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Short communication

A novel and efficient one step synthesis of 2-amino-5-cyano-6-hydroxy-4-aryl pyrimidines and their anti-bacterial activity

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ABSTRACT

The first simple and efficient approach towards one step synthesis of 2-amino-5-cyano-6-hydroxy-4-aryl pyrimidines has been developed by three component condensation of aromatic aldehydes, ethyl cyanoacetate and guanidine hydrochloride in alkaline ethanol. The synthesized compounds evaluated for their anti-bacterial activity against Gram-positive and Gram-negative bacteria. The some of the compounds showed excellent zone of inhibition against tested bacteria.

1. 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 multi-step, since they require shorter reaction time and gives higher yield with easy workup.

Heterocycles are ubiquitous to among pharmaceutical compounds [1]. Pyrimidine moiety is an important class of N-containing heterocycles widely used as key building blocks for pharmaceutical agents. It exhibits a wide spectrum of pharmacophore as it acts as bactericidal, fungicidal [2], analgesic [3], anti-hypertensive [4] and anti-tumor agents [5]. Among these; thiouracils are similarly used as for anti-inflammatory and virucidal agents [6]. Also, preclinical data from literature survey indicate continuing research in polysubstituted pyrimidine as potential anti-tumor agents [7]. The biological and synthetic significance places this scaffold at a prestigious position in medicinal chemistry research.

Sci. P. Biginelli in 1893 reported one-step synthesis of 3,4-dihydropyrimidin-2(1*H*)-one by three-component condensation of aldehydes, ethyl acetoacetate and urea in alcohol using strong mineral acid [8]. These Biginelli compounds possess several pharmaceutical properties like anti-bacterial, anti-viral, anti-inflammatory, anti-hypertensive and anti-tumor agents [9,10].

The scope of the original Biginelli reaction was gradually extended by variation of all three building blocks, allowing access to a large number of multifunctionalized dihydropyrimidones. The several protocols and different reaction conditions have been employed to improve the yield of Biginelli reaction [11–14].

Although, various methods are reported concerning the synthesis of pyrimidine derivatives, few one-pot syntheses [15,16] have been published using aromatic aldehydes, ethyl cyanoacetate and thiourea.

As per our ongoing research program aimed at the development of newer synthetic methodologies for widely used heterocyclic compounds [17,18] inspired us to synthesize 2,6-diamino-4-phenyl pyrimidine-5-carbonitrile.

In this communication, we have been reporting the first synthesis of said compounds by three-component condensation of aromatic aldehydes, ethyl cyanoacetate and guanidine hydrochloride in ethanol under alkaline medium and their anti-bacterial activity.

2. Results and discussion

As per our best knowledge, there is no method involving the one step synthesis of said pyrimidine compounds using aromatic aldehydes, ethyl cyanoacetate and guanidine hydrochloride. As

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a case study, the equimolar mixtures of 3-chloro benzaldehyde (10 mmol), ethyl cyanoacetate (10 mmol) and NaOH (0.4 g in 5 ml water) in 25 ml ethanol were stirred mechanically for 10 min, followed by addition of guanidine hydrochloride (10 mmol). The reaction mixture was then refluxed till completion. After the completion of the reaction as monitored by TLC, the reaction mixture was poured in ice-cooled water and neutralized by 1:1 HCl to get the desired product. The separated solid was filtered, washed with distilled water to remove all the acid and finally, recrystallised from ethanol to get the pure product.

The method exploited works well with variety of aromatic aldehydes as well as heteroaromatic aldehydes to afford corresponding polysubstituted pyrimidine in excellent yields.

We reasoned that the electron donating as well as electron withdrawing groups present in aryl aldehydes does not alter the theme of the method in terms of yield and reaction time. The physical and analytical data have been given in Table 1

In case of *p*-anisaldehyde, we were unable to get desired product. The proton NMR spectrum of corresponding compound showed four doublets, indicating the formation of 4-(4-methoxy)-phenyl-5-cyano-6-oxo hexahydro-2-iminopyrimidine. The same reaction was also carried out for the aliphatic aldehydes like crotonaldehyde but we did not succeed to get the desired product.

2.1. Anti-bacterial activity

The anti-bacterial activity was studied by selecting Gram-positive and Gram-negative bacteria via agar well diffusion method. The solutions were prepared in five different concentrations: (a) 750 ppm (b) 500 ppm (c) 250 ppm (d) 100 ppm and (e) 50 ppm.

2.2. Agar well diffusion method

In this method, the solution of testing compound was added in a well in the solidified agar layer in a petri dish and zone of inhibition is measured after 24 h.

