Synthesis and Characterization of Annulated Pyrimidine Derivatives Using Dibutylamine(DBA) Catalyst InAqueous Ethanol

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Abstract:

Annulated pyrimidine derivatives were synthesized via one-pot three component condensation reactions of various aromatic aldehydes, malononitrile and barbituric acid in aqueous ethanol usingdibutylamine (DBA) as catalyst. The application of DBA in organic synthesis increasing rapidly due to its reaction simplicity, minimum reaction time, high yields of the desired products (**83–94%**) and low cost chemicals. All the synthesized pyrimidine derivatives (pyrano[2,3-*d*]pyrimidines) were characterized by IR, ^{1}H NMR, ^{13}C NMR and mass spectra.

Keywords:DBA catalyst, Annulatedpyrimidines, Barbituric acid, Spectral analysis, Aromatic aldehydes, Knoevenagel-Michael addition reaction.

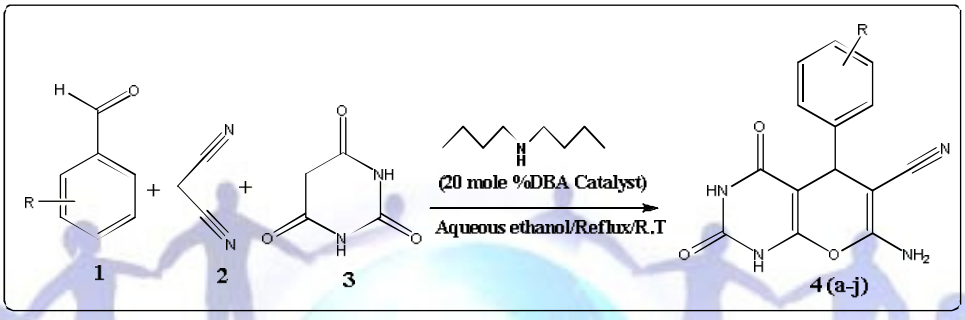
Introduction:

The study of aromatic six membered N-heterocyclic rings is always of great importance in pharmaceutical sector as it owes bio-isosteric factor which is logical for theoretical as well as practical importance. Pyrimidine rings have significant pharmacological importance as being an integral part of DNA and RNA in several biological processes [1,2]. The chemotherapeutic efficacy of annulated Pyrimidine derivatives like pyrano[2,3-*d*]pyrimidines is related to their ability to inhibit enzymes action for DNA biosynthesis, such as dihydrofolatereductase (DHFR), thymidylatesynthetase (TSase), thymidine phosphorylase (TPase) and reverse transcriptase (RTase). Pyrano[2,3-*d*] pyrimidine moieties that are annulated in to one molecule, then resultant derivative enhances its pharmaceutical activity such as, antitumor [3], antihypertensive [4], antibacterial activity [5] and antileishmanial activity [6]. Therefore, for the preparation of these complex molecules, large efforts have been made towards the synthetic manipulation of annulated pyrimidines that occupy a distinct and unique place in medicinal chemistry. Annulated pyrano[2,3-*d*]pyrimidine derivatives are unsaturated N-heterocyclic as a fusion of pyran and pyrimidine rings, consisting of one oxygen atom at 8 and two nitrogen atoms at 1 and 3 positions respectively.

Multicomponent reactions (MCRs) have gained significant interest in modern medicinal and combinatorial chemists [7,8], due to powerful bond forming efficiency, diversity-oriented synthesis (DOS), simple reaction design, atom-economy, environmental concerns, and the possibility to construct target compounds using several assorted elements in a single chemical procedure [9,10]. Pyrano[2,3-*d*]pyrimidine derivativies was reported using different catalysts such as Zn[(*L*)proline]$_2$ [11], [BMIm]BF_4[12], N-methylmorpholine [13], DAHP [14], SBA-Pr-SO_3H [15]. Et_3N was used as a catalyst for synthesis of Pyrano[2,3-*d*]pyrimidine

derivatives under microwave irradiation [16]. Catalyst free procedure was also examined for the preparation of Pyrano[2,3-*d*]pyrimidine derivatives [17]. In addition, ultrasonic irradiation [18] and ball-milling technique [19] were used for the synthesis of Pyrano[2,3-*d*]pyrimidine derivatives.

In continuation of the current researchfrom our laboratoryto develop an efficient multicomponent reactions (MCRs) for the preparation of pyrimidine annulated bioactive molecules [20], we report here, the dibutylamine (DBA) catalyzed efficient, simple and fast synthesis of annulated pyrimidine derivatives (Pyrano[2,3-*d*]pyrimidine) via one-pot three-component domino Knoevenagel-Michael addition reaction in aqueous media (**Scheme 1**).



Scheme 1. General synthesis of substituted pyrano[2,3-*d*]pyrimidines**4(a-j)**.

Material and methods:

All chemicals were obtained from Merck and S.D. Fine Chem. Co. and used without further purification. Melting points were determined by open capillary method and were uncorrected. IR spectra were recorded on a Perkin–Elmer 298 spectrophotometer using KBr pellet. ^{1}H and ^{13}C NMR spectra were recorded using a Bruker instrument (^{1}H at 400 MHz and ^{13}C at 100 MHz) in DMSO-d_6 solvent andtetramethylsilaneas internal standard.Chemical shifts are reported in ppm. Mass spectra were recorded on Shimadzu GC-MS-QP-2010 model using Direct Injection Probe technique. Reactions have monitored by thin layer chromatography on 0.2-mm precoated plates of silica gel G60 F254 (Merck).

