

SOLVENT-FREE SPLENDID ONE POT SYNTHESIS OF 2-AMINO-6-(SUBSTITUTEDPHENYL)-5-METHYLPYRIMIDIN-4-OL USING PEG-400

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Abstract:

The simple and efficient approach towards one step synthesis of 2-amino-6-(substitutedphenyl)-5-methylpyrimidin-4-ol derivatives has been developed by three component condensation of aromatic aldehydes, ethyl propionate and guanidine hydrochloride using PEG as reaction medium.

Key Words: 2-Amino-6-aryl-5-methylpyrimidin-4-ol, Aromatic aldehydes, Ethyl propionate, Guanidine hydrochloride, PEG-400.

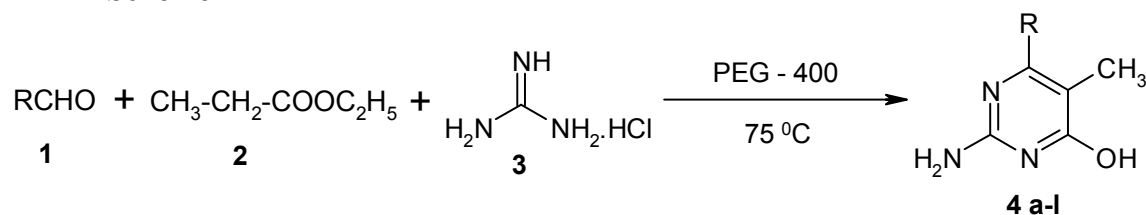
Introduction

The development of simple synthetic routes for widely used organic compounds from readily available reagents is one of the major tasks in organic synthesis. Now days, the one step methods involving three-component condensation are popular in synthetic organic chemistry for the synthesis of heterocyclic compounds. The one step methods are more convenient as compared with multistep, since they require shorter reaction time and gives higher yield with easy workup. Pyrimidine does not exist in nature but in the form of its different derivatives are found as a part of more complex systems and are widely distributed. Pyrimidines are integral part of the genetic materials viz. DNA and RNA. Their analogues have been extensively studied over a century due to their diverse biological activities [1,2,3]. They possess antibacterial, antiviral, antitumor [4]. Antihypertensive [5] and anti-inflammatory activities [6]. Therefore, the research on the synthesis of the pyrimidine and its analogues has been going on continuously in search of new biologically active molecules. The various approaches have been reported on the synthesis of pyrimidine derivatives [7,8,9].

Now a day, the development of one-step methods involving three-component condensation is popular in synthetic organic chemistry which requires shorter reaction time, and gives better yield with easy work up. A one-step method generally involves three components condensations to yield the target molecules. The first one-step synthesis of 3,4-

dihydropyrimidin-2(1*H*)-one by three-component condensation of aldehydes, ethyl acetoacetate and urea has been reported by Sci. P. Biginelli in 1893 ^[10]. But due to the drawback of biginelli reaction, several new methodologies ^[11,12,13,14], use of micro wave irradiation ^[15] and some involved in the use of ionic liquids ^[16] have been reported for the synthesis of 3,4-dihydropyrimidin-2(1*H*)-one. Thiouracils were also reported by one pot condensation between aromatic aldehydes, ethyl cyanoacetate and thiourea ^[17,18]. Recently, Knoevenagel condensation has been reported in water using aromatic aldehydes and malononitrile ^[19] while Tong-Shou Jin and his coworkers reported the synthesis of dihydropyrano[2,3-*c*]pyrazoles in aqueous media ^[20]. Many of the synthetic protocols for pyrimidines suffer from one or more disadvantages such as harsh reaction conditions, poor yields, prolonged time period, use of hazardous and expensive catalysts. So the development of clean, high-yielding and environmentally friendly approaches is still desirable and much in demand. Recently PEG-400 is found to be an interesting solvent system. It is inexpensive, thermally stable, non-volatile, non-toxic and easily degradable, has emerged as reaction medium in organic synthesis ^[21,22]. As a part of our ongoing research interest in PEG ^[23], in this communication, we wish to report a simple but effective synthesis of said compounds by three-component condensation of aromatic aldehydes, ethyl propionate and guanidine hydrochloride using as PEG-400 as reaction medium (**Scheme –1**).

Scheme - 1



Results and Discussion

In the initial studies, benzaldehyde (4 mmol), ethyl propionate (7 mmol) and guanidine hydrochloride (7 mmol) was performed in different solvents without any added catalyst to synthesize the compound **4a**. It was observed that among the tested solvents (**Table 1**, entries 5–8), the reaction in PEG-400 was more facile and proceeded to give best yield (90%) when the reaction mixture was stirred at 75 °C for 1.5 h. Moreover, there are many potential advantages of replacing these volatile or toxic organic solvents with PEG-400. So, PEG-400 is the optimal reaction medium for the reaction.

