 1-(2, 3-dihydro-3-methyl-5-(thiophen-2-yl)-2-thioxothieno [2,3-d] pyrimidin-4(1H)-ylidene)-3-methyl or 3-phenylthiourea (3a,b) were obtained. The IR spectra of products 3a, b were charachterized by the

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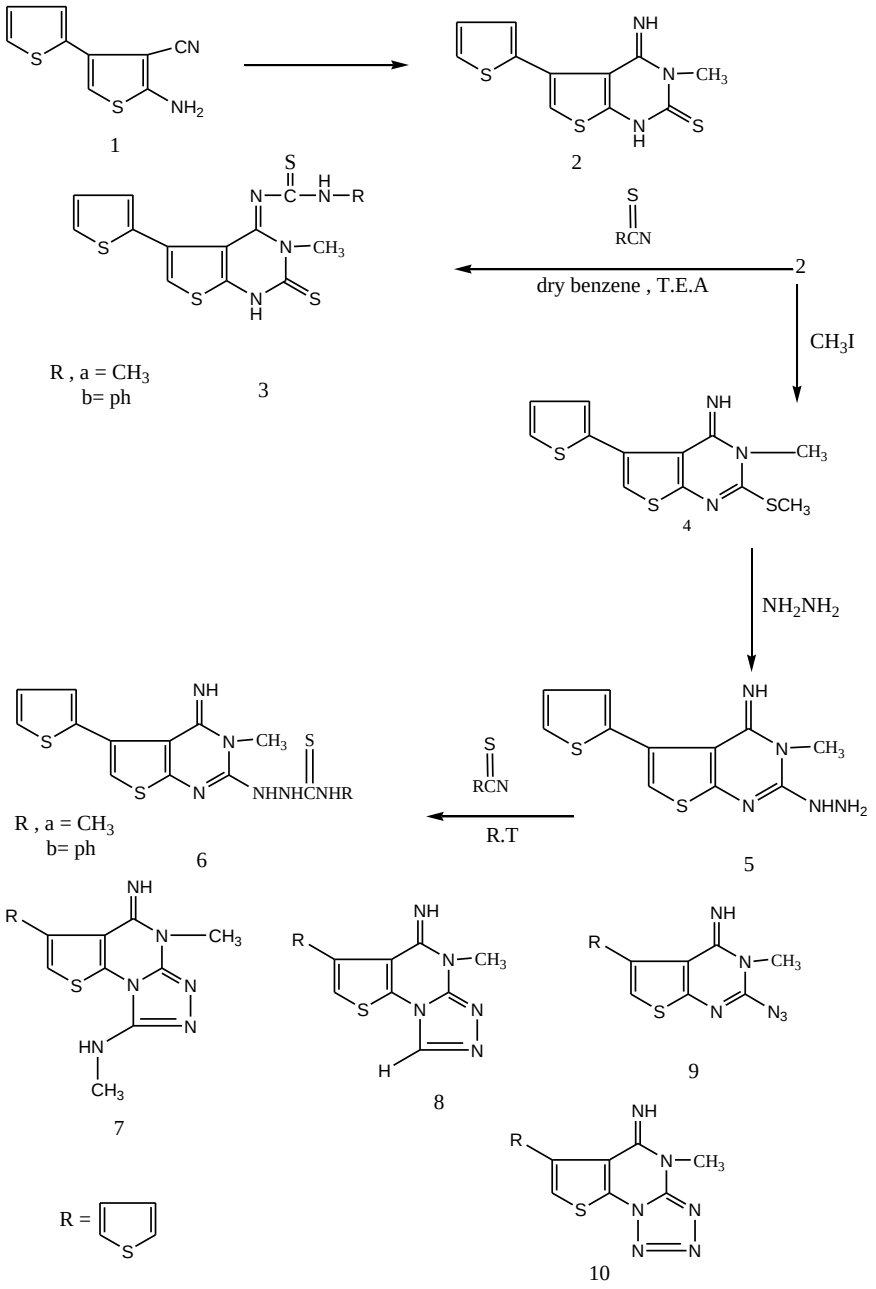
presence of γ NH at 3275, 3067 and γc=s at 1246, 1212 cm^{-1} regions. Also, reaction of 2 with methyl iodide in the presence of anhydrous potassium carbonate yielded 3-methyl-2-(methyl thio)-5-(thiophen-2-yl) thieno [2,3-d] pyrimidine-4(3H) imine (4). Structure of product 4 was characterized by the presence of only one γ NH at 3334 cm^{-1} region.

