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Bronsted base catalysed efficient one pot three component synthesis of dihydropyrimidinone derivatives

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ABSTRACT

An efficient method for the synthesis6-amino-4-aryl-pyrimidinone-5-carbonitrile is described. This involves three-component Biginelli-type condensation of aldehyde, malononitrile, and urea in the presence of catalytic amount of t-BuOK. The reactions proceeded efficiently at 90°C in ethanol medium to afford the desired products in good yields. Products were confirmed by IR, NMR and mass spectral analysis.

Key words: Biginelli, Bronsted base, Dihydropyrimidinones, One pot synthesis

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INTRODUCTION

The utilization of multicomponent reactions(MCRs) to synthesize novel, drug-like scaffold has permeated in organic transformations from last few decades due to their molecular economy and potential of producing diversified products in single step. The Biginelli reaction is found to be one of the most recognized multicomponent reactions [1].A simple and one pot synthesis of dihydropyrimidinones were first observed by P.Biginelliinvolving three component condensation of a ketoester with an aldehyde and urea[2].Recently, the use of other active methylene compounds in addition to β-ketoester in conventional Biginelli reaction has emerged as one of the major research areas in terms of the preparation of various novel dihydropyrimidinones [3,4].

More attention has been paid toward developing highly efficient Biginelli reaction owing to the exhibition of a wide range of biological activities in dihydropyrimidinones such as antiviral, antitumor, antibacterial, and anti-inflammatory properties as well as calcium channel modulating activity [5-8]. Inspired by their pharmacological importance, several attempts have been made to develop more diverse dihydropyrimidinones using conventional acid catalyzed Bigineli-type reactions. Due to the low yields in these methods, base catalyzed reactions havegained importance because of their moderate to good yields compared to the acid catalyzed reaction[9].

Bronsted base catalyzed Biginelli type reactions were reported [10], where they utilized t-BuOK as a catalyst for the synthesis of Biginelli type condensation of aldehyde, 2-phenylacetophenone, and urea/thioureato form 4,5,6-triaryl-3,4-dihydropyrimidin-2(1H)-ones in moderate to good yields. This prompted us to develop Bronsted base catalyzed Biginelli type condensation of aldehyde, malononitrile and urea.

On reviewing the literatures, we found that, there are reports on Biginelli type condensation between an aldehyde, malononitrile and urea using P_2O_5 and microwave irradiation methods [11, 12]. But in both the cases, it ended up with 2-hydroxy-4-aryl pyrimidine derivatives. In our present work, Bronsted base catalyst is used for the same reaction which resulted in dihydropyrimidinones as a predominant product.

EXPERIMENTAL SECTION

Chemicals were procured from different distributors like Spectro Chem, Sigma Aldrich etc. and were used as such without any purification. Progress of the reaction was monitored using thin layer chromatographic technique(TLC) using precoated aluminum sheets alichrosep silica gel-60/UV_{254} with I_2 and UV light as detecting agents. Melting point was determined using Thiele's tube in open capillary tube and was uncorrected. IR spectra were recorded on Shimadzu Infrared spectrometer-8400s using KBr as background. NMR analysiswas done with Bruker NMR-400MHz using TMS as an internal standard. Mass spectral analysis was done by Agilent 6520 ESIQTOF MS spectral analyzer.

Selection of catalyst and optimization of reaction conditions

Selection of catalyst and reaction condition optimization was done with malononitrile(1mmol), p-chlorobenzaldehyde(1mmol) and urea(1.5mmol) with ethanol(3mL) under reflux condition. Various bases and their effects on the conversion are tabulated (**Table 1** entry 1-4).

Table 1: Optimization of Reaction Conditions Using different bases

Entry	Catalyst	Time	yield (%)
1.	MeONa (10mol%)	5 h	52
2.	NaOH (10mol%)	6 h	65
3.	KOH (10mol%)	6 h	62
4.	t-BuOK (10mol%)	3 h	89

As shown in the **Table 1**, attempt to select the suitable base catalyst from four different bases like MeONa, NaOH, KOH and t-BuOK was done at reflux condition. Results are tabulated in the **Table 1**, where it is clear that the t-BuOK is better catalyst being showed highest conversion in shortest time.

