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Note

A novel and environmental friendly, one-step synthesis of 2,6-Diamino-4-phenyl pyrimidine-5-carbonitrile using potassium carbonate in water

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A green, simple and environmentally friendly approach has been carried out towards one-step synthesis of 2,6-diamino-4-phenyl pyrimidine-5-carbonitrile by three-component condensation of aromatic aldehydes, malononitrile and guanidine hydrochloride in aqueous medium using potassium carbonate and in the presence of tetrabutyl ammonium bromide.

Keywords: Green synthesis, pyrimidine, phase transfer catalyst, Potassium carbonate.

Currently, Chemist have used to carry out green synthesis by using solvents and catalysts, which are not harmful to the environment. Recently, organic reactions in water have attracted much attention, because of its usefulness as a cheap, safe and environment friendly solvent[1].

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[2-4]. They possess antibacterial, antiviral, antitumor[5], antihypertensive[6] and anti-inflammatory[7] activities.

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[8-10].

Now a days, the development of one-step methods involving three-component condensation is popular in synthetic organic chemistry which require shorter reaction time, and gives better yield with easy work up. A one-step method generally involves three-component condensation to yield the target molecule.

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[11]. But due to the drawback of Biginelli reaction, several new methodologies [12-15], use of micro wave irradiation[16] and some involved in the use of ionic liquids[17] 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[18-19].

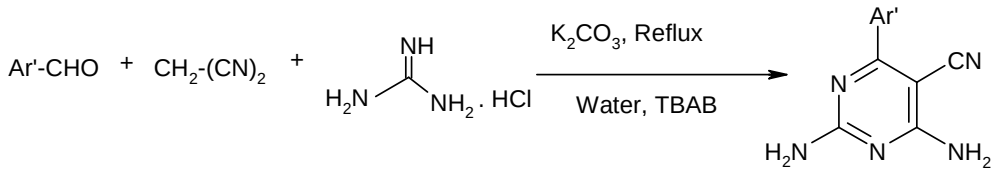
Recently, Knowevengel condensation has been reported in water using aromatic aldehydes and malononitrile[20] while Tong-Shou Jin and his co-workers reported the synthesis of dihydropyrano[2,3-*c*] pyrazoles in aqueous media[21].

The reports on above two reactions in water and the success in the Biginelli reaction by using phosphorus pentoxide[22] inspired to synthesize of 2,6-diamino-4-phenyl pyrimidine-5-carbonitrile by three-component condensation of aromatic aldehydes, malononitrile and guanidine hydrochloride using water as a green solvent using potassium carbonate and tetra butyl ammonium bromide as a phase transfer catalyst (**Scheme I**)

Results and Discussion

In this methodology, the uses of hazardous organic solvents have been avoided during the synthesis. This method is quite satisfactory with respect to yield and the reaction time. The water is a universally accepted green solvent and is easily available. Therefore, the reactions carried out in water are more beneficial as compared to conventional methods which involve the use of dangerous, flammable, carcinogenic solvents like alcohol, carbon tetrachloride, chloroform, benzene, DMF, diethyl ether etc.

As a trial case *p*-hydroxy benzaldehyde 1.22 g, malononitrile 0.660 g and potassium carbonate1.0 g were mixed thoroughly in a 250 mL round bottomed flask in 30 mL distilled water. The resulting reaction-mixture was then stirred at least for 10 min. Then, the guanidine hydrochloride (1.425g) and a pinch of TBAB were added to the same reaction-mixture and



Scheme I

Table I − The synthesis of 2,6-diamino-4-phenly-5-carbonitrile by using potassium carbonate*

Entry	Aryl-CHO	Time (hr)	Yield (%)
a	4-OH-C_6H_4	3.0	70
b	3,4-$(OCH_3)_2$-C_6H_3	3.5	64
c	3-Cl-C_6H_4	3.0	75
d	C_6H_5-	4.0	63
e	C_6H_4-CH=CH-	3.5	65
f	*N*, *N*- $(CH_3)_2$-C_6H_4	3.0	68
g	4-OCH_3-C_6H_4	3.5	63
h	2-OH-C_6H_4	4.0	64

*Reaction condition: Reflux

Table II − Effect of amount of potassium carbonate on the yield of 2,6-diamino-4-phenyl pyrimidine-5-carbonitrile*

Pot. Carbonate (mg)	400	600	800	1000
Yield (%)	40-45	50-55	55-62	63-75

*Reaction condition: Reflux in water

same reaction-mixture refluxed until the completion of the reaction (monitored by TLC). The resulting reaction-mixture filtered and the filtrate was acidified with 1:1 HCl to get a desired product. The same reaction was then carried out by using different aromatic aldehydes gave the product in good yields. The results are summarised in **Table I**

In presence of potassium carbonate the reaction was carried out smoothly. First the malononitrile reacts with aldehydes to give aryl methylene malononitrile, which subsequently reacts with guanidine to gives the corresponding polyfunctional pyrimidine. The tetrabutyl ammonium bromide helps for the uniform dispersion of organic compounds in water.

