Functionlization and Heteroannelation of Ethyl 2-(4'-Chlorophenyl)-4-mercapto-6-methylpyrimidine-5-carboxylate

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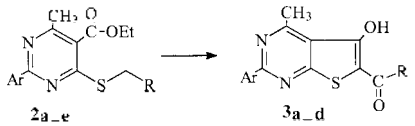
Pyrimidine derivatives and heterocyclic annelated pyrimidines continue to attract great interest due to the wide variety of interesting biological activities observed for these compounds such as anti-convulsant,[1] inflammatory,[2] bactericidal,[3] fungicidal[4] and anti-fertility[5] activities.

The alkylation of *o*-mercapto carbonyl and related compounds with activated halomethylene compounds has been found to be a general method for the synthesis of condensed thiophene *via* the intermediate alkylthio derivatives.[6-10] The reaction of 4-mercaptopyrimidine 1 with benzyl chloride in ethanolic solution containing equivalent amount of sodium ethoxide gives 4-benzyl mercaptopyrimidine **2a**. 4-Mercaptopyrimidine 1 was allowed to react with one equivalent of ethyl bromoacetate in the presence of triethyl amine (TEA) to produce ethoxycarbomethyl mercaptopyrimidine **2b**. Refluxing of pyrimidine **2b** in alcoholic sodium ethoxide yielded the corresponding thieno[2,3-*d*]pyrimidine **3a**. Compound **3a** was also obtained upon heating compound 1 and ethyl bromoacetate in the presence of sodium ethoxide. Alkylation of compound **1** using chloroacetamides yielded the corresponding alkyl thiopyrimidines **2c**, **d**. Compounds **2c**, **d** undergo intramolecular cyclization using sodium ethoxide affording the corresponding thieno[2,3-*d*]pyrimidine-6-carboxamides **3b**, **c** respectively. Depending on the reaction condition mercaptopyrimidine **1** was reacted with phenacyl bromide to give either of alkylthiopyrimidine **2e** or thienopyrimidine **3d**. Thus, refluxing of **1** and phenacyl bromide in the presence of (TEA) afforded **2e** while using sodium ethoxide produced thienopyrimidine **3d**.



2a_e

a, R = C_6H_5
b, R = CO_2Et
c, R = $CONH_2$
d, R = $CONHC_6H_5$
e, R = COC_6H_5

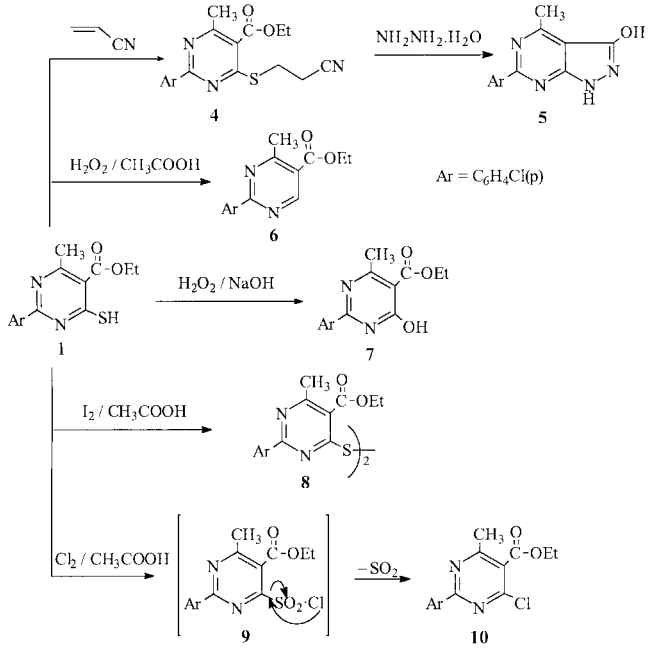
3a_d

a, R = OC_2H_5
b, R = NH_2
c, R = NHC_6H_5
d, R = C_6H_5

Ar = $C_6H_4Cl(p)$

Compound **1** undergo Michael type addition to acrylonitrile to give the corresponding 4-cyanoethylmercaptopyrimidine **4**.