So, further optimization of reaction conditions were done with t-BuOK. Optimization of catalyst loading was done by varying the catalyst concentration 5-30mol%. Results of which were tabulated in the **Table 2**. As shown in the table, there was no formation of product without the catalyst. Reactions were carried out with lowest concentration of 10mol% and highest concentration of 30mol% t-BuOK. Best conversion was observed with 20 mol% of catalyst and there was no significant effect with further increase in the catalyst loading. The decreased yield and prolonged reaction time was observed in the catalyst loading less than 20mol%.

Table 2: Optimization of Reaction Conditions with varied catalyst loading

Entry	t-BuOK loading	Time	yield (%)
1.	0	12 h	-
3.	10 mol%	6 h	62
4.	20 mol%	3 h	89
5.	30 mol%	3h	83

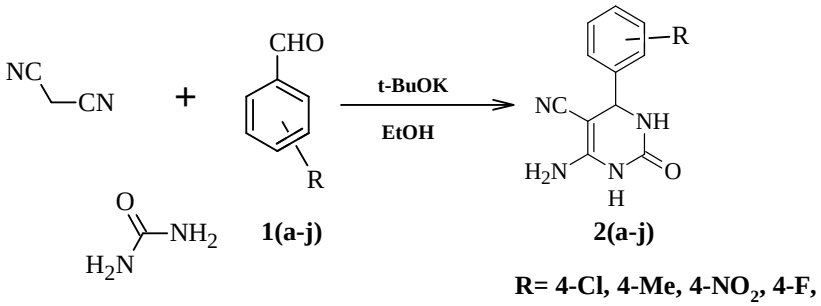
Next step in the optimization of reaction condition was to select suitable solvent. Both polar and non-polar solvents were tested for the better conversion. Polar protic solvents like EtOH, MeOH and aprotic solvent like DMF were used. THF and toluene were used as nonpolar solvents. Effect of solvents on the conversion is tabulated in **Table 3**. As shown in the table, polar solvents observed to be more useful than the nonpolar solvents. EtOHfound to be a better solvent for the reaction. But, no significant improvement in the yield was observed by extending the reaction time and varying the temperature.

Table 3: Optimization of Reaction Conditions with different solvents

Entry	Solvent	yield (%)
1.	EtOH	91
2.	MeOH	82
3.	DMF	76
4.	Toluene	49
5.	THF	52

Thus, by considering overall effect of catalyst loading, solvent, temperature and reaction time, further reactions were carried out with 20 mol% of t-BuOK catalyst at 90°C using ethanol as a solvent for 3h.

General procedure for the synthesis of Dihydropyrimidinones:
To a Mixture of malononitrile(1mmol) and aldehyde(1mmol) in Ethanol(3 mL), 20 mol% of potassium tertiary butoxide (0.2mmol) was added. The reaction mixture was stirred vigorously at room temperature for 5min. Urea (2mmol)was then added to the mixture and refluxed at 90°C.After completion of the reaction (confirmed by TLC), reaction mixture was cooled down to room temperature. Solid thus formed was filtered, then washed with 40% EtOH and dried under vacuum. Product was recrystallized from ethanol and water mixture in 10: 1 ratio respectively.



Scheme-1: Synthesis of target compounds 2(a-j).

6-amino-4-phenyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carbonitrile(2a):Yield: 90%; m.p. 210°C; IR(KBr, cm^{-1}): 1546 (C=C), 1681 (C=O), 2190 (CN), 3325 and 3398 (N-H);^{1}H-NMR(400MHz-DMSO-d_6-ppm): 5.033(s 1H C-H), 6.20(s 2H NH_2) 7.24-7-48(m 4H Ar), 9.76(s 1H N-H) and 10.05(s 1H N-H);^{13}C-NMR(100MHz-DMSO-d_6-ppm):49.8, 79.9,116.3, 128.7, 128.9, 134.5, 137.3, 159.7, 164.1;Anal. calcd. for $C_{11}H_{10}N_4O$: C, 61.67; H, 4.71; N, 26.15; O, 7.47 %; Found: C, 61.62; H, 4.68; N, 26.16; O, 7.48 %; MS(m/z): 214.08.