About 10–15 g of molten agar was spread into each sterilized petri dish by taking the usual precautions to avoid the contaminations. All the petri dishes were marked in a specific way. Sterile cork borer was used to make well. The agar plates were inoculated with the suspension of particular organism by spread plate technique.

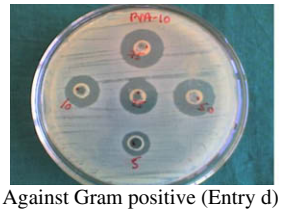
Finally, the agar well plates were filled with 0.5 ml of the test solution. After the addition of the tested samples, the plates were kept in freeze for diffusion and incubated at 37 °C for 1 h. The zone of inhibition if any was then measured in mm for the particular compound and specific organism.

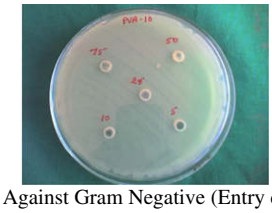
All the microbial strains used were of non-invasive species of their genera and thus applicable for analytical work. *Escherichia coli* and *Staphylococcus aureus* are common bacteria causing food poisoning. Therefore we have selected these two bacteria for the screening work. The results i.e. zone of inhibition have been introduced in Table 2.

Table 1
Synthesis of 2-amino-5-cyano-6-hydroxy-4-aryl pyrimidines (a–l).

Sr. No. (Entry)	Aryl aldehyde	Time (h)	Yield (%)[a]
a	4-N, N–(CH_3) 2-C_6H_4	1.0	92
b	3-NO_2–C_6H_4	1.0	94
c	3,4-(OCH_3)$_2$–C_6H_3	1.5	92
d	C_6H_5–	1.5	90
e	C_6H_4–CH=CH–	1.5	92
f	3-ClC_6H_4	1.5	95
g	4-$OCH_3C_6H_4$	2.5	90
h	2-$NO_2C_6H_4$	2.0	88
i	3,4,5-(OCH_3) 3-C_6H_2	2.0	89
j	4-OHC_6H_4	1.5	93
k	Thiophene2-aldehyde	2.5	83
l	2-ClC_6H_4	3.0	79

[a] Yields refer to pure products.


Against Gram positive (Entry d)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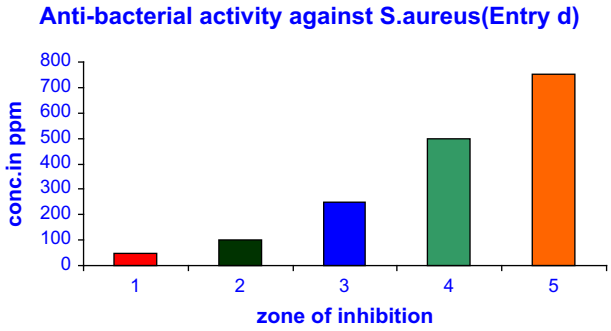


The anti-bacterial study of the synthesized compounds shows good to excellent activity against tested Gram-positive and Gram-negative bacteria. Among these, interestingly, the 2-amino-5-cyano-6-hydroxy-4-phenyl pyrimidine found to be selectively active against Gram-positive *S. aureus* bacteria and also noted that the substituent on the aromatic aldehydes reduces the biological property.

2.3. General procedure for the synthesis of desired compounds

The equimolar mixture of aromatic aldehyde, (10 mmol), ethyl cyanoacetate (10 mmol) and NaOH (0.4 g in 5 ml water) in 25 ml ethanol was stirred mechanically for at least 10 min, then guanidine hydrochloride (10 mmol) was added to the above reaction mixture and reaction mixture was refluxed till completion of reaction as monitored by TLC. After the completion of reaction, the reaction mixture was poured into ice-cooled water and neutralized by 1:1 HCl to get the desired product. The separated solid was filtered, washed with little distilled water to remove acid. Finally, the crude product was purified by recrystallisation from ethanol to get pure product in almost quantitative yield (Scheme 1).

2.4. Experimental part

The melting points of products were taken in open capillary and are found to be uncorrected. All above products have been fully characterized by IR, proton NMR, ^{13}C NMR spectroscopy and mass spectrometry as well as elemental analysis. The data found were in consistent with the proposed structure. The proton NMR and ^{13}C spectra were recorded in DMSO-d_6 solvent on Brucker 400 MHz spectrometer using tetramethyl silane as internal standard. The reaction was monitored by TLC using silica gel 60-F 254 plates.

