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A Green and Facile Synthesis of 6-Methyl-2-(alkylthio)pyrimidin-4(3*H*)-one

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Reaction of 2-thiouracil **(1)** with alkylating agents, namely dimethyl sulphate, diethyl sulphate and benzyl chloride in the presence of potassium carbonate as a mild base, under green conditions, such as simple physical grinding of reactants or in solvents such as ethanol and PEG-600 and under microwave irradiation, gave, respectively 6-methyl-2-(methylthio)pyrimidin-4(3*H*)-one (**2a,** *i.e.*, R=CH_3), 6-methyl-2-(ethylthio) pyrimidin-4(3*H*)-one (**2b**, *i.e.*, R = C_2H_5) and 6-methyl-2-(benzylthio)pyrimidin-4(3*H*)-one (**2c**, *i.e.*, R = $PhCH_2Cl$). Alternately, condensation of ethyl acetoacetate with S-methylisothiouronium hemisulfate, S-ethylisothiouronium hemisulfate and S-benzyl isothiouronium chloride in ethanolic potassium hydroxide under reflux for 3 h gave **2a-c** respectively.

Key Words: 2-Thiouracil, Alkylating agent, PEG-600, 6-Methyl-2-(alkylthio)pyrimidin-4(3*H*)-one.

INTRODUCTION

Pyrimidine nucleus constitutes an important component of nucleic acids and it is used as a building block in pharmaceutics for the synthesis of antiviral[1], anticancer[2], antibacterial and antifungal[3] agents. Similarly, the related thiouracil derivatives are potential therapeutics and are known to possess antiviral[4] and anticancer[5] properties.

EXPERIMENTAL

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.

Preparation of 6-methyl-2-(alkylthio)pyrimidin-4(3*H*)-one (2) from 2-thiouracil (1)

In solid phase: A mixture of **1** (1.42 g, 10 mM), K_2CO_3 (2.76 g, 20 mM) and alkylating agent (10 mM) were ground together for 5-10 min in a mortar and pestle at room temperature to obtain a homogeneous mixture. The latter was then treated with ice-cold water (≈ 30-40 mL). The separated solid was filtered, washed with water (2 × 10 mL) and dried to obtain crude **2(a-c)**. The crude product was recrystallized from ethanol to obtain pure **2(a-c)** (Table-1).

In solution phase

In ethanol: A mixture of **1** (1.42 g, 10 mM), K_2CO_3 (2.76 gms, 20 mM), ethanol (50 mL) and the alkylating agent (10 mM) was stirred at room temperature for 2 h. The progress of reaction was monitored on TLC for the disappearance of **1**. After the completion of the reaction, (≈ 2 h), the excess ethanol was rotary evaporated and the residual mixture poured into ice-cold water (2 × 20 mL). The separated solid was filtered, washed with water (2 × 10 mL) and dried. The crude product was recrystallized from ethanol to obtain pure **2(a-c)** (Table-1).

TABLE-1
PREPARATION OF **2** FROM **1** UNDER DIFFERENT CONDITIONS

S. No.	Sub states	Reagent	Products	Solid phase			Green solvent (solution phase)				Microwave irradiation		
							PEG-600		Ethanol				
				Time (min)	Temp.	Yield* (%)	Time (min)	Yield* (%)	Time (min)	Yield* (%)	Time (min)	Temp./Wattage	Yield* (%)
		DMS	**2a**	5-10	RT	82	120	97	120	95	5	RT/450W	96
1	1	DES	**2b**	5-10	RT	90	120	92	120	89	5	RT/450W	90
		$Ph\text{-}CH_2Cl$	**2c**	5-10	RT	90	120	89	120	85	5	RT/450W	89
2	3	**4a, 4b**	**2a, 2b**	–	–	–	–	–	180	89	–	–	–
3	3	5	**2c**	–	–	–	–	–	180	86	–	–	–

m.p. of **2a** 217-220 ºC. (Lit.[6] m.p. 218-219 ºC). *Yields refer to processed crude products. m.p. of **2b** 143-147 ºC. (Lit.[6] m.p. 145-146 ºC). m.p. of **2c** 169-174 ºC.

In PEG-600: A mixture of **1** (1.42 g, 10 mM), alkylating agent (10 mM) and PEG-600 (20 mL) was stirred at RT for 2 h. At the end of this period, the mixture was poured into ice-cold water (50 mL). The separated solid was filtered, washed with water (2 × 10 mL) and dried. The crude product was recrystallized from ethanol to obtain pure **2(a-c)**. For yields, please see Table-1.