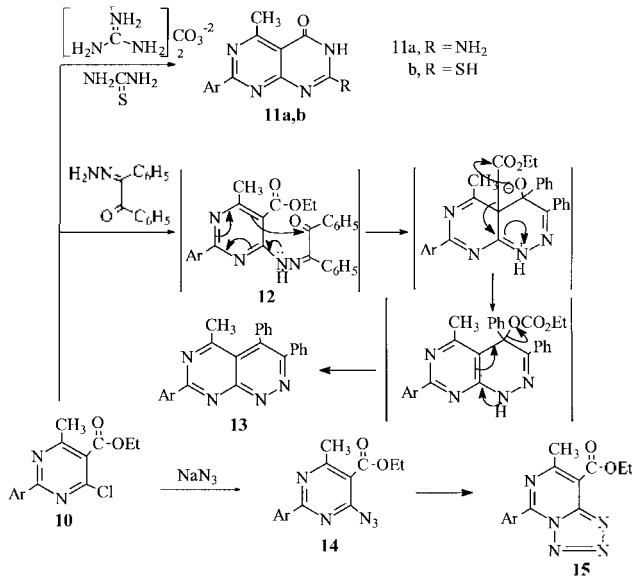
Hydrazinolysis of compound **4** using hydrazine hydrate afforded pyrazolopyrimidine **5**. The reaction of mercaptopyrimidine **1** with hydrogen peroxide in acetic acid desulfurization took place affording ethyl pyrimidine carboxylate **6**. Treatment of compound **1** with hydrogen peroxide in aqueous sodium hydroxide resulted in hydrolysis affording hydroxypyrimidine **7**. Oxidation of mercaptopyrimidine using iodine in acetic acid gives disulphide **8**. The chloronation of **1** by chlorine in acetic acid yielded the ethyl 2-(*p*-chlorophenyl)-4-chloro-6-methylpyrimidine-5-carboxylate **10**. The conversion of **1** into **10** may be proceeded through the formation of pyrimidine-4-sulphonyl chloride **9** which liberate SO_2 to give **10**.[11]



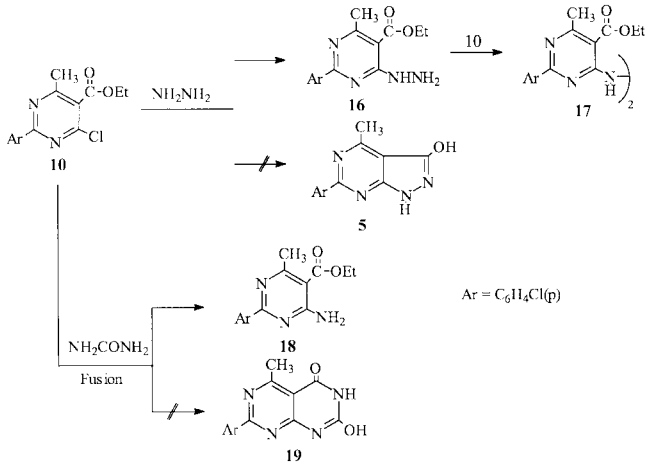
Electron deficient nature of pyrimidine ring facilitates the synthesis of large number of pyrimidine derivatives through nucleophilic aromatic substitution of suitable leaving groups. The halogens have been especially useful in this regard.[12,13] Thus, compound **10** reacts with guanidinum carbonate and/or thiourea to afford the corresponding pyrimidopyrimidine **11a, b** respectively.

Condensation of **10** with benzilmonohydrazone gave the corresponding pyrimidopyridazine **13** *via* the initial formation of nonisolate open form **12** that underwent the intramolecular cyclocondensation. The reaction of compound **10** with sodium azide gave the corresponding tetrazolopyrimi-