The following sequence of reaction explains the formation of the desired products (**Scheme II**).

The same reaction was also extended for the aliphatic aldehydes like crotonaldehyde but was not successful.

To find out the optimum quantity of potassium carbonate, the same reaction was studied by varying the quantity of pot. carbonate. The results are summarized in **Table II**

Experimental Section

The melting points are found to be uncorrected**.** All the above products were characterized by ^{1}H NMR, IR and ^{13}C. The ^{1}H NMR spectra were recorded by using $CDCl_3$ solvent on a Brucker 300 MHz spectrometer with tetra methyl silane as an internal standard. TLC using silica gel 60-F 254 plates monitored the reaction.

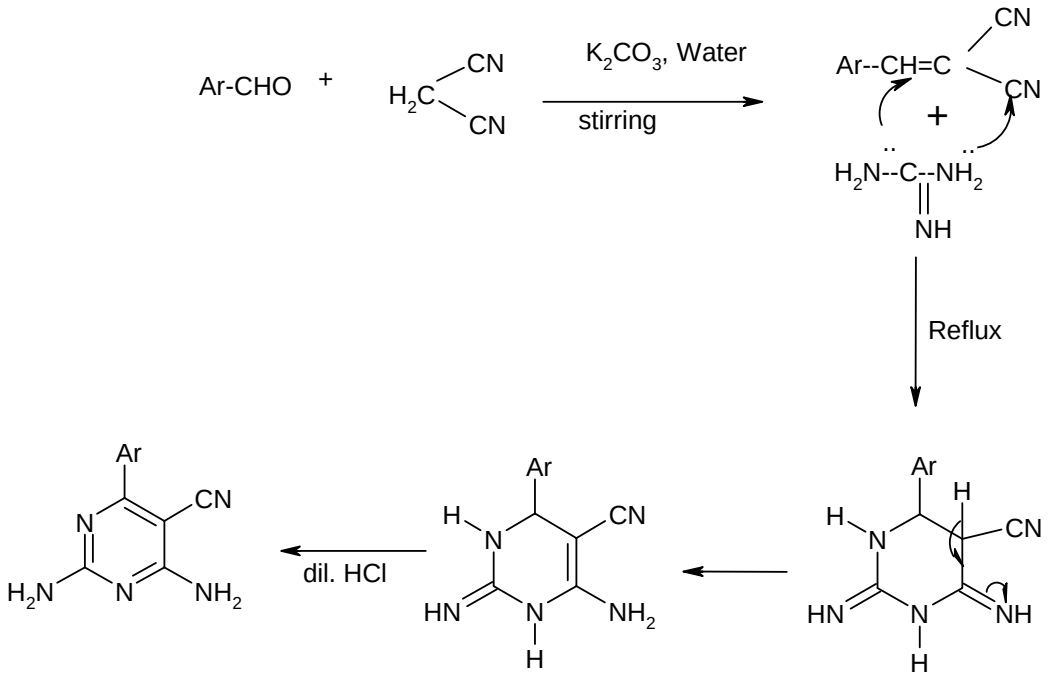
General procedure

The mixture of *p*-hydroxy benzaldehyde (1.22 g), (0.660 g) malononitrile and potassium carbonate 1.0 g in 30 mL distilled water were stirred at least for 10 min, then guanidine hydrochloride (1.425 g) and a pinch of TBAB were added to the above reaction-mixture and reaction mixture refluxed still completion of reaction. The reaction was monitored by TLC. After the completion of reaction, the reaction mixture was filtered and the filtrate was collected in ice-cold water (50 mL) and neutralized by 1:1 HCl to get desired product. The separated solid was filtered, washed with pet. ether and the resulting solids were purified by column chromatography.

The procedure described here provides a green approach for the synthesis of 2,6-diamino-4-phenyl pyrimidine-5-carbonitrile using water as solvent. The one step method, use of universal solvent and easy separation of pure product, in comparison with the two-step strategies and conventional methods, are the unique features of this method.

