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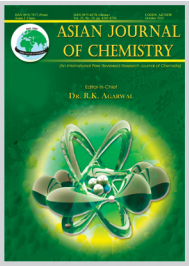

Synthesis and Pharmacological Activity of 2-((4,5-Disubstituted pyridin-2-yl)methylthio)-6-methoxypyrimidin-4-ol

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2-(Chloromethyl)-4,5-disubstitutedpyridine hydrochloride **1** (**1a, 1b**) on condensation with 2-mercapto-6-methylpyrimidin-4-ol(**2**)under conventional and green conditions gave 2-[(4,5-disubstitutedpyridin-2-yl)methylthio]-6-methoxypyrimidin-4-ol (**3**) (**3a, 3b**). The structures of compound **3** have been established by their spectral and analytical data.

Key Words: 2-(Chloromethyl)-4,5-dimethoxypyridine hydrochloride, 2-mercapto-6-methylpyrimidin-4-ol, triethylamine, K_2CO_3, PEG-600.

INTRODUCTION

Pyrimidine is the parent heterocyclic ring of a very important group of compounds that have been extensively studied because of their occurrence in living systems[1]. Compounds containing pyrimidine rings have been reported to posses diverse types of biological activities, which include antibacterial[2], antifungal[3] and anti-HIV activities[4]. Pyrimidines are of great importance in fundamental metabolism[5-7]. Various analogues of thiopyrimidines such as 2-thiouracil and 2,4-dithiouracil posses useful biological properties besides being fundamental constituents of nucleic acids[8-14]. Pyrimidine-2-thiones and their derivatives are also known to exhibit different types of biological activities[15].

EXPERIMENTAL

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 with Perkin-Elmer 1000 instrument in KBr phase. ^{1}H NMR on Varian 400 MHz instrument and mass spectra on Agilent-LC-MS instrument giving only M^+ values using Q+1or Q-1 mode. MWI were done using a domestic microwave oven with an intensity of 70 % for 2 mins. **1a** and **1b** required in this work were obtained from commercial sources. **2** was prepared using a reported procedure in literature[16].

Preparation of 3a and 3b respectively from 1a and 1b and 2: Two synthetic routes have been established for the preparation of **3a** and **3b**.

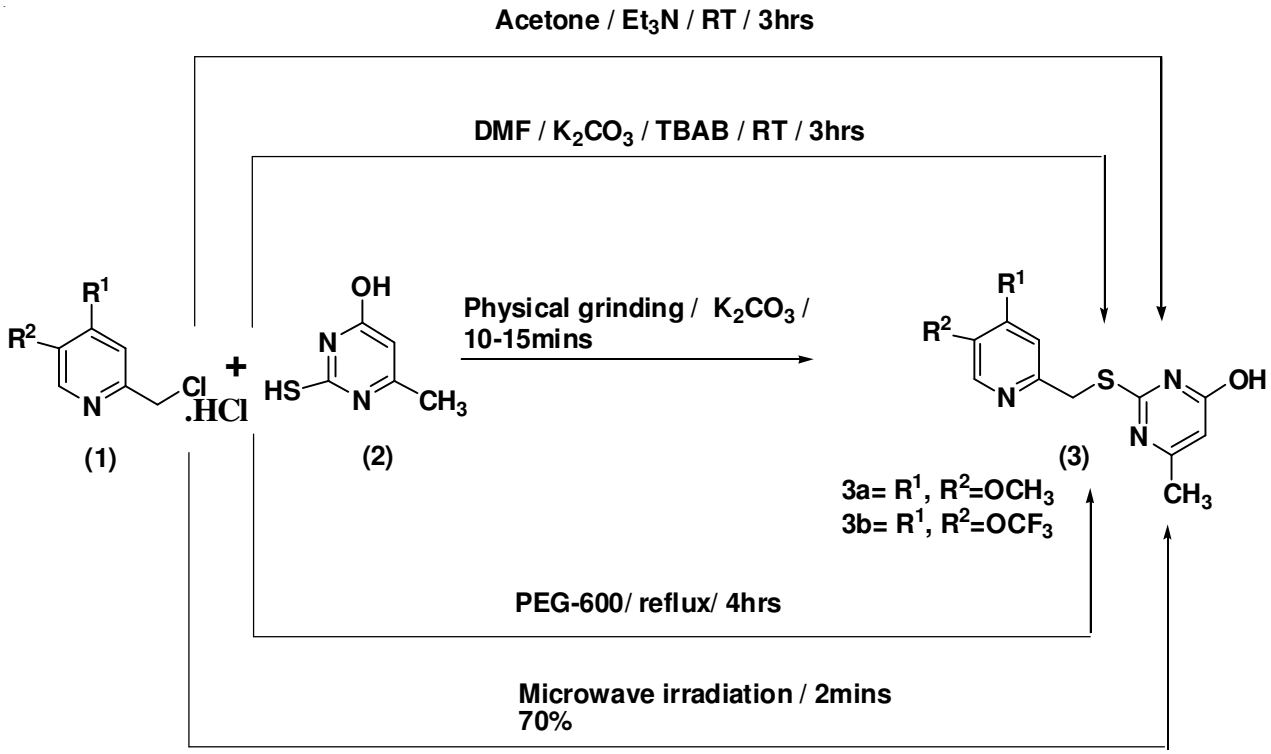
Conventional methods: a) A mixture of **1** (**1a** or **1b**) (10 mmol), **2** (10 mmol), acetone (30 mL) and triethylamine (1-2 mL) was stirred for 3 h at room temperature. After completion of reaction, the mixture was poured into ice-water. The separated solid was filtered, washed with water (50 mL) and dried. Yield (%) is given in Table-1. Crude product was recrystallized from methanol to obtain pure **3** (**3a** or **3b**).