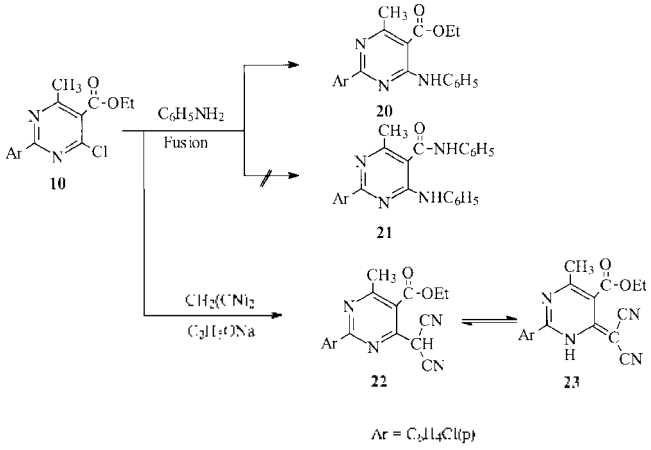
dine **15** presumably *via* the formation of azido form **14**. The structure of **15** was proven by the disappearance of azido group in IR spectrum.



When hydrazine hydrate was used in this reaction the initially formed hydrazinopyrimidine **16** reacted with another molecule of **10** to give 1.2-bis(phenylpyrimidin-4-yl)hydrazine **17** and none of the expected pyrazolopyrimidine **5** was obtained. Fusion of compound **10** with urea resulted in dechloroamination affording ethyl-4-amino-6-methyl-2-(*p*-chloro-phenyl)pyrimidin-5-carboxylate **18** not the corresponding pyrimidopyrimidine **19**. On treatment of compound **10** with aniline led to the formation of the corresponding 4-aryl-aminopyrimidine derivative **20**.



It is interesting to note that under the drastic condition none of the anilide **21** was obtained presumably due to the decrease of electrophilic character of ester group. Compound **10** also reacted with malononitrile in presence of sodium ethoxide resulting in 4-dicyanomethylpyrimidine derivative **22**. Compound **22** present in its tautomeric form **23** as evidence from its spectra.



Experimental Section

Melting points are all incorrected. IR spectra (KBr) were recorded on a Pyeunicam-SP-1100 spectrophotometer. ^{1}H NMR were recorded on a Varian A GEMINI 200 MHz spectrophotometer. The Microanalytical Center, Cairo University carried out microanalysis.

Ethyl 4-alkylthio-2-(*p*-chlorophenyl)-6-methylpyrimidine-5-carboxylate 2a-e. A mixture of 1 (0.01 mol) and appropriate alkylating agent (0.01 mol) and TEA (3 drops) in ethanol was refluxed for 30 minutes. The precipitate obtained upon cooling and dilution with water was collected and crystallized from methanol to give colorless crystals of **2a-e** respectively (Table 1).

2-(*p*-Chlorophenyl)-5-hydroxy-4-methylthieno[2,3-*d*]-pyrimidine derivatives 3a-d. a) A mixture of appropriate pyrimidine **2b-e** (0.01 mol) and sodium ethoxide (0.01 mol) was heated under reflux for 30 minutes. The precipitate formed after cooling and acidification with hydrochloric acid (3 mL. 60%) was collected and crystallized from ethanol to give colorless crystals of **3a-b** (Table 1).

b) A mixture of **1** (0.01 mol) ethyl bromoacetate or phenacyl bromide (0.01 mol) and sodium ethoxide (0.01 mol) in ethanol (10 mL) was heated under reflux for 2 hours. After cooling and acidification with hydrochloric acid (3 mL, 60%) a precipitate formed which collected and crystallized from ethanol to give colorless crystals of **3a** and **3d** respectively (Table 1).

Ethyl 2-(*p*-chlorophenyl)-4-cyanoethylmercapto-6-methylpyrimidine-5-carboxylate 4. A mixture of **1** (0.01 mol) and acrylonitrile (0.01 mol) and TEM (3 drops) in ethanol (10 mL) was heated under reflux for one hour. After cooling the precipitate was collected and crystallized from ethanol to give colorless crystals of **4** (Table 1).

Pyrazolo[5,4-*d*]pyrimidine 5. A mixture of **4** (0.01 mol) and hydrazine hydrate (0.015 mol) in ethanol (20 mL) was refluxed for 2 hours. The precipitate obtained upon cooling was collected and crystallized from ethanol to give colorless crystals of **5** (Table 1).

Table 1.

