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Research Letter

A Novel and One-Pot Synthesis of 6-arylpyrimidin-4-ol

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We have developed a novel and one-pot synthesis of 6-arylpyrimidine-4-ol by reacting commercially available alkyl 3-oxo-3-arylpropanoate with formamide in the presence of stoichiometric amount of ammonium acetate.

1. Introduction

Pyrimidine derivatives are very well known for their various therapeutic applications. Pyrimidine derivatives are used as anticancer [1], anti-HIV [2], antibacterial [3], antimalarial [4], antihypertensive [5], sedative, hypnotics [6], anticonvulsant [7], antithyroid [8], antihistaminic agents [9], and antibiotics [10]. A very recent review describes the significance of pyrimidine derivatives as anti-inflammatory agents [11]. 2-thiopyrimidine derivatives possess potent activity against inflammation and immune disorders [12]. Recently, various pyrimidine derivatives have been reported as vanilloid receptor antagonists [13].

After looking at the diverse properties of pyrimidine derivatives, we selected 4,6-disubstituted pyrimidines as a part of our pharmacophore to synthesize novel anti-inflammatory agents. Literature survey revealed that 4,6-disubstituted pyrimidines can be prepared using either Biginelli approach [14] or reaction of β-iminoesters with formamide [15] or reaction of 4,6-dichloropyrimidines with appropriate boronic acids [16]. The only competitive method similar to our approach described in the literature uses formamidine in DMF and affords the product in only 14% after a reaction time of 3 days [17]. During the course of our research work on synthesis on various 4,6-disubstituted pyrimidines, we developed a novel and one-pot method for the synthesis of 6-arylpyrimidine-4-ol using commercially available raw materials. The method comprises reaction between 3-oxo-3-arylpropanoate, stoichiometric amount of ammonium acetate, and formamide at elevated temperature.

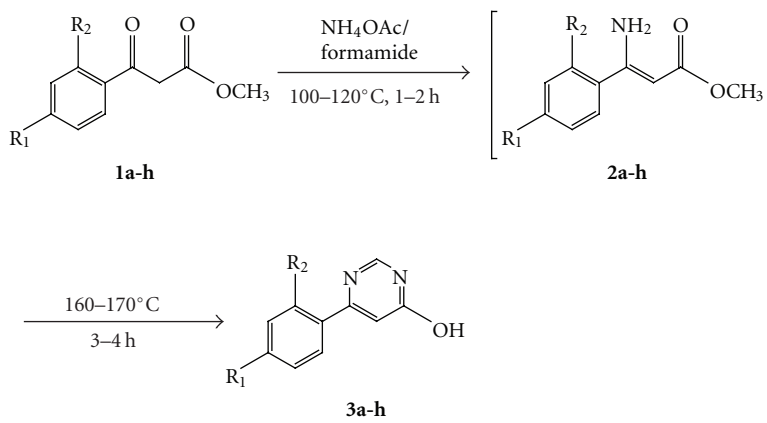
2. Results and Discussion

Various 6-arylpyrimidin-4-ols **3a-h** were prepared by reacting methyl-3-oxo-3-arylpropanoates **1a-h** with formamide in the presence of ammonium acetate with a yield of 50–70%.

The reaction of methyl-3-oxo-3-arylpropanoates **1** with the in situ generated ammonia gives the intermediate methyl 3-amino-3-arylacrylate **2**, which subsequently reacts with formamide to give 6-arylpyrimidin-4-ols **3** (Scheme 1). One of the intermediates methyl 3-amino-3-phenylacrylate was isolated in 80% yield and characterized. Isolation and characterization of **2a** confirm the reaction pathway (Table 1). The procedure described in the experimental part provides a novel and one-pot approach for the synthesis of 6-arylpyrimidin-4-ol.

3. Experimental

Commercial solvents and reagents were used without further purification. ^{1}H NMR spectra were recorded on a Varian 300 MHz spectrometer. Melting points are uncorrected. Elemental analysis was performed on a Perkin-Elmer analyzer. Mass spectra were recorded on Thermo Finnigan LCQ DECA XP MAX (ION TRAP) mass spectrometer using atmospheric pressure chemical ionization (APCI) source in positive/negative mode at capillary voltage 3.14 V and capillary temperature 250°C.