Table 1: Synthesis of 2-amino-6-aryl-5-methylpyrimidin-4-ol in different solvents.

Entry	Solvent	Temperature (°C)	Time	Yield %
1	PEG-400	25	24	5
2	PEG-400	75	1.5	90
3	PEG-400	110	1.5	90
4	PEG-400	120	1.5	86
5	MeOH	65	5	71
6	EtOH	75	5	75
7	CH ₃ CN	78	5	51
8	DMF	110	5	67

The effect of temperature was also studied by carrying out the model reaction of **4a** in PEG-400 at different temperature. As shown in Table 1 (entries 1), the reaction did proceed but the yield obtained remained low even after longer reaction time (24 h) when the reaction temperature was 25 °C. However, at elevated temperature (75–110 °C) using PEG-400 gave better results in terms of yield and reaction time. Hence, the conditions of entry 2 shown in **Table 1** were the optimized reaction conditions. Using more than 4 mmol of PEG-400 did not improve the yield of the product, and at the same time, very low yield of the product was obtained in the absence of PEG-400. Since only 4 mmol of PEG-400 is used it cannot act as a solvent, thus it is the promoter for the reaction without requiring any additional catalyst. We investigated our protocol with various PEGs with molecular weights 200, 400, 600, 4000, and 6000 (0.05 mol % each) for our modal reaction with benzaldehyde (4 mmol), ethyl propionate (7 mmol) and guanidine hydrochloride (7 mmol). The reaction occurred and giving excellent yields (**Table 2**) with low as well as high molecular weight PEGs.

Table 2: Synthesis of 2-amino-6-aryl-5-methylpyrimidin-4-ol (**4a-l**) using PEG-400 as reaction medium

Product	R	Time (h)	Yield %
4a	C ₆ H ₅	1.5	90
4b	3-Cl-C ₆ H ₄	2.0	86
4c	2-Cl-C ₆ H ₄	2.0	92
4d	3,4-(OMe) ₂ -C ₆ H ₃	1.5	87
4e	3,4,5-(OMe) ₃ -C ₆ H ₂	2.5	91
4f	C ₆ H ₄ -CH=CH-	1.5	85
4g	2-NO ₂ -C ₆ H ₄	1.5	91
4h	3-NO ₂ -C ₆ H ₄	2.0	88
4i	4-CH ₃ -C ₆ H ₄	2.0	90
4j	4-OH-C ₆ H ₄	1.5	89
4k	CH ₃ -CH ₂ -	1.5	91
4l	CH ₃ -CH ₂ -CH ₂ -	2.0	88

Conclusion

In conclusion, we have developed a simple, efficient and catalyst-free, synthesis of 2-amino-6-(substitutedphenyl)-5-methylpyrimidin-4-ol derivatives **4a-j** in high yields in the presence of PEG-400 under solvent- free conditions at 75 °C. In this reaction PEG-400 act as a very efficient ‘green’ promoter and this methodology works equally well with both low and high molecular weight PEGs. Therefore this is a very general and environmentally benign eco-friendly procedure, which would prove beneficial to both academic and industrial fields.

Experimental Section

All reagents and solvents were purchased and used without further purification. Melting points were determined on a Fisher–Johns melting point apparatus were uncorrected. Crude products were purified by column chromatography on silica gel of 60–120 mesh. IR spectra were obtained on a Perkin Elmer BX serried FT-IR 5000 spectrometer using KBr pellet. The NMR spectra were recorded on a varian 300 MHz spectrometer for ¹H NMR. The chemical shifts were reported as ppm down field using TMS as an internal standard. LCMS Mass spectra were recorded on a MASPEC low resolution mass spectrometer operating at 70 eV.

General procedure for the synthesis of 2-amino-6-(substitutedphenyl)-5-methylpyrimidin-4-ol derivatives: A mixture of an benzaldehyde (4 mmol), ethyl propionate (7 mmol) and guanidine hydrochloride (7 mmol), and PEG-400 (4 mmol) was heated at 75 °C for specified time (**Table 2**). The reaction mixture was monitored by TLC till the disappearance of the starting aldehyde. After cooling, the reaction mixture was washed with water (15 mL) and residue recrystallized from MeOH to afford the pure 2-amino-6-(substitutedphenyl)-5-methylpyrimidin-4-ol compounds.