6-amino-4-(4-Chlorophenyl)-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carbonitrile(2b):Yield: 91 %; m. p. 213°C; IR (KBr, cm^{-1}): 1549(C=C str.), 1681 (C=O str.), 2220 (CN str.), 3327and 3402 (N-H str.);^{1}H-NMR(400MHz-DMSO-d_6-ppm): 5.033(s 1H C-H), 6.20(s 2H NH_2) 7.24-7-48(m 4H Ar), 9.76(s 1H N-H) and 10.05(s 1H N-H);^{13}C-NMR(100MHz-DMSO-d_6-ppm): 50.7, 79.7,115.9, 128.9, 130.1, 133.9, 138.1, 160.1, 166.2;Anal. calcd. for $C_{11}H_9N_4OCl$: C, 53.13; H, 3.65; N, 22.53; O, 6.47 %; Found: C, 53.12; H, 3.61; N, 22.58; O, 6.48 %;MS (m/z): 248.04.

6-amino-4-(4-methoxyphenyl)-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carbonitrile(2c):Yield: 86 %; m. p. 203°C; IR (KBr, cm^{-1}): 1539 (C=C str.), 1685 (C=O), 2198 (CN), 3319 and 3401 (N-H);^{1}H-NMR(400MHz-DMSO-d_6-ppm):3.72(s 3H OCH_3), 5.06(s 1H C-H), 6.18(s 2H NH_2) 7.19-7-46(m 4H Ar), 9.80(s 1H N-H) and 10.10(s 1H N-H);^{13}C-NMR(100MHz-DMSO-d_6-ppm):51.3, 60.7, 76.8,116.5, 129.1, 129.7, 134.2, 136.9, 160.7, 167.1;Anal. calcd. For $C_{11}H_{12}N_4O_2$: C, 59.01; H, 4.95; N, 22.94; O, 13.10 %; Found: C, 59.04; H, 4.91; N, 22.98; O, 13.08 %; MS (m/z): 244.09.

6-amino-4-(4-methylphenyl)-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carbonitrile(2d):Yield: 88 %; m. p. 187°C; IR (KBr, cm^{-1}): 1546 (C=C), 1681 (C=O), 2190 (CN), 3325 and 3398 (N-H);^{1}H-NMR(400MHz-DMSO-d_6-ppm) 2.12(s 3H CH_3), 5.033(s 1H C-H), 6.20(s 2H NH_2) 7.24-7-48(m 4H Ar), 9.76(s 1H N-H) and 10.05(s 1H N-H);^{13}C-NMR(100MHz-DMSO-d_6-ppm) 22.5, 49.8, 79.9,116.3, 128.7, 128.9, 134.5, 137.3, 159.7, 164.1;Anal. calcd. for $C_{11}H_{10}N_4O$: C, 63.15; H, 5.30; N, 24.55; O, 7.01 %; Found: C, 63.13; H, 5.34; N, 24.55; O, 6.98 %;MS (m/z): 214.08.

6-amino-4-(4-fluorophenyl)-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carbonitrile(2e):Yield: 83 %; m. p. 193°C; IR (KBr, cm^{-1}): 1546 (C=C), 1681 (C=O), 2190 (CN), 3325 and 3398 (N-H);^{1}H-NMR(400MHz-DMSO-d_6-ppm): 5.033(s 1H C-H), 6.20(s 2H NH_2) 7.24-7-48(m 4H Ar), 9.76(s 1H N-H) and 10.05(s 1H N-H);^{13}C-NMR(100MHz-DMSO-d_6-ppm): 49.8, 79.9,116.3, 128.7, 128.9, 134.5, 137.3, 159.7, 164.1;Anal. calcd. for $C_{11}H_9N_4OF$: C, 56.89; H, 3.91; N, 24.13; O, 6.89 %; Found: C, 56.85; H, 3.89; N, 24.12; O, 6.87 %; MS (m/z): 232.07.

6-amino-4-(4-nitrophenyl)-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carbonitrile(2f):Yield: 79 %; m. p. 201˚C; IR (KBr, cm^{-1}): 1546 (C=C), 1681 (C=O), 2190 (CN), 3325 and 3398 (N-H);^{1}H-NMR(400MHz-DMSO-d_6-ppm): 5.033(s 1H C-H), 6.20(s 2H NH_2) 7.24-7-48(m 4H Ar), 9.76(s 1H N-H) and 10.05(s 1H N-H);^{13}C-NMR(100MHz-DMSO-d_6-ppm): 49.8, 79.9,116.3, 128.7, 128.9, 134.5, 137.3, 159.7, 164.1; anal. calcd. for $C_{11}H_{10}N_4O$: C, 50.97; H, 3.50; N, 27.02; O, 18.52 %; Found: C, 50.93; H, 3.49; N, 27.04; O, 18.53 %; MS (m/z): 259.06.

