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SYNTHESIS OF 4-CHLORO-2-(3,5-DIMETHYL-1H-PYRAZOL-1-YL)-6-METHYLPYRIMIDINE

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Abstract: Reaction of each of alkylated thiouracil **(1)** with hydrazine hydrate (**2**) in ethanol under refluxing conditions for 3 hrs gave 2-hydrazino-6-methylpyrimidin-4one(**3**). **3** on treated with $POCl_3$ under refluxing conditions for 2 hrs gave 4-chloro-2-hydrazino-6-methylpyrimidine **(4).** Latter **4** on condensation with acetyl acetone (**5**) in ethanol under refluxing conditions for 3 hrs gave the corresponding pyrazole derivatives (**6**). Alternately, Reaction of S-alkylatedthiouracil (**1**) with $POCl_3$ under refluxing conditions for 2 hrs gave the corresponding chloro compound 4-chloro-6-methyl-2-(methylthio)pyrimidine (**7**).**7** on condensation with hydrazine hydrate (**2**) in ethanol under refluxing conditions for 3 hrs gave the corresponding hydrazinyl derivative **4.**

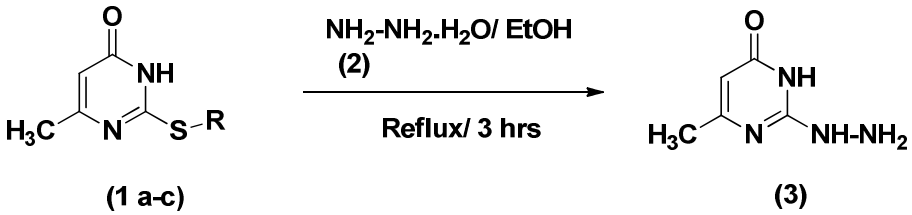
Keywords:. 2-mercapto-6-methyl-3-phenylpyrimidin-4(3H)-one, hydrazine hydrate, $POCl_3$, acetyl acetone.

Introduction: Pyrazole derivatives are known to possess a wide range of biological activities[i] . These derivatives have been the subject of many research studies due to their wide-spread potential biological activities such as anti-hyperglycemic[ii], analgesic[iii], anti-inflammatory [iv] , antipyretic [v], antibacterial [vi], antimicrobial [vii], antihypertensive[viii] activities. 2-Thiopyrimidines have also been known to show divers types of biological activities.

General Conditions: Melting points are uncorrected and were determined in open capillary tubes in sulphuric acid bath. TLC was performed on silica gel-G and spotting was done using iodine or UV-light. IR spectra were recorded using Perkin-Elmer 1000 instrument in KBr phase. ^{1}H-NMR spectra were recorded using a varian 400 MHz instrument and Mass spectra on Agilent-LC-MS instrument giving only $M^{+\cdot}$ values using Q+1or Q-1 mode.

Results and Discussion:

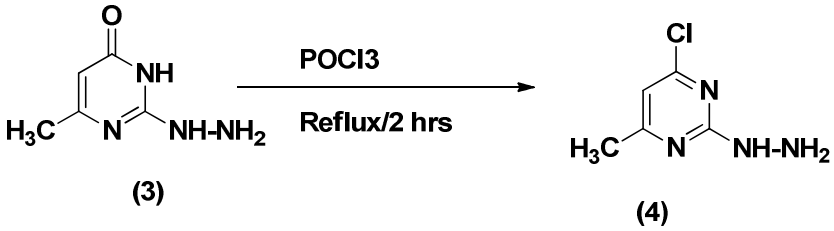
Reaction of each of alkylated thiouracil [ix] **(1a-c)** with hydrazine hydrate (**2**) in ethanol under refluxing conditions for 3 hrs gave 2-hydrazino-6-methylpyrimidin-4one **(3) (Scheme-1.1)** .



(1 a-c) (3)

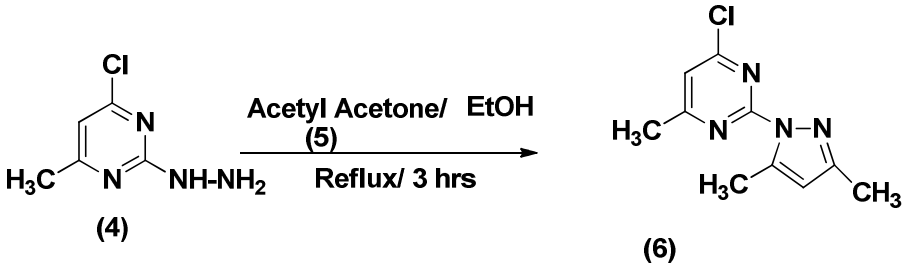
1c= Me. 1b= Ethyl. 1c=Benzyl.