2-Amino-5-methyl-6-phenylpyrimidin-4-ol (4a). Yellow solid; Yield 90%; m.p. 175-177 °C; IR (KBr): 3454, 3285, 2789, 2258, 1615, 1589, 1430, 1290, 1175, 1082, 758, 692 cm^{-1} . ^1H NMR (300 MHz, DMSO- d_6): δ 2.14 (s, 3H, CH₃), 3.42 (br. s, 2H, NH₂), 7.11-7.24 (m, 5H, Ar-H), 8.35 (s, 1H, OH); LCMS (m/z) 202 (M+H). Anal. Calcd. for C₁₁H₁₁N₃O: C, 65.66, H, 5.54, N, 20.78; Found: C, 65.74, H, 5.68, N, 20.63.

2-Amino-6-(3-chlorophenyl)-5-methylpyrimidin-4-ol (4b). Pale yellow solid; Yield 86%; m.p. 142-143 °C; IR (KBr): 3331, 3227, 2899, 2558, 1668, 1558, 1433, 1292, 1190, 776, 686 cm^{-1} . ^1H NMR (300 MHz, DMSO- d_6): δ 2.24 (s, 3H, CH₃), 3.54 (br. s, 2H, NH₂), 7.35-7.52 (m, 3H, Ar-H), 8.10 (s, 1H, Ar-H), 8.42 (s, 1H, OH); LCMS (m/z) 236 (M+H). Anal. Calcd. for C₁₁H₁₀ClN₃O: C, 56.10, H, 4.33, N, 17.84; Found: C, 55.89, H, 4.52, N, 17.92.

2-Amino-6-(2-chlorophenyl)-5-methylpyrimidin-4-ol (4c). Yellow solid; Yield 92%; m.p. 198-199 °C; IR (KBr): 3419, 3189, 2572, 1673, 1582, 1485, 1476, 1423, 1271 cm^{-1} . ^1H NMR (300 MHz, DMSO- d_6): δ 2.28 (s, 3H, CH₃), 3.58 (br. s, 2H, -NH₂), 7.55-8.15 (m, 4H, Ar-H), 8.48 (s, 1H, -OH); LCMS (m/z) 236 (M+H). Anal. Calcd. for C₁₁H₁₀ClN₃O: C, 56.10, H, 4.33, N, 17.84; Found: C, 55.89, H, 4.52, N, 17.92.

2-Amino-6-(3,4-dimethoxyphenyl)-5-methylpyrimidin-4-ol (4d). Yellow solid; Yield 87%; m.p. 228-229 °C; IR (KBr): 3469, 3229, 2941, 1765, 1667, 1590, 1498, 1423, 1264, 1174, 1012, 824, 776 cm^{-1} . ^1H NMR (300 MHz, DMSO- d_6): δ 2.18 (s, 3H, CH₃), 3.48 (br. s, 2H, NH₂), 3.76 (s, 3H, OCH₃), 3.85 (s, 3H, OCH₃), 6.98-7.51 (s, 3H, Ar-H), 8.38 (s, 1H, OH); LCMS (m/z) 261 (M⁺). Anal. Calcd. for C₁₃H₁₅N₃O₃: C, 59.80, H, 5.83, N, 16.01; Found: C, 59.92, H, 6.03, N, 15.87.

2-Amino-6-(3,4,5-trimethoxyphenyl)-5-methylpyrimidin-4-ol (4e). Pale yellow solid; Yield 91%; m.p. 165-166 °C; IR (KBr): 3429, 2939, 2838, 1666, 1591, 1507, 1462, 1240, 1126, 1004, 836 cm^{-1} . ^1H NMR (300 MHz, DMSO- d_6): δ 2.19 (s, 3H, CH₃), 3.50 (br. s, 2H, NH₂), 3.84 (br. s, 9H, -OCH₃), 6.12-6.74 (m, 2H, Ar-H), 8.32 (s, 1H, OH); LCMS (m/z) 292 (M+H). Anal. Calcd. for C₁₄H₁₇N₃O₄: C, 57.72, H, 5.88, N, 14.51; Found: C, 57.91, H, 6.05, N, 14.78.