Thermal fusion of 4 with hydrazine hydrate afforded the 2-hydrazinyl-3-methyl-5-(thiophen-2-yl) thieno [2,3-d] pyrimidine-4(3H)-imine (5). However, upon heating product 4 with hydrazine hydrate under reflux in ethanol, the expected 2-hydrazinyl-3-methyl-5-(thiophen-2-yl) thieno [2,3-d] pyrimidine-4-(3H)-imine 5 cannot be isolated.

IR spectrum of product 5 was characterized by the presence of γ NH, NH_2 at 3400, 3300, 3100cm^{-1} and it's ^{1}HNMR spectrum showed signals at δ: 4.10-4.30 (b,1H NH) , 4.40-4.60 (b,1H,NH) ppm (D_2O exch.)

Compound 5 was stirred at room temp. (ca≈25°) with methyl or phenylisothiocyante to give 1-(3, 4-dihydro-4-imino-3-methyl-5(thiophen-2-yl) thieno [2, 3-d] pyrimidin-2-yl)-4-methyl or phenylthiosemicarbazide (6a, b). The IR spectra of products 6a, b were characterized by the presence of *ν*NH at 3400-3100 beside C=S at 1225 cm^{-1} regions. ^{1}HNMR spectrum of product 6a was characterized by the presence of two signals at δ: 2.50 and 3.30 for CH_3 and N-CH_3 protons. When 5 was reacted with formic acid, 9-methyl-8-imino-7-(thiophen-2-yl) thieno[2,3-d]-triazolo pyrimidine (8) was obtained in good yield. Compound 8 was characterized by the presence of CH signal of the triazole ring in its ^{1}HNMR spectrum at δ: 8.20 ppm. Upon reacting hydrazinothienoprimidine (5) with methylisothiocyante in the presence of catalytic amount of triethylamine, afforded the 9-methyl-8-imino-7-(thiophen-2-yl) thieno [2, 3-d] - triazolopyrimidine (7) . Structure of product 7 was characterized by the presence of *ν*NH at 3400, 3100 cm^{-1} region, in it's IR spectrum and the absence of *ν*C=S. ^{1}HNMR spectrum accords with the proposed structure. Mass spectrum revealed m/z (M^+) at: 316. Furthermore, when the hydrazinothienopyrimidine (5) was allowed to react with nitrous acid at room temperature (≈25°C), the 2-azido-3-methyl-5 (thiophen-2-yl) thieno [2,3-d] pyrimidin-4(3H)-imine (9) was obtained rather than the expected terazolo-thienopyrimidine (10) . Structure of product 9 was elucidated by its IR, ^{1}HNMR and mass spectral data. The IR spectrum revealed the presence of the azido absorption at 3133 cm^{-1} region.


1
2
3
R , a = CH3
b= ph
RCN
dry benzene , T.E.A
CH3I
4
NH2NH2
5
RCN
R.T
6
R , a = CH3
b= ph
7
8
9
10
R =

Scheme 1

Experimental

Melting points were determined on the Electrothermal 9100 melting point apparatus (Electrothermal, UK) and are uncorrected. Microanalytical date (Elementar, Vario El, USA) were found within ± 0.4% of the theoretical values. The IR spectra (KBr) were recorded on a FT-IR NEXCES spectrophotometer (Shimadzu, Japan). The ^{1}H NMR spectra were measured with a Jeol ECA 500 MHz (Japan) in DMSO-d_6 or $CDCl_3$ and chemical shifts were recorded in δ ppm relative to TMS. Mass spectra (El) were run at 70 eV with a finnigan SSQ 7000 spectrometre (Thermo-Instrument System Incorporation, USA). The reaction was followed by TLC (silica gel, aluminum sheets 60 F_{254}, Merck, Germany).

1-(2,3-Dihydro -3- methyl-5- (thiophen-2-yl)-2-thioxothieno [2,3-d] pyrimidine-4(1H)-ylidene)-3-methyl or phenylthiourea (3a,b)

General procedure

A mixture of 2 (0.01mol) and methyl or phenylisothiocyanate (0.12 mol) in dry benzene (50 ml), and in presence of drops of triethylamine was heated under reflux for 15 hr. The reaction mixture was concentrated and left to cool and then the solid product separated out was filtered off, dried and reclystallized from methanol to give 3a, b (*c.f.* Tables 1 and 2).