Scheme 1

Table 1: Yield and melting point of compounds *3a-h* and *2a*.

Compound	R_1	R_2	Yield (%)	M. P. (°C)
3a	H	H	65	271-272
3b	Cl	H	70	213–215
3c	Br	H	68	311–313
3d	F	H	61	313–315
3e	CH_3	H	57	291-292
3f	OCH_3	H	53	282–284
3g	OCH_3	OCH_3	50	252–254
3h	H	Cyclopentyloxy	55	260–264
2a	H	H	80	—

*Methyl 3-amino-3-phenylacrylate (**2a**)*

To a stirred solution of methyl 3-oxo-3-phenylpropanoate (1 mmol) in formamide (5.0 mL) was added ammonium acetate (5 mmol) at ambient temperature. Reaction mixture was then heated to 110–120°C over a period of 1 hour and then held at 110–120°C for 1 more hour. It was then cooled to room temperature; diluted with cold water; and extracted with diethyl ether. The residue obtained after removal of diethyl ether was purified through silica gel column using ethyl acetate: petroleum ether (8:2) as an eluent to give methyl 3-amino-3-arylacrylate **2a** as thick oil. IR (KBr): 3445, 1622, 1491, 1320 cm^{-1}. ^1H NMR (DMSO- d_6): δ 3.56 (S, 3H); 4.78 (s, 1H); 7.34–7.59 (m, 5H); 7.95 (brs, 2H). $[M-1]^-$: 176.23. Anal. calcd for $C_{10}H_{11}NO_2$: C, 67.78; H, 6.26; N, 7.90. Found: C, 67.65; H, 6.24; N, 7.91.

*General Procedure for Preparation of 6-arylpyrimidine-4-ol (**3a-h**)*

A stirred solution of appropriate methyl 3-oxo-3-arylpropanoate **1** (1 mmol) in formamide (50 mol) was added ammonium acetate (5 mmol) and heated to 100–120°C over a period of 1 hour and held at 110–120°C for 1 more hour. It was then stirred for 4-5 hours at 160–170°C. Reaction mixture was cooled to room temperature and diluted with cold water. The precipitated material was extracted with ethyl acetate. The solid product obtained after removal of ethyl acetate was washed with diethyl ether to get pure product.

*6-phenylpyrimidine-4-ol (**3a**)*

This compound was obtained as light yellow solid. IR (KBr): 3435, 1668, 1592, 1252, 1024 cm^{-1}. ^1H NMR (DMSO- d_6): δ 6.87 (s, 1H); 7.45–7.47 (m, 3H); 8.02-8.03 (m, 2H); 8.25 (s, 1H); 12.51 (brs, 1H). MS $[M + 1]^+$: 172.32. Anal. calcd for $C_{10}H_8N_2O$: C, 69.76; H, 4.68; N, 16.27. Found: C, 69.74; H, 4.69; N, 16.31.

*6-(4-chlorophenyl)pyrimidine-4-ol (**3b**)*

This compound was obtained as light yellow solid. IR (KBr): 3339, 1667, 1594, 1243, 1014 cm^{-1}. ^1H NMR (DMSO- d_6): δ 6.91 (s, 1H); 7.52 (d, 2H, J = 8.4 Hz); 8.05 (d, 2H, J = 8.7 Hz); 8.26 (s, 1H); 12.54 (brs, 1H). MS $[M + 1]^+$: 207.39. Anal. calcd for $C_{10}H_7ClN_2O$: C, 58.13; H, 3.41; N, 13.58. Found: C, 58.20; H, 3.42; N, 13.61.

*6-(4-bromophenyl)pyrimidine-4-ol (**3c**)*

This compound was obtained as light yellow solid. IR (KBr) 3445, 1685, 1589, 1257, 1010 cm^{-1}. ^1H NMR (DMSO- d_6): δ 6.91 (s, 1H); 7.66 (d, 2H, J = 9 Hz); 7.98 (d, 2H, J = 8.4 Hz); 8.26 (s, 1H); 12.54 (bs, 1H). MS $[M + 1]^+$: 251.39. Anal. calcd for $C_{10}H_7BrN_2O$: C, 47.84; H, 2.81; N, 11.16. Found: C, 47.89; H, 2.80; N, 11.15.