Treatment of **3** with $POCl_3$ under refluxing conditions for 2 hrs gave 4-chloro-2-hydrazino-6-methylpyrimidine **(4). (Scheme-1.2).**



(3) (4)

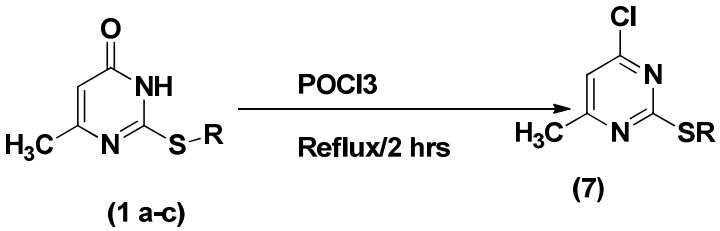
Reaction of **4** with acetyl acetone (**5**) in ethanol under refluxing conditions for 3 hrs gave the corresponding pyrazole derivative **6**(**Scheme-1.3**).



(4) (6)

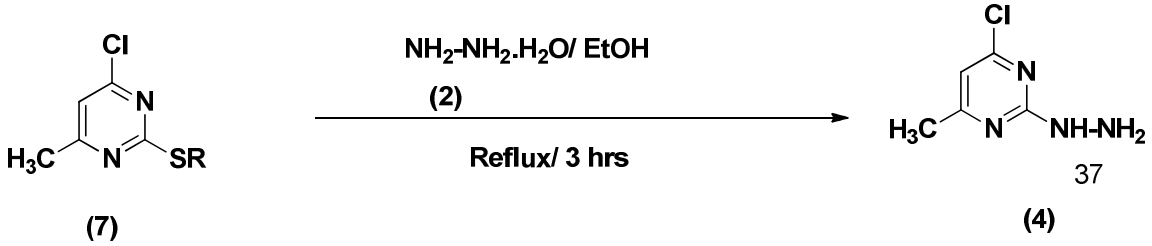
Alternate synthesis of 4

Reaction of S-alkylatedthiouracil (**1a-c**) with $POCl_3$ under refluxing conditions for 2 hrs gave the corresponding chloro compound 4-chloro-6-methyl-2-(methylthio)pyrimidine (**7**) (**Scheme-1.4**).



(1 a-c) (7)

Reaction of **7** with hydrazine hydrate (**2**) in ethanol under refluxing conditions for 3 hrs gave the corresponding hydrazinyl derivative **4** . Structures of all the compounds, **2**, **3** , **4** , **6 &7** obtained above have been established by spectral data. (For details, please see the Experimental Section). (**Scheme-1.5)**



(7) 37 (4)

Experimental section:

A mixture of (**1a-c)** (10 mM) and hydrazine hydrate (**2**)(10 mM) in ethanol (50 mL) was heated on water bath for 2 hrs. The progress of the reaction was monitored by TLC. After completion of the reaction, the mixture was poured into ice-cold water(100 mL). The separated solid was filtered, washed with ethanol (50 mL) and dried.

3 Yield 79% (1.23 g) M.P190-195 ^{0}C ;IR (KBr): 3325 cm^{-1} (br, marching with –NH & -N**H$_2$**), 1675 cm^{-1} (very broad, -**CO**); ^{1}H-NMR (DMSO-d$_6$/TMS): δ 2.14 (s, 3H, -C**H**$_3$), 4.50 (s, 2H, -N**H$_2$**, D$_2$O exchangeable) 6.28 (s, 1H, -C**H**- pyrimidine ring), 8.60 (s, H, -N**H**, D$_2$O exchangeable), 11.56 (s, 1H, **D$_2$**O exchangeable –N**H**): MS (CI): m/z 156 [M$^{\cdot+}$+1].

A mixture of **3** (1.56 g, 10 mM) and $POCl_3$ (10 mM) was heated at 100 ^{0}C for 2 hrs. The progress of the reaction was monitored by TLC. After completion of the reaction, the mixture was poured into ice cold water (100 mL), Neutralized with $NaHCO_3$ solution and P^H was adjusted to 7. The separated solid was filtered, washed with ethanol (50 mL) and dried.

Yield= 88% (1.54 g) M.P= 310-135 ^{0}C;IR (KBr): 3325 cm^{-1} (very broad, -N**H$_2$**), 3250 cm^{-1} (very broad, -N**H**); ^{1}H-NMR (DMSO-d$_6$ /TMS): δ 2.14 (s, 3H, -C**H**$_3$), 4.50 (s, 2H, -N**H$_2$**, D$_2$O exchangeable) 6.01 (s, 1H, -C**H**-pyrimidine ring) , 8.60 (s, H, -N**H**, D$_2$O exchangeable) : MS (CI): m/z 174 [M$^{\cdot+}$+1].