3-Methyl-2-(methylthio)-5- (thiophen-2-yl thieno [2,3-d] - pyrimidin-4(3H)-imine (4)

A mixture of 2 (0.01 mol) and methyl iodide (0.012 mol) in dry acetone (50 ml) was heated under reflux for 1 hr in presence of anhydrous potassium carbonate (0.01 mol). The reaction mixture was filtered off while hot; the filtrate was concentrated and then left to cool. The solid product which separated out was filtered off, dried and reclystallized from ethyl acetate to give 4 (*c.f.* Table 1 and 2).

2-Hydrazinyl-3-methyl-5-(thiophen-2-yl)-thieno [2,3-d]-pyrimidin-4(3H-imine (5)

A mixture of 2 and hydrazine hydrate (20 ml) was heated at 170-180° (thermal fusion for one hour). The residue obtained after cooling was washed with methanol, filtered off, dried and crystallized from ethanol to give 5 (*c.f.* Tables 1 and 2).

1-(3,4-Dihydro-4-imino-3methyl-5-(thiophen-2-ylthieno[2,3-d] pyrimidin-2-yl)-4-methyl or phenylthiosemicarbazide (6 a,b)

A mixture of 5 (0.01 mol) and methylisothiocyanate (0.012 mol) in methylenechloride and in presence of triethylamine (0.5 ml), was stirred at room temp. for 24 hr. the solvent was evaporated till dryness under reduced pressure. The residue remained was treated with methanol and the solid product obtained was filtered off, dried and crystallized from ethanol to give 6 a,b *(c.f.* Tables 1 and 2).

TABLE 1. Characterization of the synthesized products .

Compd.	Yield %	M.P , °C (solvent)	Molecular Formula	Analysis (calc. / Found)		
				C %	H %	N %
3 a	80	140 °C (Me. OH)	$C_{13}H_{12}N_4S_4$ (352)	Cal : 44.28 , F : 44.15 ,	3.43 , 3.40 ,	15.89 15.80
3b	90	100 °C (Me. OH)	$C_{18}H_{14}N_4S_4$ (414)	Cal : 52.14 , F : 52.16 ,	3.42 , 3.40 ,	13.51 13.35
4	70	220 °C (ethyl acetate)	$C_{12}H_{11}N_3S_3$ (293.42)	Cal : 49.12 , F : 49.05,	3.77 , 3.70 ,	14.32 14.28
5	75	265 °C (Et. OH)	$C_{11}H_{11}N_5S_2$ (276.34)	Cal : 47.80 , F : 47.65 ,	3.64 , 3.55 ,	25.34 25.26
6 a	65	210 °C (Et. OH)	$C_{13}H_{14}N_6S_3$ (350.48)	Cal : 44.54 , F : 44.50 ,	4.02 , 4.00 ,	23.98 23.90
6 b	90	100 °C (Et. OH)	$C_{18}H_{16}N_6S_3$ (412)	Cal : 52.40 , F : 52.28 ,	3.90 , 3.85 ,	20.37 20.30
7	70	237 °C (Et. OH)	$C_{13}H_{12}N_6S_2$ (316.40)	Cal : 49.34 , F : 49.25 ,	3.82 , 3.80 ,	26.56 26.48
8	75	290 °C (But. OH)	$C_{12}H_9N_5S_2$ (287.35)	Cal : 50.15 , F : 50.05 ,	3.15 , 3.10 ,	24.37 24.30
9	60	280 °C (But. OH)	$C_{11}H_8N_6S_2$ (288.34)	Cal : 45.81 , F : 45.75 ,	2.79 , 2.70 ,	29.14 29.10

TABLE 2. Spectral determinations of products (3-9) .