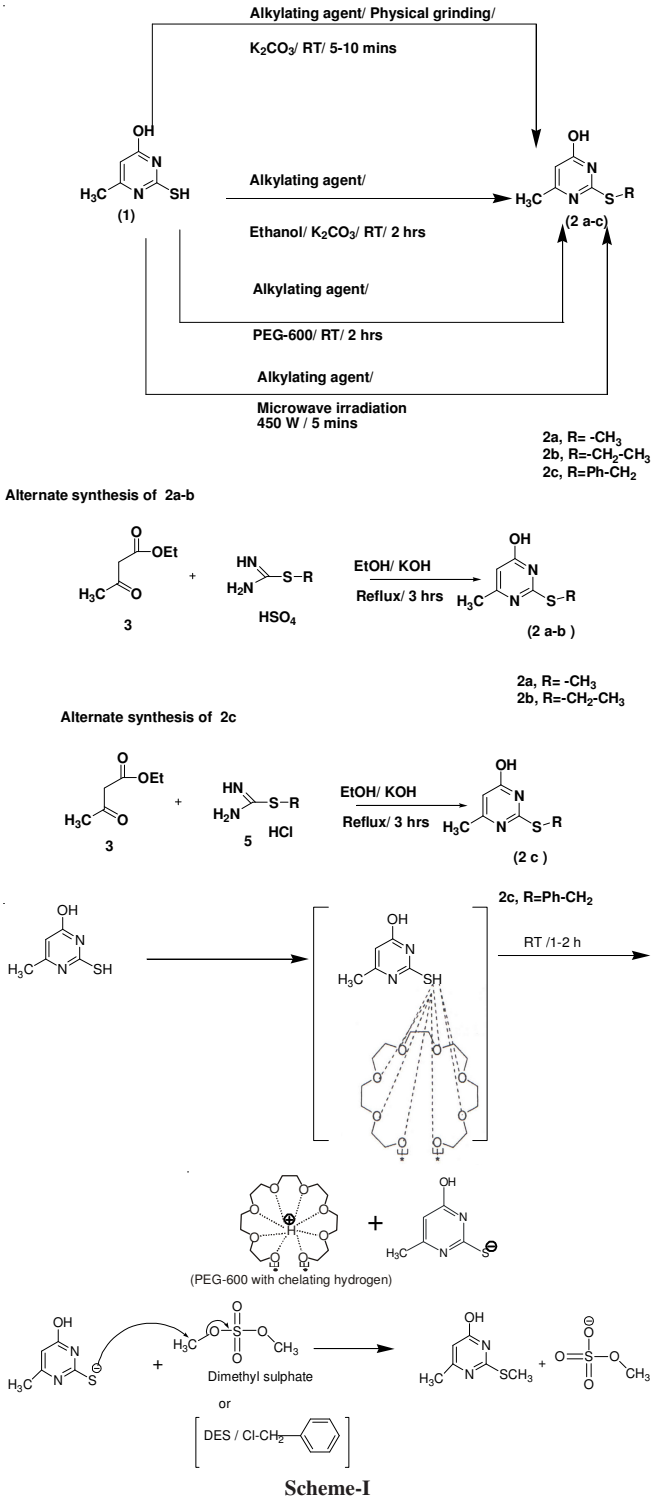
Under microwave irradiating conditions: Mixture of **1** (1.42 g, 10 mM) and alkylating agent (10 mM) was taken in a 10 mL CEM-reaction tube sealed by rubber stopper and subjected to microwave irradiation for 5 min at 130 ºC in the commercial micro-wave reactor. After that, the tube was cooled and the completion of reaction was checked by TLC. Then, the mixture was poured into ice-cold water (2 × 20 mL). The separated solid was filtered, washed with water (2 × 10 mL) and dried. The crude product was recrystallized from ethanol to obtain pure **2(a-c)**. For yields please see Table-1.

RESULTS AND DISCUSSION

Reaction of **1** with each of the alkylating agents, like dimethyl sulphate (DMS), diethyl sulphate (DES) and benzyl chloride ($PhCH_2Cl$), in the presence of K_2CO_3 as a mild base, by a simple physical grinding of the reaction mixture in a mortar and pestle under solvent-free conditions for 10-15 min at room temperature, followed by processing, gave, respectively 6-methyl-2-(methylthio)pyrimidin-4(3*H*)-one (**2a**, *i.e.*, R = CH_3), 6-methyl-2-(ethylthio)pyrimidin-4(3*H*)-one (**2b**, *i.e.*, R = C_2H_5) and 6-methyl-2-(benzylthio)pyrimidin-4(3H)-one (**2c**, *i.e.*, R = $PhCH_2Cl$), as the products identical with the one reported in the earlier methods[6-9] in all respects (m.p. m.m.p and co-tlc analysis).