2.5. Spectroscopic data of representative compounds

*2.5.1. 2-Amino-6-hydroxy-4-(4-*N,N*-dimethylaminophenyl)-pyrimidine-5-carbonitrile (entry a).* M.p.: 215 °C. IR (KBr): 3434, 2924, 2215, 1661, 1611, 1565, 1293, 1190, 1171, 813 cm^{-1}. PMR (DMSO-d_6)

Table 2
Zone of inhibition against *Escherichia coli* and *Staphylococcus aureus*.

Entry	*E. coli*					*S. aureus*				
	Conc. in ppm					Conc. in ppm				
	50	100	250	500	750	50	100	250	500	750
a	–	–	4 mm	7 mm	11 mm	–	–	7 mm	9 mm	11 mm
b	–	–	–	–	–	–	–	4 mm	8 mm	14 mm
c	–	–	–	–	–	–	–	–	–	–
d	–	–	–	–	–	10 mm	12 mm	15 mm	15 mm	18 mm
e	–	–	7 mm	9 mm	12 mm	–	–	–	5 mm	9 mm
f	–	–	4 mm	7 mm	11 mm	–	–	–	–	5 mm
g	–	–	–	–	–	–	–	–	–	5 mm
h	–	–	3 mm	5 mm	9 mm	–	–	–	12 mm	15 mm
i						–	–	–	10 mm	13 mm
j	–	–	–	6 mm	10 mm	–	–	5 mm	8 mm	11 mm
k	–	–	–	–	–	–	–	6 mm	9 mm	13 mm
l	–	–	–	8 mm	10 mm	–	–	5 mm	9 mm	14 mm

δ 3.0 (s, 6H, N–$(CH_3)_2$), 6.80–6.82 (dd, 2H, Ar-H $J = 8.0$ Hz), 7.91–7.93 (dd, 2H, Ar-H $J = 8.0$ Hz), 8.05 (s, 1H, OH), 13.23 (s, 2H, NH_2). ^{13}C NMR (DMSO-d_6) δ 40.17, 93.5, 110.9, 111.6, 117.7, 118.4, 133.4, 153.4, 153.7, 164.7. M^+ 255, C, H, and N analyses: C 61.12 (61.17), H 5.15 (5.13), N 27.42 (27.43).

2.5.2. 2-Amino-6-hydroxy-4-(3-nitro-phenyl)-pyrimidine-5-carbonitrile (entry b). M.p.: 176 °C. IR (KBr): 3400, 2924, 2854, 2223, 1632, 1611, 1529, 1351, 1101, 1171, 809, 740 cm^{-1}. PMR (DMSO-d_6) δ 3.6 (s, 2H, NH_2), 7.0 (s, 1H, OH), 7.37–7.39 (dd, 1H, Ar-H, $J = 8.0$ Hz), 8.11–8.13 (dd, 1H, Ar-H, $J = 8.0$ Hz), 8.52 (m, 1H, Ar-H), 8.62 (s, 1H, Ar-H). ^{13}C NMR (DMSO-d_6) δ 121.4, 122.8, 123.3, 124.6, 126.7, 127.9, 130.8, 133.0, 134.4, 135.2, 136.5, 140.7, 147.6, 148.3, 152.0. M^+ 257, C, H, and N analyses: C 51.32 (51.37), H 2.15 (2.74), N 27.19 (27.23).

2.5.3. 2-Amino-6-hydroxy-4-(3,4-dimethoxyphenyl)-pyrimidine-5-carbonitrile (entry c). M.p.: 240 °C. IR (KBr): 3473, 3233, 2924, 2222, 1717, 1677, 1592, 1510, 1428, 1260, 1167, 1008, 811, 778 cm^{-1}. PMR (DMSO-d_6) δ 3.4 (br. s, 2H, NH_2), 3.79 (s, 3H, OCH_3), 3.85 (s, 3H, OCH_3), 7.15–7.17 (dd, 1H, Ar-H, $J = 8.0$ Hz), 7.67–7.69 (dd, 1H, Ar-H, $J = 8.0$ Hz), 7.74 (s, 1H, Ar-H), 8.23 (s, 1H, OH). ^{13}C NMR (DMSO-d_6) δ 55.48, 55.83, 99.7, 111.8, 112.7, 116.7, 124.1, 126.4, 148.7, 153.2, 154.0, 163.6. M^+ 272, C, H, and N analyses: C 57.32 (57.35), H 4.45 (4.44), N 20.56 (20.58).