2-Amino-6-(cinnamyl)-5-methylpyrimidine-4-ol (4f). Colourless solid; Yield 85%; m.p. 189-190 °C; IR (KBr): 3338, 2946, 2835, 1694, 1662, 1571, 1278, 1088, 724 cm^{-1} . ^1H NMR (300 MHz, DMSO- d_6): δ 2.38 (s, 3H, CH₃), 3.48 (s, 2H, NH₂), 7.25 (d, 1H, Ar-CH=CH), 7.30-7.58 (m, 5H, Ar-H), 8.0 (d, 1H, Ar-CH=CH), 8.24 (s, 1H, OH); LCMS (m/z) 227 (M⁺). Anal. Calcd. for C₁₃H₁₃N₃O: C, 68.72, H, 5.83, N, 18.59; Found: C, 68.91, H, 5.65, N, 18.35.

2-Amino-6-(2-nitrophenyl)-5-methylpyrimidin-4-ol (4g). Yellow solid; Yield 91%; m.p. 210-211 °C; IR (KBr): 3425, 3027, 1634, 1568, 1452, 1125, 841, 776, cm^{-1} . ^1H NMR (300 MHz, DMSO- d_6): δ 2.42 (s, 3H, CH_3), 3.54 (br. s, 2H, NH_2), 7.54-8.18 (m, 4H, Ar-H), 8.75 (br. s, 1H, OH); LCMS (m/z) 247 (M+H). Anal. Calcd. for $\text{C}_{11}\text{H}_{10}\text{N}_4\text{O}_3$: C, 53.68, H, 4.12, N, 22.81; Found: C, 53.94, H, 4.42, N, 22.88.

2-Amino-6-(3-nitrophenyl)-5-methylpyrimidin-4-ol (4h). Pale yellow solid; Yield 88%; m.p. 168-169 °C; IR (KBr): 3410, 2938, 2868, 1647, 1639, 1531, 1362, 1120, 1174, 810, 745 cm^{-1} . ^1H NMR (300 MHz, DMSO- d_6): δ 2.40 (s, 3H, CH_3), 3.52 (s, 2H, NH_2), 7.65-8.25 (m, 4H, Ar-H), 8.62 (s, 1H, OH); LCMS (m/z) 247 (M+H). Anal. Calcd. for $\text{C}_{11}\text{H}_{10}\text{N}_4\text{O}_4$: C, 53.68, H, 4.12, N, 22.82; Found: C, 53.89, H, 4.25, N, 22.69.

2-Amino-6-(p-methylphenyl)-5-methylpyrimidin-4-ol (4i). Yellow solid; Yield 90%; m.p. 158-159 °C; IR (KBr): 3337, 2937, 2844, 2224, 1694, 1590, 1590, 1429, 1263, 1177, 1071, 837, 686 cm^{-1} . ^1H NMR (DMSO- d_6): δ 2.16-2.22 (s, 6H, 2 CH_3), 3.40 (br. s, 2H, NH_2), 7.25-7.53 (m, 4H, Ar-H), 8.32 (s, 1H, OH); LCMS (m/z) 216 (M+H). Anal. Calcd. for $\text{C}_{12}\text{H}_{13}\text{N}_3\text{O}$: C, 66.98, H, 6.12, N, 19.58; Found: C, 67.15, H, 6.45, N, 19.21.

2-Amino-6-(p-hydroxyphenyl)-5-methylpyrimidin-4-ol (4j). Pale yellow solid; Yield 89%; m.p. 235-236 °C; IR (KBr): 3307, 3233, 2924, 2231, 1672, 1562, 1510, 1435, 1288, 1175, 842, 736 cm^{-1} . ^1H NMR (300 MHz, DMSO- d_6): δ 2.38 (s, 3H, CH_3), 3.56 (br. s, 2H, NH_2), 6.95-7.52 (m, 4H, Ar-H), 8.52 (s, 1H, OH), 10.58 (s, 1H, Ar-OH); LCMS (m/z) 217 (M^+). Anal. Calcd. for $\text{C}_{11}\text{H}_{11}\text{N}_3\text{O}_2$: C, 60.85, H, 5.15, N, 19.42; Found: C, 61.03, H, 4.97, N, 19.48.

2-Amino-6-ethyl-5-methylpyrimidin-4-ol (4k). White solid; Yield 91%; m.p. 135-137 °C; IR (KBr): 3307, 3233, 2924, 2231, 1672, 1562, 1510, 1435, 1288, 1175, 842, 736 cm^{-1} . ^1H NMR (300 MHz, DMSO- d_6): δ 1.18 (t, 3H, CH_2CH_3), 2.20 (s, 3H, CH_3), 2.84 (q, 2H, CH_2CH_3), 3.54 (br. s, 2H, NH_2), 8.36 (s, 1H, OH); LCMS (m/z) 153 (M^+). Anal. Calcd. for $\text{C}_7\text{H}_{11}\text{N}_3\text{O}$: C, 54.89, H, 7.24, N, 27.43; Found: C, 54.73, H, 7.32, N, 27.48.