b) A mixture of **1** (**1a** or **1b**) (10 mmol), **2** (10 mmol), K_2CO_3 (5 mmol), tetrabutyl ammonium bromide (10 mg) and DMF (100 mL) was stirred at room temperature for 3-4 h. After the completion of reaction, as shown by TLC, the mixture was poured into ice-water (250 mL). The separated solid was filtered, washed with water (2 × 10 mL) and dried to obtain crude **3**. For yields, (Table-1) was recrystallized from methanol to obtain pure **3** (*i.e.* **3a** or **3b** as the case may be).

Green methods

a) Physical grinding method: A mixture of **1** (**1a** or **1b**) (10 mmol), K_2CO_3 (2.76 g, 20 mM) and 2 (0.1418 g, 10 mM) were ground together for about 10-15 min in a mortar and pestle at room temperature to obtain a homogeneous mixture. The mixture was then treated with ice-cold water (*ca.* 30-40 mL). The separated solid was filtered, washed with water (2 × 10 mL) and dried to obtain crude **3**. For yields, (Table-1) re-crystallization of the crude product from a suitable solvent gave pure **3** (**3a** or **3b** as the case may be).

b) In PEG-600: A mixture of **1** (**1a** or **1b**) (10 mmol), **2** (0.14 g, 10 mM) and PEG-600 (20 mL) was heated on a steam-bath at 100 ºC for 4-5 h. At the end of this period, the mixture was cooled to room temperature and poured into ice-cold water



Scheme-I

(*ca.* 50 mL). The separated solid was filtered, washed with water (2 × 10 mL) and dried. For yields, (Table-1). The crude product was recrystallized from a suitable solvent to obtain pure **3** (*i.e.* **3a** or **3b** as the case may be).

TABLE-1

Substrate	Reaction condition	Product	Yield (%)	m.p. (°C)
1a+2 1b+2	Acetone / Et_3N RT / 3h	3a	89	235-240
		3b	82	>245
	DMF/K_2CO_3/ TBAB RT/ 3 h	3a	85	235-240
		3b	81	>245
	Physical grinding	3a	81	235-240
		3b	79	>245
	Green Solvent (PEG-600)/ reflux/4 h	3a	65	235-240
		3b	62	>245
	Microwave Irradiation/2 min/70 w	3a	89	235-240
		3b	77	>245

TBAB = Tetrabutyl ammonium bromide.

c) Under microwave condition: A mixture of **1** (**1a** or **1b**) (10 mmol) and **2** (10 mM) was taken in an Erlenmeyer flask capped with a funnel. The mixture was kept in a domestic microwave oven for microwave irradiation at 450 watts for 2 min. Then, the mixture was cooled to room temperature and treated with ice-cold water (2 × 10 mL). The separated solid was filtered, washed with water (2 × 10 mL) and dried. For yields, (Table-1). The crude product was recrystallized from a suitable solvent to obtain pure **3** (*i.e.* **3a** or **3b** as the case may be).