6-amino-4-(2,4-dichlorophenyl)-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carbonitrile(2g):Yield: 89 %; m. p. 219˚C; IR (KBr, cm^{-1}): 1554 (C=C), 1678 (C=O), 2196 (CN), 3328 and 3401 (N-H);^{1}H-NMR(400MHz-DMSO-d6-ppm): 5.07(s 1H C-H), 6.29(s 2H NH_2) 7.30-7-49(m 4H Ar), 9.87(s 1H N-H) and 10.11(s 1H N-H);^{13}C-NMR(100MHz-DMSO-d6-ppm): 49.6, 80.4,116.7, 128.9, 130.4, 134.9, 138.7, 160.7, 166.1;Anal. calcd. for $C_{11}H_{10}N_4O$: C, 46.67; H, 2.85; N, 19.79; O, 5.65 %; Found: C, 46.69; H, 2.83; N, 19.80; O, 5.64 %; MS (m/z): 282.00.

6-amino-2-oxo-4-(4-hydroxy)-1,2,3,4-tetrahydropyrimidine-5-carbonitrile(2h):Yield: 84 %; m. p. 210 ˚C; IR (KBr, cm^{-1}): 1549 (C=C), 1686 (C=O), 2197 (-CN), 3318 and 3393 (N-H stretching), 3422 (OH);^{1}H-NMR(400MHz-DMSO-d_6-ppm): 5.12(s 1H C-H), 6.23(s 2H NH_2) 7.19-7-42(m 4H Ar), 9.81(s 1H N-H) and 10.03(s 1H N-H);^{13}C-NMR(100MHz-DMSO-d_6-ppm) 50.3, 80.7,116.6, 128.9, 129.5, 135.3, 138.1, 160.3, 165.3;Anal. calcd. for $C_{11}H_{10}N_4O$: C, 57.39; H, 4.38; N, 24.34; O, 13.90 %; Found: C, 57.40; H, 4.38; N, 24.32; O, 13.91 %; MS (m/z): 230.08.

6-amino-2-oxo-4-(3-hydroxy-4-methoxyphenyl)-1,2,3,4-tetrahydropyrimidine-5-carbonitrile(2i):Yield: 87 %; m. p. 210 ˚C; IR (KBr, cm^{-1}): 1547 (C=C), 1681 (C=O), 2190 (CN), 3325 and 3398 (N-H), 3422 (O-H);^{1}H-NMR(400MHz-DMSO-d6-ppm): 4.01(s 3H OCH_3), 5.033(s 1H C-H), 6.20(s 2H NH_2), 7.24-7-48(m 4H Ar), 9.76(s 1H N-H) and 10.05(s 1H N-H);^{13}C-NMR(100MHz-DMSO-d_6-ppm) 49.8, 59.8, 79.9,116.3, 128.7, 128.9, 134.5, 137.3, 159.7, 164.1;Anal. calcd. for $C_{11}H_{10}N_4O$: C, 55.38; H, 4.65; N, 21.53; O, 18.44 %; Found: C, 55.39; H, 4.62; N, 21.55; O, 18.44 %; MS (m/z): 260.09.

6-amino-4-(2,4-dimethoxy-phenyl)-2-oxo-1,2,3, 4-tetrahydropyrimidine-5-carbonitrile(2j):Yield: 88 %; m. p. 210 ˚C; IR (KBr, cm^{-1}): 1546 (C=C), 1681 (C=O), 2190 (CN), 3325 and 3398 (N-H); ^{1}H-NMR(400MHz-DMSO-d6-ppm): 3.68 (s 6H OCH_3) 5.033(s 1H C-H), 6.20(s 2H NH_2) 7.24-7-48(m 4H Ar), 9.76(s 1H N-H) and 10.05(s 1H N-H);^{13}C-NMR(100MHz-DMSO-d_6-ppm): 49.8, 61.7, 79.9,116.3, 128.7, 128.9, 134.5, 137.3, 159.7, 164.1;Anal. calcd. for $C_{11}H_{10}N_4O$: C, 56.93; H, 5.14; N, 20.43; O, 17.50 %; Found: C, 56.93; H, 5.14; N, 20.43; O, 17.50 %; MS (m/z): 274.10.

RESULTS AND DISCUSSION

In the present study, initially the selection of the catalyst and optimization of reaction conditions were done. One-pot three-component condensation of 4-chlorobenzaldehyde, malononitrile and urea in ethanol at 90˚C for 3 h was used as a model reaction for catalyst selection and reaction condition optimization.