2,6-Diamino-4-(4-hydroxy)-phenyl pyrimidine-5-carbonitrile (entry a): m.p. 260ºC (d); IR (KBr): 3308, 3210, 2219, 1644, 1588, 1290, 835, 771 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 2.49 (s, 2H, NH_2), 3.62 (br. S, 1H, OH), 6.95-6.98 (dd, 2H, Ar-H), 7.86-7.89 (dd, 2H, Ar-H), 8.28(s, 2H, NH_2); ^{13}C NMR ($CDCl_3$): δ 114.1, 116.6, 122.8, 130.1, 133.8, 157.8, 158.9, 160.5, 163.9

2,6-Diamino-4-(3,4-dimethoxy)-phenyl pyrimidine-5-carbonitrile(entry b): m.p. 205ºC; IR (KBr): 3332, 3310, 2926, 2213, 1650, 1595, 1267, 1141, 806,



Scheme II

764 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ, 2.2 (br. s, 2H, NH_2), 3.8 (s, 3H, OCH_3), 3.9 (s, 3H, OCH_3) 6.75-7.00(dd, 2H, Ar-H), 7.43-7.49 (m, 1H, Ar-H), 9.9 (s, 2H, NH_2); ^{13}C NMR ($CDCl_3$): δ 19.3, 25.4, 56.01, 67.00, 109.3, 110.5, 121.3, 126.9, 35.0, 144.8, 149.2, 154.6, 170.6

2,6-Diamino-4-(3-chloro)-phenyl pyrimidine-5-carbonitrile(entry c): m.p. 222ºC; IR (KBr): 3330, 3240, 3025, 2194, 1651, 1465, 1267, 876, 756 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 2.87 (br. s, 2H, NH_2), 6.9-7.7 (m, 4H, Ar-H), 11.8-12.0 (br.s, 2H, NH_2) ; ^{13}C NMR ($CDCl_3$): δ 114.0, 118.2, 126.5, 128.8, 130.3, 132.8, 136.5, 138.9, 156.4, 160.7, 167.0.

2,6-Diamino-4-phenyl pyrimidine-5-carbonitrile (entry d): m.p. 215-17ºC; IR (KBr): 3378, 3376, 3154, 2205, 1611, 1543, 1276, 777, 700 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 6.4-6.5 (br. s, 2H, NH_2), 7.2-7.4 (m, 3H, Ar-H), 7.43-7.60 (dd, 2H, Ar-H) 11.8-12.0 (br.s, 2H, NH_2) ; ^{13}C NMR ($CDCl_3$): δ 114.0, 120.4, 127.8, 128.4, 128.5, 130.3, 134.7, 139.0, 156.6, 150.7, 162.5.

2,6-Diamino-4-cinnamyl pyrimidine-5-carbonitrile (entry e): m.p. 180ºC; IR (KBr): 3378, 3376, 3154, 2205, 1611, 1543, 1276, 777, 700 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 3.49 (s, 2H, NH_2), 6.43-6.48 (d, 1H, Ph-CH=C**H**), 7.2 (s, 2H, NH_2), 7.33-7.44 (m, 3H, Ar-H), 7.54-7.57 (dd, 2H, Ar-H), 7.76-7.81 (d, 1H. Ph-C**H**=**C**H), ^{13}C NMR ($CDCl_3$): δ 97.7, 100.2, 102.6, 111.1, 118.1, 128.7, 130.7, 131.8, 134.9, 136.7, 147.0, 148.1.

2,6-Diamino-4-(4-*N*,*N*-dimethyl)-phenyl pyrimidine-5-carbonitrile(entry f): m.p. 210ºC; IR (KBr): 3300, 2924, 2215, 1688, 1612, 1173,942, 816, 709 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 3.1 (s, 6H, N- $(CH_3)_2$), 6.70-6.73 (dd, 2H, Ar-H), 7.2 (s, 2H, NH_2), 7.96-7.99 (dd, 2H, Ar-H) 8.12(s, 2H, NH_2) ; ^{13}C NMR ($CDCl_3$): δ 21.5, 110.2, 122.7, 128.6, 136.9, 144.4, 156.8, 165.0, 170.2.

2,6-Diamino-4-(4-methoxy)-phenyl pyrimidine-5-carbonitrile(entry g): m.p. 240ºC; IR (KBr): 3187, 3247, 2026, 2214, 1650, 1501, 1263, 1177, 1021, 832, 771 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 2.5 (br. s, 2H, NH_2), 3.82 (S, 3H, OCH_3), 7.0-7.2 (dd, 2H, Ar-H), 7.4-7.5 (dd, 2H, Ar-H), 11.6-12.0 (br.s, 2H, NH_2); ^{13}C NMR ($CDCl_3$): δ 56.6, 114.4, 116.2, 124.2, 126.5, 129.6, 130.4, 133.1, 156.2, 162.0.

2,6-Diamino-4-(2-hydroxy)-phenyl pyrimidine-5-carbonitrile(entry g): m.p. 172ºC; IR (KBr): 3187, 3247, 2026, 2214, 1650, 1501, 1263, 1177, 1021, 832, 771 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 3.49 (br. s, 1H, OH), 7.2 (s, 2H, NH_2), 7.46-7.51(dd, 2H, Ar-H), 7.76-7.82 (m, 2H, Ar-H), 8.96 (br.s, 2H, NH_2); ^{13}C NMR ($CDCl_3$): δ 110.2, 117.2, 120.3, 122.5, 126.2, 130.4, 135.7, 151.4, 153.6, 166.3, 183.8.

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