Compound No.	M. P. C° (yield %)	Molecular formula (M.W)	Analysis calc./found % C	H	N
2a	88-90 (60)	$C_{21}H_{19}ClN_2O_2S$ (398.91)	63.23 63.20	4.80 4.75	7.02 7.08
2b	73-75 (70)	$C_{18}H_{19}ClN_2O_4S$ (394.87)	54.75 54.68	4.85 4.79	7.09 7.10
2c	198-200 (50)	$C_{16}H_{16}ClN_3O_3S$ (365.83)	52.53 52.49	4.41 4.38	11.49 11.50
2d	220-221 (60)	$C_{22}H_{20}ClN_3O_3S$ (441.93)	59.79 59.75	4.56 4.50	9.51 9.50
2e	166-168 (55)	$C_{22}H_{19}ClN_2O_3S$ (426.92)	61.90 61.89	4.49 4.48	6.56 6.50
3a	135-136 (60)	$C_{16}H_{13}ClN_2O_3S$ (348.80)	55.10 55.10	3.76 3.72	8.03 8.10
3b	258-260 (70)	$C_{14}H_{10}ClN_3O_2S$ (319.76)	52.59 52.50	3.15 3.12	13.14 13.18
3c	248-250 (75)	$C_{20}H_{14}ClN_3O_2S$ (395.86)	60.68 60.70	3.56 3.51	10.61 10.55
3d	209-210 (60)	$C_{20}H_{13}ClN_2O_2S$ (380.85)	63.08 63.07	3.44 3.41	7.36 7.33
4	89-90 (65)	$C_{17}H_{16}ClN_3O_2S$ (361.85)	56.43 56.44	4.46 4.45	11.61 11.60
5	93-95 (60)	$C_{12}H_9ClN_4O$ (260.68)	55.29 55.25	3.48 3.49	21.49 21.45
6	165-168 (70)	$C_{14}H_{13}ClN_2O_2$ (276.72)	60.77 60.75	4.73 4.74	10.12 10.13
7	288-290 (50)	$C_{14}H_{13}ClN_2O_3$ (292.72)	57.45 57.43	4.48 4.44	9.57 9.53
8	187-190 (60)	$C_{28}H_{24}Cl_2N_4O_4S_2$ (615.55)	54.64 54.60	3.93 3.90	9.10 9.11
10	116-118 (65)	$C_{14}H_{12}Cl_2N_2O_2$ (311.17)	54.04 54.00	3.89 3.88	9.00 9.02
11a	74-75 (70)	$C_{13}H_{10}ClN_3O$ (287.71)	54.27 54.25	3.50 3.52	24.34 24.30
11b	208-210 (70)	$C_{13}H_9ClN_4OS$ (304.75)	51.24 51.19	2.98 3.00	18.38 18.35
13	203-205 (60)	$C_{25}H_{17}ClN_4$ (408.89)	73.44 73.40	4.19 4.20	13.70 13.71
15	>300 (65)	$C_{14}H_{12}ClN_5O_2$ (317.73)	52.92 52.90	3.81 3.80	22.04 22.00
17	78-80 (75)	$C_{28}H_{26}ClN_6O_4$ (581.46)	57.84 57.88	4.51 4.50	14.45 14.41
18	49-50 (80)	$C_{14}H_{14}ClN_3O_2$ (291.74)	57.64 57.66	4.84 4.82	14.40 14.44
20	108-110 (60)	$C_{20}H_{18}ClN_3O_2$ (367.83)	65.31 65.36	4.93 4.92	11.42 11.41
22	108-110 (60)	$C_{17}H_{13}ClN_4O_2$ (340.77)	59.92 59.91	3.85 3.88	16.44 16.44

Ethyl 2-(*p*-chlorophenyl)-6-methylpyrimidine-5-carboxylate 6. A mixture of **1** (0.01 mol) and hydrogen peroxide (30 mL. 30%) and acetic acid (20 mL) was stirred for 10 minutes. After cooling with ice water and scratching, the crystalline precipitate was collected and crystallized from ethanol to give yellow crystals of **6** (Table 1).

Ethyl 2-(*p*-chlorophenyl)-4-hydroxy-6-methylpyrimidine-5-carboxylate 7. A mixture of **1** (0.01 mol) and hydrogen peroxide (60 mL. 30%) and sodium ethoxide (20 mL, 5%) was stirred for one hour. The solid obtained after acidification with hydrochloric acid (20 mL. 10%) was collected and crystallized from ethanol to give white crystals of **7** (Table 1).