The best catalyst was selected from four different base catalysts MeONa, NaOH, KOH and t-BuOK. Among them, t-BuOK observed to be an efficient catalyst for the synthesis of pyrimidinone derivative being showed better conversion in less time compared to other catalysts.t-BuOKwas further used as a catalyst for reaction condition optimization. In optimizing the reaction conditions for t-BuOK catalysed reaction, concentration of catalyst and solvents were varied. Thus by considering all the observations, it was found that 20mol% of the catalyst, ethanol as the solvent and 90 ˚C werethe optimal condition for the efficient synthesis of 6-amino-4-aryl-pyrimidine-5-carbonitrile.

All the molecules showed characteristic peaks for their corresponding structures as listed above. In the IR spectrum of compound **2a**there was a peak at 1681 cm^{-1} for carbonyl group and 2190 cm^{-1} for nitrile group. There was characteristic peak 3258 cm^{-1} and 3398 cm^{-1} for N-H of primary and secondary amine respectively. Further confirmation of the structures was done by using both ^{1}H and ^{13}C NMR characterization. In ^{1}H NMR, peak at 5.03 ppm was observed corresponds to asymmetric C-H proton which is characteristic to dihydropyrimidine ring. Also there were peaks at 6.20 ppm, 9.76 ppm and 10.05 ppm for primary and secondary amines respectively, which confirmed the formation of cyclized product. Even in ^{13}C-NMRcharacteristicsignal for carbonyl and asymmetric carbon were observed at 164.1 and 49.8 ppm respectively.

The mechanism of base catalysed conventional Biginelli reactions were reported[13].They observed that there will be formation of a hemiaminal intermediate to form Biginelli product. But in the presence of malononitrile as an active methylene component, of aryledenemalononitrile will be formed as an intermediate **1**(Figure 1)[14,15].Since, aldehyde and malononitrile in ethanol were added first and stirred with the catalyst at room temperature there was a formation of adduct. Then urea was added and refluxed. On adding urea, an arylidenemalononitrile undergo nucleophilic substitution of urea and cyclizes to form pyrimidinonering**4**.

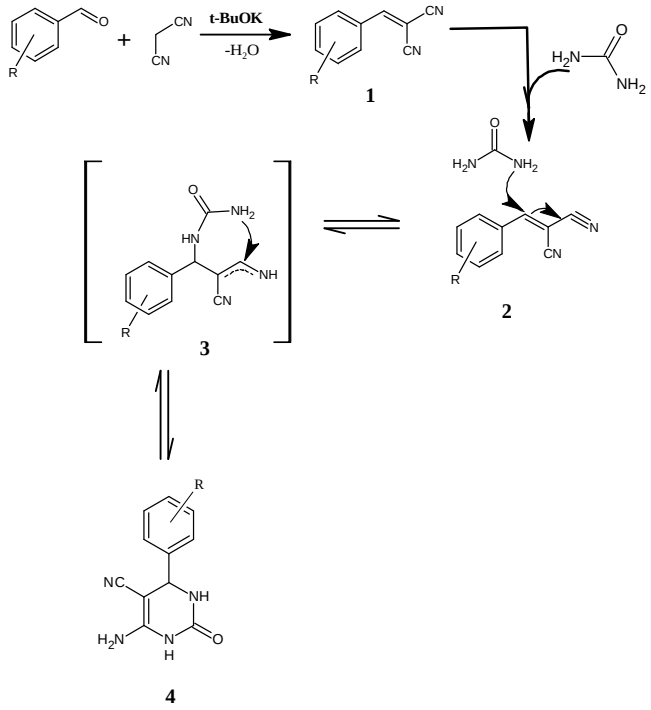


Figure 1: Proposed mechanism for the formation of dihypyrimidinone

CONCLUSION

In conclusion, we have described a Bronsted base mediated one-pot procedure for the preparation of wide variety of 6-amino-4-aryl-pyrimidinone-5-carbonitrile via a three-component condensation of aldehyde, malononitrile, and urea. Mechanism of the reaction found to involve formation of arylidenemalononitrile as an intermediate, which further undergo nucleophilic substitution of urea to form titled compound. The method is simple, convenient, efficient, and expected to be useful synthetic protocol for the synthesis of wide range of novel drug-like dihydropyrimidinones.

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