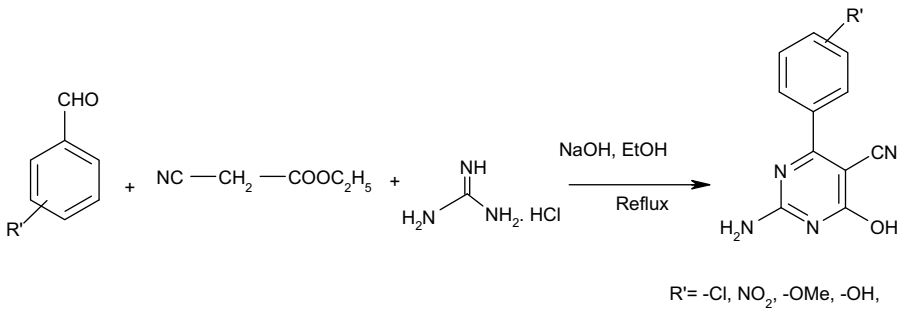
2.5.4. 2-Amino-6-hydroxy-4-(phenyl)-pyrimidine-5-carbonitrile (entry d). M.p.: (175 °C). IR (KBr): 3473, 3233, 2850, 2221, 1693, 1605, 1577, 1427, 1286, 1170, 1081, 753, 690 cm^{-1}. PMR (DMSO-d_6) δ 2.9 (s, 1H, OH), 3.5 (br. s, 2H, NH_2), 7.18 (m, 5H, Ar-H). ^{13}C NMR (DMSO-d_6) δ 126.2, 126.6, 128.1, 128.8, 129.1, 130.3, 135.6, 143.2. M^+ 212, C, H, and N analyses: C 62.20 (62.26), H 3.75 (3.80), N 26.39 (26.40).

2.5.5. 2-Amino-6-hydroxy-4-(cinnamyl)-pyrimidine-5-carbonitrile (entry e). M.p.: 196 °C. IR (KBr): 3324, 2934, 2823, 2225, 1690, 1650, 1560, 1284, 1085, 690 cm^{-1}. PMR (DMSO-d_6) δ 7.25 (d, 1H, Ar–CH=C**H**), 7.30 (d, 2H, Ar-H), 7.48 (br. s, 3H, Ar-H), 7.59 (s, 2H, NH_2), 7.63 (s, 1H, –OH), 8.0 (d, 1H, Ar–C**H**=CH–). ^{13}C NMR (DMSO-d_6) δ 103.4, 113.9, 123.0, 127.1, 128.2, 128.8, 129.2, 131.6, 134.5, 150.4, 157.2, 166.8. M^+ 238.

2.5.6. 2-Amino-6-hydroxy-4-(3-chlorophenyl)-pyrimidine-5-carbonitrile (entry f). M.p.: 170 °C. IR (KBr): 3334, 3231, 2958, 2513, 2229, 1694, 1562, 1427, 1294, 1090, 786, 687 cm^{-1}. PMR (DMSO-d_6) δ 3.3 (br. s, 2H, NH_2), 7.60 (m, 1H, Ar-H), 7.69–7.70 (dd, 1H, Ar-H $J = 4.0$ Hz), 8.00–8.01 (dd, 1H, Ar-H $J = 4.0$ Hz), 8.10 (s, 1H, OH), 8.35 (s, 1H, Ar-H). ^{13}C NMR (DMSO-d_6) δ 105.8, 115.6, 128.8, 129.9, 131.0, 132.4, 133.6, 133.8, 152.6, 162.8. M^+ 246, C, H, and N analyses: C 53.52 (53.57), H 2.84 (2.86), N 22.69 (22.71).

2.5.7. 4-(4-Methoxy)-phenyl-6-oxo hexahydro-2-iminopyrimidine-5-carbonitrile (entry g). M.p.: 224 °C. IR (KBr): 3337, 2937, 2844, 2224, 1694, 1590, 1590, 1429, 1263, 1177, 1071, 837, 686 cm^{-1}. PMR (DMSO-d_6) δ 2.5 (s, 1H, NH), 3.8 (s, 3H, OCH_3), 3.9 (s, 1, NH), 7.05 (dd, 1H, Benzylic H), 7.15 (dd, 1H, CN–H), 7.8 (dd, 2H, Ar-H), 8.15 (dd, 2H, Ar-H), 8.25 (br. s, 1H, C=NH). ^{13}C NMR (DMSO-d_6) δ 55.4, 55.7, 84.1, 99.8, 113.6, 114.8, 116.6, 117.3, 124.1, 127.8, 130.2, 133.2, 153.8, 155.9, 161.3, 161.6, 163.2, 163.7, 169.3. M^+ 244.