RESULTS AND DISCUSSION

2-(Chloromethyl)-4,5-disubstituted pyridine hydrochloride **1** (**1a** and **1b**) on condensation with 2-mercapto-6-methyl-pyrimidin-4-ol[16] (2) gave 2-((4,5-disubstituted pyridin-2-yl)methylthio)-6-methoxypyrimidin-4-ol 3 (**3a** and **3b**). The condensation reaction has been studied under two sets of conditions, namely, (i) conventional and (ii) green conditions.

(i) Under Conventional conditions: This has also been studied under two different conditions- one that involves solution phase with a homogeneous base and the other that involves solution phase with a heterogeneous base assisted by a PTC.

(a) The reaction was carried out in acetone as a solvent and triethylamine as base with stirring for 3-4 h at room temperature. The product was isolated by subsequent simple processing of the reaction mixture. For yields *etc.*, (Table-1). Structures of the products have been assigned based on spectral and analytical data which is given below:

3a: IR (KBr, ν_{max}, cm^{-1}): 3100-2700 cm^{-1} (br, m, -OH); ^1H NMR (400 MHz, DMSO-d_6/TMS): δ 3.07 (s, 3H, $-CH_3$), 3.91 (br, 1H, -OH), 3.95 (s, 6H, 2 × $-OCH_3$ of pyridine ring), 4.20 (s, 2H, $-CH_2$-), 5.90 (s,1H,-, CH- of pyrimidine ring), 7.20 (s, 1H, aromatic ring proton), δ 8.10 (s, 1H, aromatic ring proton) MS (CI): m/z 295 [M^++1]. m.p. : 235-240 °C. Analytical calcd. for $C_{13}H_{15}N_3O_3S$:Analysis %, calcd. C = 53.23, H = 5.15, N = 14.32, Found: C = 53.79, H = 5.21, N = 14.41.

3b: IR (KBr, ν_{max}, cm^{-1}): 3100-2700 cm^{-1} (br, m, -OH); ^1H NMR(400 MHz, DMSO-d_6/TMS): δ 3.07 (s, 3H, $-CH_3$), δ 3.91 (br, 1H, -OH), 4.20 (s, 2H, $-CH_2$-), 5.90 (s, 1H,-, CH- of pyrimidine ring), 7.20 (s, 1H, aromatic ring proton), 8.10 (s, 1H, aromatic ring proton) MS (CI): m/z 403 [M^++1]. m.p.: 212-215 °C. Analytical calcd. for $C_{13}H_9N_3O_3SF_6$: Analysis %, calcd. C = 38.91, H = 2.26, N = 10.47, Found: C = 39.01, H = 2.32, N = 10.57.

b) In this method, the reaction was carried out in DMF as a solvent, in the presence of K_2CO_3 as a base and a trace amount of tetrabutylammonium bromide (TBAB) as phase transfer

catalyst, with stirring for 3-4 h at room temperature. The products (**3a** and **3b**) were isolated by subsequent simple processing of the reaction mixture. Yields % is given in Table-1.

(ii) Under green conditions: This has also been studied under three different conditions, one in the solid phase, the second in the solution phase using green solvents and the third involving microwave irradiation technique.

(a) In solid phase: 1a and **1b** each, independently, on treating with **2** in the presence of K_2CO_3 as a mild base, by simple physical grinding of the reaction mixture in a mortar and pestle, under solvent-free conditions, for 10-15 mints at room temperature followed by processing gave respectively **3a** and **3b** identical with the same products obtained above. For yields *etc.*, (Table-1).

(b) In solution phase: The reaction was carried out by heating a mixture of **1a** and **1b** each, independently, with **2** in PEG-600 at 100 ºC for 3 h without the use of any base. Simple processing of the reaction mixture gave respectively **3a** and **3b** identical with the same products obtained above. For yields *etc.*, (Table-1).

(c) Under microwave irradiation: 1a and **1b** each, independently, on treating with **2** under microwave irradiation conditions for **2** min in the presence of triethylamine as a base and subsequent processing, gave respectively **3a** and **3b** identical with the same products obtained above (**Scheme-I**). For yields *etc.*, (Table-1).

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