Compd.	IR (KBr) / Cm^{-1} υNH	υC=S	^{1}HNMR (DMSO-d_6 or $CDCl_3$) δ	Mass
3a	3275 3067	1246 1212	$CDCl_3$: 1.62 (s,3H , CH_3) , 3.40 (t , 3H, N-CH_3) , 5.54 (s, 1H , NH) , 6.80-7.50 (m , 4H thio , NH)	352
3b	3300 3100	1240 1226	$CDCl_3$: 3.80 (t, 3H, N-CH_3), 6.80-7.90 (m, 4H thio, 5 ph, NH), 9.15 (s, 1H, NH).	414
4	3334		DMSO : 1.20 (s,3H , CH_3) , 3.40 (t , 3H, N-CH_3) , 6.80-7.60 (m , 4H thio , NH).	293
5	3400 3310 3100		DMSO : 3.26 (t , 3H, N-CH_3) , 4.10-4.30 (b , 1H , NH) , 4.40 – 4.60 (b , 1H , NH) , 6.80-7.60 (m , 4H thio , NH).	276
6a	3400 3300 3100	1225	$CDCL_3$:2.50 (s , 3H, CH_3) , 3.30 (s , 3H , N-CH_3) , 5.00 (s , 1H , NH) , 5.30 (s , 1H , NH) ,6.80-7.60 (m , 4H thio , NH).	350
6b	3310 3270 3100	1224	$CDCL_3$: 3.40 (s, 3H, N-CH_3), 4.30 (s, 1H, NH), 4.50 (s , 1H , NH) ,6.90-7.60 (m , 4H thio , 5H ph , NH), 11.00 (s , 1H , NH).	412
7	3400 3100		$CDCL_3$: 3.80 (s, 3H, N-CH_3), 3.60 (s, 3H, CH_3), 4.60 (s, 1H, NH), 6.80-7.60 (m, 4H thio, NH).	316
8	3400 , 1614 (C=N) 1573 (C=C)		DMSO: 3.60 3.90 (s, 3H, N-CH_3), 6.80-7.60 (m, 4H thio, NH), 8.20 (s, 1H, triazole).	287
9	3416 , 3133 (azide)		DMSO: 3.95 (s, 3H, N-CH_3), 6.80-7.60 (m, 4H thio, NH).	288

Reaction of 2-Hydrazinylthienopyrimidin-4-imine 5

With formic acid

A mixture of 5 (0.01 mol.) and formic acid (20 ml) was heated under reflux for 2 hr. Excess of the acid was evaporated till dryness under reduced pressure. The residue remained was treated with methanol and the solid product obtained was filtered off, dried and crystallized from n-butanol to give the triazolo pyrimidine (8) (*c.f.* Tables 1 and 2).

With methylisothiocyanate

A mixture of 5 (0.01 mol) and methylisothiocyanate (0.015 mol) in ethyl alcohol was heated under reflux for 4 hr in presence of triethylamine (0.5 ml). The reaction mixture was evaporated till dryness; the oily residue obtained was triturated with methanol. The solid product was filtered off and crystallized from n-butanol to gave (7) (*c.f.* Tables 1 and 2).

With nitrous acid

To a solution of 5 (0.01 mol.) in acetic acid solution (50 ml, 50%), sodium nitrite solution (0.15 mol in 5 ml H_2o) was added. The resulting mixture was stirred at room temp. (ca $\approx 25^{\circ}$) for 15 min. The solid product which separated out was filtered off, washed with water, dried and crystallized from n-butanol to give (9) (*c.f.* Tables 1 and 2).

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تشييد مركبات جديدة من الثينو [٢-٣ د] بيريميدين ذات احتمالية نشاط بيولوجى

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تم فى هذا البحث تشييد مركبات جديدة من مشتقات الثينوبيريمدين باستخدام المركب ٤-امينو-٣ ن (احلال) -٥- (ثيوفين– ٢-ايل) – ٣، ٤ – داى هيدروثيينو (٣،٢-د) بيريميدين – ٢ (١-H) ثيون رقم ٢ كمادة بادئة.

وتم ايضا تحضير المركب ٢ هيدرازنينيل -٣- ميثيل -٥- (ثيوفين-٢-ايل) ثينيو (٣،٢-د) بيريميدين -٤- (٣ H) ايمين ٥ و الذى تمت مفاعلته مع مشتقات من الايزوثيوسيانات فى ظروف مختلفة و ايضا تمت مفاعلته مع حمض الفورميك وحمض النيتروز للحصول على مشتقات محلوقة من التريازولوبيريميدنيات.

وتم التعرف على التركيب الكيميائى للمركبات المحضرة عن طريق اجراء التحاليل الدقيقة للعناصروطيف الاشعة تحت الحمراء و طيف الكتلة و كذلك الرنين النووى المغناطيسى لذرة الهيدروجين.