A mixture of **4** (1.74 g, 10 mM) and **5** (10 mm) was heated on water bath for 2 hrs. The progress of the reaction was monitored by TLC. After completion of the reaction, The reaction mixture was poured into ice-cold water (50 ml). The separated solid was filtered, washed with water (3x20 ml) and dried to obtain the crude **6**. The crude product was recrystallised from ethanol to obtain pure **6.**

6 Yield 88% (1.94 g) M.P= 210-215 ^{0}C; IR (KBr): absence of –NH and amide carbonyl group ; ^{1}H-NMR (DMSO-d$_6$/TMS)): δ 2.13 (s, 3H, -C**H**$_3$), 3.89 (s, 3H, -C**H**$_3$), 3.92 (s, 3H, -C**H**$_3$), 5.93 (s, 1H, -C**H**-pyrimidine ring) , 7.03 (s, H, -C**H**= pyrazole ring) : MS (CI) : m/z 223 [M$^{\cdot+}$+1].

Alternate synthesis of 4;

A mixture of **1a-c** (10 mM) , and $POCl_3$ (0.25 g, 10 mM) was heated on water bath for 2 hrs. the progress of the reaction was monitored by TLC. After completion of the reaction, The reaction mixture was neutralised with $NaHCO_3$ solution and maintained the P^H= 7. The separated solid was filtered, washed with water (100 mL) and dried.

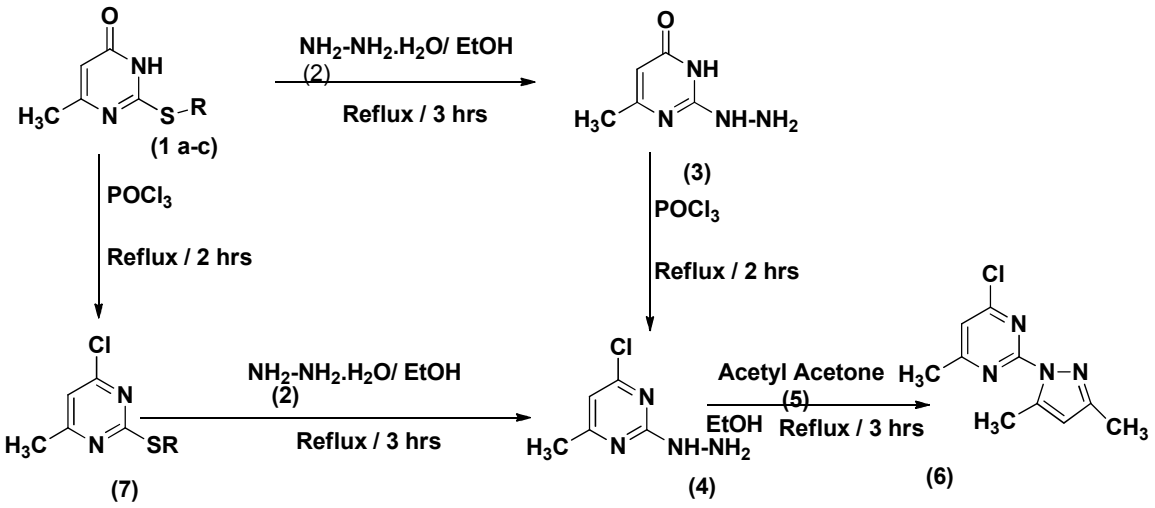
7a. (i.e. a= CH_3) Yield 94% (1.64 g), M.P= 120-125 ^{0}C;IR (KBr):absence of –NH and amide carbonyl group ; ^{1}H-NMR (DMSO-d6/TMS): δ 2.15 (s, 3H, -C**H**$_3$) , 2.51 (s, 2H, -SC**H**$_3$), 6.28 (s, 1H, -C**H**- pyrimidine ring): MS (CI): m/z 175 [M$^{\cdot+}$+1].

7b. (i.e. b= CH_2-CH_3) Yield 88% (1.50 g) M.P= 135-142 ºC ; Its ^{1}H-NMR (DMSO-d6/TMS): δ 1.77 (t, 3H, -CH_3), 2.14 (s, 3H, -C**H**$_3$) , 4.30 (s, 2H, -S-**C**H_2-), 6.28 (s, 1H, -C**H**- pyrimidine ring), 7.2-7.8 (m, 5H, aromatic ring proton), MS (CI): m/z 189 [M^{+}+1].

7c. (i.e. c= CH_2-Ph) Yield 80% (2.01 g) M.P= 140-144 ºC; Its ^{1}H-NMR (DMSO-d6/TMS): δ 2.14 (s, 3H, -C**H**$_3$) , 4.30 (s, 2H, -S-**C**H_2-), 6.28 (s, 1H, -C**H**- pyrimidine ring), 7.2-7.8 (m, 5H, aromatic ring proton),: MS (CI): m/z 251 [M^{+}+1].

A mixture of **7** (0.64 g, 10 mM) , and hydrazine hydrate **2** (10 mM) in ethanol (10 mL) was heated on water bath for 2 hrs. The progress of the reaction was monitored by TLC. After completion of the reaction, The separated solid was filtered, washed with water (3x20 ml) and dried. Identical with the ones reported in the earlier methods in all respects (m.p. m.m.p and co-tlc analysis).

Summary of all the above reactions Scheme-1.6



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