2-Amino-6-propyl-5-methylpyrimidin-4-ol (4l). White solid; Yield 88%; m.p. 157-159 °C; IR (KBr): 3307, 3233, 2924, 2231, 1672, 1562, 1510, 1435, 1288, 1175, 842, 736 cm^{-1} . ^1H NMR (300 MHz, DMSO- d_6): δ 0.91 (t, 3H, $\text{CH}_2\text{CH}_2\text{CH}_3$), 1.34 (m, 2H, $\text{CH}_2\text{CH}_2\text{CH}_3$), 2.18 (t, 2H, $\text{CH}_2\text{CH}_2\text{CH}_3$), 2.27 (s, 3H, CH_3), 3.48 (br. s, 2H, NH_2), 8.32 (s, 1H, OH); LCMS (m/z) 168 (M+H). Anal. Calcd. for $\text{C}_8\text{H}_{13}\text{N}_3\text{O}$: C, 57.46, H, 7.84, N, 25.13; Found: C, 57.39, H, 7.91, N, 25.19.

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References

1. E.R. El-Bendary, M.A. El-Sherbeny and F.A. Badri, *Bull Chim Farm.* 137, 115-121 (1998).
2. K. Tsuji and H. Ishikawa, *Bioorg. Med. Chem. Let.* 4, 1601-1606 (1994).
3. G. Kirpal, *US Pat.* 5,869,494, *Chem Abstr.* 130, 163202 (1999).
4. K.S. Atwal, B.N. Swanson, S.E. Unger, D.M. Floyd, S. Moreland, A. Hedberg and B.C. O'Reilly, *J. Med. Chem.* 34, 806-811 (1991).
5. H.A. Walker, S. Wilson, E.C. Atkins, H.E. Garrett and A.R. Richardson, *J. Pharmacol. Exp. Ther.* 101, 368-378 (1951).
6. G.E. Hardtmann and F.G. Kathawala, *U.S. Patent.* 4,053,600 (1977). *Chem Abstr.* 88, 22970 (1978).
7. W. Yan-Chao, Z. Xiao-Mao, H. Fang-Zhong and Y. Hua-Zheng, *J. Heterocyc. Chem.* 42, 609-613 (2005).
8. O.A. Fathalla, H.H. Radwan, H.M. Awad and M.S. Mohamed, *Indian. J. Chem.* 45B, 980-985 (2006).
9. E.A. Akhite, A.G. Al-Sehemi and Y. Yamada, *J. Heterocyc. Chem.* 42, 1069-1077 (2005).
10. P. Biginelli, *Gazz. Chim. Ital.* 23, 360-416 (1893).
11. C.O. Kappe, *Chem Res.* 33, 879-888 (2000).
12. K.V.N.S. Srinivas and B. Das, *Synthesis.* 13, 2091-2093 (2004).
13. Q. Sun, Y. Wang, Z. Ge, T. Chang and R.A. Li, *Synthesis.* 13, 1047-1051 (2004).
14. Z. Wang, L. Xu, C. Xia and H. Wang, *Tetrahedron Lett.* 45, 7951-7953 (2004).
15. C.O. Kappe and A. Stadler, *J. Chem. Soc. Perk Trans II.* 1363-1368 (2000).
16. A.R. Gholap, K. Venkatesan, T. Danier, R.I. Lahoti and K.V. Srinivasan, *Green Chem.* 6, 147-152 (2004).
17. S. Kambe and H.A. Salto Kishi, *Synthesis.* 4, 287-289 (1979).
18. L. Ji-Tai, L. Zhi-Ping, H. Jun-Fen and L. Tong-Shuang, *Synthetic Commu.* 34, 2623-2631 (2004).
19. J. Tong-shou, Z. Jian-She, W. Ai-Qing and L. Tong-Shuang, *Synthetic Commu.* 34, 2611-2618 (2004).
20. J. Tong-Shou, Z. Rui-Qiao and L. Tong-Shuang, *Arkivok.* XI, 176-182 (2006).
21. V.V. Kouznetsov, D.R. Merchan Arenas and A.R. Romero Bohorquez, *Tetrahedron Lett.* 49, 3097-3100 (2008).
22. B. Das, M. Krishnaiah, P. Thirupathi and K. Laxminarayana, *Tetrahedron Lett.* 48, 4263-4265 (2007).
23. X.C. Wang, Z.J. Quan and Z. Zhang, *Tetrahedron.* 63, 8227-8233 (2007).

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