Bis[2-(*p*-chlorophenyl)-6-methylpyrimidyl-4-disulphide 8. To a solution of **1** (0.01 mol) in acetic acid (20 mL) iodine was added (0.01 mol) portion wise with stirring. the solid formed was collected by filtration and crystallized from ethanol to give yellow crystals of **8** (Table 1).

Ethyl 2-(*p*-chlorophenyl)-4-chloro-6-methylpyrimidine-5-carboxylate 10. Chlorine gas was bubbled through a suspension of **1** (5 gm) in acetic acid (50 mL, 25%) for about 3 hours. The resulting colorless precipitate was collected by filtration. washed with water and dried to give **10** (Table 1).

7-(*p*-Chlorophenyl)-5-methyl-3(H)pyrimido[4,5-*d*]pyrimidin-4-one 11a, b. A mixture of **10** (0.01 mol) and guanidinum carbonate/or thiourea (0.01 mol) in ethanol (30 mL) in presence of TEA (3 drops) was refluxed for 3 hours. The solid that separated after cooling and pouring onto water was collected by filtration and crystallized from ethanol to give brown crystals of **11a** and yellow crystals of **11b** respectively (Table 1).

7-(*p*-Chlorophenyl)-3,4-diphenyl-5-methylpyrimido[4,5-*c*]pyridazine 13. A mixture of **10** (0.01 mol) and benzilmonohydrazone (0.01 mol) in ethanol (30 mL) in presence of TEA (3 drops) was refluxed for 2 hours. The solid thus separated after cooling and pouring onto water was collected by filtration and crystallized from ethanol to give yellow crystals of **13** (Table 1).

Tetrazolopyrimidine 15. A mixture of **10** (0.01 mol) and sodium azide (0.01 mol) in ethanol (30 mL) was refluxed for 4 hours. The solid that separated after cooling and pouring onto water was collected by filtration and crystallized from ethanol to give yellow crystals of **15** (Table 1).

1,2-Bis[2-(*p*-chlorophenyl)-5-ethoxycarbonyl-6-methylpyrimidin-4-yl] hydrazine 17. A mixture of **10** (0.01 mol) and hydrazine hydrate (0.01 mol) in ethanol (30 mL) in pres-

Table 2.

Compound	IR ν cm^{-1} (selected bands)
2b	1738 (C=O) and 1525 (C=N)
2c	3397 (NH), 1705 (C=O ester) and 1649 (C=O amidic)
2e	1712 (C=O ketonic) and 1698 (C=O ester)
3a	3448 (OH) and 1712 (C=O)
3d	3418 (OH) and 1720 (C=O)
5	3520-3200 (NH) and 1525 (OH)
6	1682 (C=O)
7	3545 (OH) and 1698 (C=O)
10	1729 (C=O)
11b	3448 (NH), 1623 (C=O) and 1081 (SH)
15	1690 (CO)
17	3446 (NH) and 1650 (C=O)
18	3448 (NH) and 1722 (C=O)
20	3465 (NH) and 1668 (C=O)
22	3461 (NH), 2208 (CN) and 1732 (C=O)

Table 3.