2.5.8. 2-Amino-6-hydroxy-4-(2-nitrophenyl)-pyrimidine-5-carbonitrile (entry h). M.p.: 214 °C. IR (KBr): 3415, 3010, 2223, 1601, 1556, 1428, 1091, 835, 757, cm^{-1}. PMR (DMSO-d_6) δ 7.80 (m, 1H, Ar-H), 7.9–8.0 (m, 2H, Ar-H), 8.3 (dd, 1H, Ar-H), 8.75 (br. s, 1H, OH), 14.4 (br. s, 2H, NH_2). ^{13}C NMR (DMSO-d_6) δ 108.7, 114.6, 125.1, 128.3, 130.5, 132.2, 134.6, 147.2, 153.9, 162.3. M^+ 257, C, H, and N analyses: C 51.30 (51.37), H 2.50 (2.74), N 27.22 (27.23).



Scheme 1.

2.5.9. 2-Amino-6-hydroxy-4-(3,4,5-trimethoxy)-phenyl-pyrimidine-5-carbonitrile (entry i). M.p.: 170 °C. IR (KBr): 3429, 2939, 2838, 1666, 1591, 1507, 1462, 1240, 1126, 1004, 836 cm^{-1}. PMR (DMSO-d_6) δ 3.8 (br. s, 9H, $-OCH_3$), 6.0–6.6 (m, 2H, two Ar-H) 6.7 (s, 1H, OH), 7.3 (br. s, 2H, NH_2). ^{13}C NMR (DMSO-d_6) δ 56.2, 60.8, 105.5, 109.0, 132.4, 138.0, 153.1. M^+ 302, C, H, and N analyses: C 55.62 (55.63), H 4.84 (4.67), N 18.51 (18.53).

2.5.10. 2-Amino-6-hydroxy-4-(4-hydroxyphenyl)-pyrimidine-5-carbonitrile (entry j). M.p.: 240 °C. IR (KBr): 3307, 3233, 2924, 2231, 1672, 1562, 1510, 1435, 1288, 1175, 842, 736 cm^{-1}. PMR (DMSO-d_6) δ 6.92–6.94 (dd, 2H, Ar-H, J 8.0 Hz), 7.94–7.96 (dd, 2H, Ar-H, $J = 8.0$ Hz), 8.09 (s, 1H, OH), 10.58 (s, 1H, Ar-OH), 13.7 (br. s, 2H, NH_2). ^{13}C NMR (DMSO-d_6) δ 98.4, 115.8, 116.3, 116.8, 122.6, 132.0, 133.6, 154.0, 162.5, 163.9, 190.8. M^+ 226, C, H, and N analyses: C 57.73 (57.89), H 3.15 (3.53), N 24.52 (24.55).

2.5.11. 2-Amino-6-hydroxy-4-(thiophenyl)-pyrimidine-5-carbonitrile (entry k). M.p.: 240 °C. IR (KBr): 3420, 3177, 2924, 2214, 1647, 1530, 1494, 1422 cm^{-1}. PMR (DMSO-d_6) δ, 6.96 (br. s, 1H, –OH), 7.25–7.26 (t, 1H, Ar-H, $J = 4.0$ Hz), 7.27 (d, 1H, Ar-H), 8.16–8.17 (d, 1H, Ar-H, $J = 4.0$ Hz), 11.60 (br. s, 2H, NH2). M^+ 218.

2.5.12. 2-Amino-6-hydroxy-4-(2-chlorophenyl)-pyrimidine-5-carbonitrile (entry I). M.p.: 198–199 °C. IR (KBr): 3421, 3177, 2221, 1596, 1494, 1485, 1418, 1260 cm^{-1}. PMR (DMSO-d_6) 2.49 (br. s, 2H, –NH2), 7.55–7.69 (m, 3H, Ar-H), 8.08–8.11 (d, 1H, Ar-H), 8.48 (s, 1H, –OH). ^{13}C NMR (DMSO-d_6) 90.07, 108.09, 115.8, 120.02, 127.88, 129.81, 134.51, 145.79, 149.99, 156.38, 162.49 and 176.00. M^+ 246, C, H, and N analyses: C 53.50 (53.57), H 2.81 (2.86), N 22.68 (22.71).

3. Conclusion

The straightforward approach, simplicity and first one-step method make it an interesting approach for the synthesis of said compounds. All the synthesized compounds are new one as per our knowledge. The anti-bacterial study of the synthesized compounds shows good to excellent activity against tested Gram-positive and Gram-negative bacteria. Among these, interestingly, the 2-amino-5-cyano-6-hydroxy-4-phenyl pyrimidine found to be selectively active against Gram-positive bacteria is the main findings of this article.

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