The reaction was also carried out in ethanol as a solvent. Thus, treatment of **1**, independently, with each of dimethyl sulphate (DMS), diethyl sulphate (DES) and benzyl chloride ($PhCH_2Cl$) in ethanol at room temperature for 2 h in the presence of K_2CO_3 as a base, followed by simple processing, gave, respectively, **2a** (*i.e.*, **2**, R = CH_3), **2b** (*i.e.*, **2**, R = C_2H_5) and **2c** (*i.e.*, **2**, R = $PhCH_2$) identical with the same products obtained above (**Scheme-I**).

The reaction was also carried out in PEG-600 as a solvent. Thus, treatment of **1**, independently, with each of dimethyl sulphate (DMS), diethyl sulphate (DES) and benzyl chloride ($PhCH_2Cl$) in PEG-600 at room temperature for 2 h without the use of any base, followed by simple processing, gave, respectively, **2a** (*i.e.*, **2**, R = CH_3), **2b** (*i.e.*, **2**, R = C_2H_5) and **2c** (*i.e.*, **2**, R = $PhCH_2$) identical with the same products obtained above (**Scheme-I**). In the case of PEG-600, it was found that the use of K_2CO_3 as a base was not required. Mechanistic explanation[10] of these results is that, probably PEG-600 dissolves the substrates **1** and the reagent (*i.e.* the alkylating agent, DMS, DES *etc.*), bringing them together thereby providing an effective means for chemical reaction to occur. Further, PEG-600 is able to extract the hydrogen from the -SH of thiouracil and is able to retain it in its claws by chelation through several lone pairs of electrons in its oxygen containing chain. The sulphanyl anion from the substrate **1** then attacks the positively polarised methyl carbon of the alkylating agent bringing about product formation. *i.e.*, **2** this role of PEG-600 is



Scheme-I

similar to that of the crown ethers or that of the proton sponge (*i.e.*, 1, 8-dimethylaminonaphthalene). The latter acts as a very strong base due to its ability to extract hydrogen from an acidic substrate and then retain it by chelation through lone pair of electrons on the two nitrogen atoms of the two amino groups (**Scheme-I**).

2(a-c) could also be prepared by an alternative method. Thus, **1** on reaction independently, with each of dimethyl sulphate, diethyl sulphate and benzyl chloride under microwave irradiation conditions for 5 min and subsequent processing, gave, respectively **2a** (*i.e.*, **2**, R = CH_3), **2b** (*i.e.*, **2**, R = C_2H_5)

and **2c** (*i.e.*, **2**, R = $PhCH_2$) identical with the products obtained earlier above.

Alternatively, S-methylisothiouronim hemisulfate, S-ethylisothiouronim hemisulfate and S-benzylisothiouronium chloride was commercially available condensation with ethyl acetoacetate in the presence of ethanolic KOH under reflux for 3 h gave, respectively, **2a-c**, as the products identical with the ones reported in the earlier methods[6-9] in all respects (m.p. m.m.p and co-tlc analysis) (**Scheme-I**).

2C: IR (KBr, ν_{max}, cm^{-1}): 3100-2700 (br, m, -OH); ^1H NMR (400 MHz, DMSO-d_6/TMS): δ 2.40 (s, 3H, $-CH_3$), 4.30 (s, 2H, $-CH_2-$), 6.05 (s, 1H, =CH- of pyrimidine ring), 7.02 (vbr, 1H, -OH), 7.2-7.8 (m, 5H, aromatic ring proton), MS (CI): m/z 233 [M^+ + 1]. m.p. 169-174 ºC. Analytical calcd. (%) for $C_{12}H_{12}N_2OS$:C = 62.04, H = 5.21, N = 12.06; found (%): C = 62.10, H = 5.25, N = 13.01.

Conclusion

It can be said that green and simple syntheses of 6-methyl-2-(alkylthio)pyrimidin-4(3*H*)-one (**2a-c**) from **1** are described. It appears from this study that Green syntheses such as solid phase synthesis (physical grinding) and microwave irradiation gave product in same yields, quality but in less reaction time the products than that over conventional methods involving green solvents like ethanol, PEG-600 *etc*.

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