Compd.	^{1}H-NMR (DMSO) δ (ppm)
2a	1.2(t, 3H, CH_3), 2.2(s, 3H, CH_3), 4.3(q, 2H, CH_2), 4.7(s, 2H, CH_2), 6.9-7.3, 7.7-7.9 (m, 4H, ArHs)
2b	1.1(t, 3H, CH_3), 1.3(t, 3H, CH_3), 2.5(s, 3H, CH3), 3.2(s, 2H, CH_2), 4.2(q, 2H, CH_2), 4.4(q, 2H, CH_2), 7.2-7.4, 8.1-8.2(m, 4H, ArHs)
2c	1.3(t, 3H, CH_3), 2.5(s, 3H, CH3), 3.8(s, 2H, SCH_2), 4.3(q, 2H, CH_2), 6.8(s, 2H, NH_2), 7.2-7.4, 8.2-8.4(m, 4H, ArHs)
2d	1.3(t, 3H, CH_3), 4.0(s, 2H, SCH_2), 4.3(q, 2H, CH_2), 6.8-7.3, 7.4-7.6, 8.1-8.4(m, 9H, ArHs), 10.1(s, 1H, NH)
2e	1.3(t, 3H, CH_3), 2.3(s, 3H, CH_3), 4.2(q, 2H, CH_2), 4.6(s, 2H,SCH_2), 7.0-7.9(m, 9H, ArHs)
3a	1.2(t, 3H, CH_3), 2.5(s, 3H, CH3), 4.1(q, 2H, CH_2), 7.2-7.4, 8.0-8.2(m, 4H, ArHs), 12.2(s, 1H, OH)
3c	2.5(s, 3H, CH_3), 7.1-8.2(m, 9H, ArHs), 11(s,1H, NH), 12.2(s, 1H, OH)
4	1.3(t, 3H, CH_3), 2.5(s, 3H, CH_3), 2.9(t, 2H,CH_2), 3.4(q, 2H,CH_2), 4.3(t, 2H, CH_2), 7.2-7.4, 8.0-8.2(m, 4H, ArHs)
6	1.6(t, 3H, CH_3), 2.7(s, 3H, CH_3), 4.5(q, 2H, CH_2), 7.2-7.4, 7.9-8.2(m, 5H, ArHs + pyrimidine proton)
7	1.2(t, 3H, CH_3), 2.0(s, 3H, CH_3), 4.0(q, 2H, CH_2), 7.1-7.3, 7.9-8.1(m, 4H, ArHs +NH proton)
8	1.4(t, 6H, $2CH_3$), 2.6(s, 6H, $2CH_3$), 4.5(q, 4H, $2CH_2$), 7.2-7.4, 7.8-8.1(m, 8H, ArHs)
11a	2.7(s, 3H,CH_3), 6.5(s, 2H, NH_2), 7.2-8.4(m, 4H, ArHs + NH proton)
13	2.4(s, 3H,CH_3), 6.9-8.2(m, 14H, ArHs)
17	1.4(t, 6H, $2CH_3$), 2.7(s, 6H,$2CH_3$), 4.2(q, 4H, $2CH_2$), 7.3-7.5, 8.1-8.4(m, 8H, ArHs), 10.1(s, 2H, 2NH)
20	1.3(t, 3H, CH_3), 2.5(s, 3H,CH_3), 4.2(q, 2H, CH_2), 6.9-7.6, 8.0-8.2(m, 9H, ArHs), 9.7(s, 1H, NH)
22	1.2(t, 3H, CH_3), 2.5(s, 3H,CH_3), 4.2(q, 2H, CH_2), 6.5(s, 1H, CH), 7.0-8.2(m, 4H, ArHs), 11.0(s, 1H, NH)

Compound **13** M−1 = 410

ence of TEA (3 drops) was refluxed for 3 hours. The solid thus separated after cooling and pouring onto water was collected by filtration and crystallized from ethanol to give yellow crystals of **17** (Table 1).

Ethyl-4-amino-2-(*p*-chlorophenyl)-6-methylpyrimidine-5-carboxylate 18. A mixture of **10** (0.01 mol) and urea (0.01 mol) was heated at 200 °C on an oil bath for 2 hours. The solid thus obtained was crystallized from ethanol to give colorless crystals **18** (Table 1).

Ethyl-4-anilino-2-(*p*-chlorophenyl)-6-methylpyrimidine-5-carboxylate 20. A mixture of 10 (0.01 mol) and aniline (0.01 mol) was heated at 200 °C on an oil bath for 2 hours. The solid thus obtained was crystallized from ethanol to give brown crystals **20** (Table 1).

Ethyl-4-dicyanomethyl-2-(*p*-chlorophenyl)-6-methyl-pyrimidine-5-carboxylate 22. A mixture of **10** (0.01 mol). malononitrile (0.01 mol) and sodium ethoxide (0.01 mol) in ethanol (30 mL) were refluxed for 4 hours. The solid thus obtained after cooling and neutralization was collected and crystallized from ethanol to give yellow crystals of **22** (Table 1).

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