*6-(4-fluorophenyl)pyrimidine-4-ol (**3d**)*

This compound was obtained as light yellow solid. IR (KBr) 3444, 1672, 1600, 1242, 1035 cm^{-1}. ^1H NMR (DMSO- d_6): δ 6.88 (s, 1H); 7.26–7.31 (m, 2H); 8.07–8.11 (m, 2H); 8.25 (s, 1H); 12.52 (brs, 1H). $[M + 1]^+$: 190.97. Anal. calcd for $C_{10}H_7FN_2O$: C, 63.16; H, 3.71; N, 14.73. Found: C, 63.12; H, 3.70; N 14.76.

*6-(4-methylphenyl)pyrimidine-4-ol (**3e**)*

This compound was obtained as light yellow solid. IR (KBr): 3422, 1664, 1592, 1254, 1175, 1037 cm^{-1}. ^1H NMR (DMSO-d_6): δ 2.34 (s, 3H); 6.81 (s, 1H); 7.26 (d, 2H, J = 7.8 Hz); 7.92 (d, 2H, J = 7.8 Hz); 8.22 (s, 1H); 12.20 (brs, 1H). $[M + 1]^+$: 186.39. Anal. calcd for $C_{11}H_{10}N_2O$: C, 70.95; H, 5.41; N, 15.04. Found: C, 71.11; H, 5.43; 15.00.

*6-(4-methoxyphenyl)pyrimidine-4-ol (**3f**)*

This compound was obtained as light yellow solid. IR (KBr) 3397, 1666, 1605, 1245, 1177 cm^{-1}. ^1H NMR (DMSO- d_6): δ 3.80 (s, 3H); 6.77 (s, 1H); 7.00 (d, 2H, J = 8.7 Hz); 8.00 (d, 2H, J = 9 Hz); 8.21 (s, 1H); 12.42 (brs, 1H). $[M + 1]^+$: 203.37. Anal. calcd for $C_{11}H_{10}N_2O_2$: C, 65.34; H, 4.98; N, 13.85. Found: C, 65.38; H, 4.97; N, 13.88.

*6-(2,4-dimethoxyphenyl)pyrimidine-4-ol (**3g**)*

This compound was obtained as light yellow solid. IR (KBr) 3414, 1673, 1610, 1270, 1170 cm^{-1}. ^1H NMR (DMSO- d_6): δ 3.81 (d, 6H, J = 4.5 Hz); 6.84 (s, 1H); 7.02 (d, 1H, J = 8.4 Hz); 7.58 (s, 1H); 7.65 (d, 1H, J = 9 Hz); 8.20 (s, 1H); 12.32 (brs, 1H). $[M + 1]^+$: 233.36. Anal. calcd for $C_{12}H_{12}N_2O_3$: C, 62.06; H, 5.21; N, 12.06. Found: C, 62.20; H, 5.23; N, 12.04.

*6-[2-(cyclopentyloxy)phenyl]pyrimidine-4-ol (**3h**)*

This compound was obtained as light yellow solid. IR (KBr): 3313, 1643, 1574, 1279, 1242 cm^{-1}. ^1H NMR (DMSO- d_6): δ 1.63–1.76 (m, 6H); 1.90–1.99 (m, 2H); 4.95 (m, 1H); 6.93 (s, 1H); 7.00 (t, 1H, J = 7.8 Hz); 7.11 (d, 1H, J = 8.4 Hz); 7.38 (t, 1H, J = 6.9 Hz); 7.93 (d, 1H, J = 6.3 Hz); 8.20 (s, 1H); 12.42 (brs, 1H). $[M + 1]^+$: 257.13. Anal. calcd for $C_{15}H_{16}N_2O_2$: C, 70.29; H, 6.29; N, 10.93. Found: C, 70.19; H, 6.27; N, 10.91.

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