2.2. General procedure for the synthesis of pyrano[2,3-d]pyrimidine derivatives **4(a-j)**: Aromatic aldehydes **1** (1m mol), malononitrile**2** (1m mol), barbituric acid **3** (1m mol) and 20 mol % dibutylamine (DBA) were taken in RB flask with 16 ml aqueous media (1 :1 ratio) and stirred for 43-129 mins at room temperature. The progress of reaction was monitored by TLC. The solid product was filtered, washed with cold water and recrystallized from ethanol to obtain pure pyrano[2,3-*d*] pyrimidine derivatives with excellent yields (**83–94%**).

2.3.1. Spectral data for synthesized pyrano[2,3-d]pyrimidine derivatives **4(a-j):** 7-Amino-5-(4-nitrophenyl)-2,4-dioxo-2,3,4,5-tetrahydro-1H-pyrano[2,3-d]pyrimidine-6-carbonitrile (**4a)**

White powder, IR (KBr, υ cm^{-1}): 3411 (NH_2), 3209, 3163 (NH), 2989 (C-H), 2206 (C ≡ N), 1732 (C=O), 1461 (C=C). ^{1}H NMR (400 MHz, DMSO-d_6): δ = 13.01 (s, 1H, NH), 8.93 (s, 1H, NH), 7.94 (d, J = 7.1 Hz, 2H, Ar-H), 7.47 (d, J = 7.1 Hz, 2H, Ar-H), 6.79 (s, 2H, NH_2), 4.96 (s, 1H, CH) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ = 176.47

(C=O), 170.60 (CNH_2), 153.93 (CONH), 151.36 (C=O), 150.32 (C-14), 147.44 (C-11), 128.99 (C-12), 123.19 (C-13), 120.41 (C≡N), 104.46 (C-5), 75.53 (C-9), 70.70 (C-10) ppm; Ms (*m/z*): 328.2 [M+H$^+$].

2.3.2. 7-Amino-5-(3-nitrophenyl)-2,4-dioxo-2,3,4,5-tetrahydro-1H-pyrano[2,3-d]pyrimidine-6-carbonitrile (**4b**)

White powder, IR (KBr υ cm^{-1}): 3314 (NH_2), 3301, 3247(NH), 2942 (C-H), 2212 (C ≡ N), 1605 (C=O), 1476 (C=C). ^{1}H NMR (400 MHz, DMSO-d_6): δ = 12.02 (s, 1H, NH), 10.21 (s, 1H, NH), 8.38 (s, 1H, Ar-H), 8.19 (d, *J* = 6.3 Hz, 2H, Ar-H), 6.82 (s, 2H, NH_2), 3.94 (s, 1H,CH) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ = 166.12 (C=O), 160.73 (CNH_2), 157.01 (CONH), 151.56 (C=O), 150.57 (C-14), 146.11 (C-11), 129.23 (C-12), 123.08 (C-13), 119.45 (C≡N), 104.42 (C-5), 79.32 (C-9), 71.10 (C-10) ppm; Ms (*m/z*): 328.2 [M+H$^+$].

2.3.3. 7-Amino-5-(2-nitrophenyl)-2,4-dioxo-2,3,4,5-tetrahydro-1H-pyrano[2,3-d]pyrimidine-6-carbonitrile (**4c**)

White Powder, IR (KBr υ cm^{-1}): 3302 (NH_2), 3331, 3142 (NH), 2938 (C-H), 2172 (C ≡ N), 1645 (C=O), 1527 (C=C). ^{1}H NMR (400 MHz, DMSO-d_6): δ = 10.12 (s, 1H, NH), 10.79 (s, 1H, NH), 7.69 – 7.63 (m, 3H, Ar-H), 6.82 (s, 2H, NH_2), 3.94 (s, 1H, CH)ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ = 179.44 (C=O), 170.14 (CNH_2), 159.59 (CONH), 156.79 (C=O), 149.87 (C-14), 134.52 (C-11), 132.12 (C-12), 130.05 (C-13), 127.31 (C≡N), 91.81 (C-5), 84.24 (C-9), 57.01 (C-10) ppm; Ms (*m/z*): 350.02 [M+Na$^+$].

2.3.4. 7-Amino-5-(4-hydroxyphenyl)-2,4-dioxo-2,3,4,5-tetrahydro-1H-pyrano[2,3-d]pyrimidine-6-carbonitrile (**4d**)

Yellow powder, IR (KBr, υ cm^{-1}): 3457 (OH), 3260 (NH_2), 3131, 3088, (NH), 2293(C-H), 2242 (C≡N), 1729(C=O), 1678(C=O), 1555(C=C). ^{1}H NMR (400 MHz, DMSO-d_6): δ = 10.87 (s, 1H, NH), 10.79 (s, 1H, NH), 6.98 (d, *J* = 7.5 Hz, 2H, Ar-H), 6.82 (s, 2H, NH_2), 6.61 (d, *J* = 7.6 Hz, 2H, Ar-H), 6.05 (s, 1H, OH), 4.31 (s, 1H, CH) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ = 168.93 (C=O), 157.19 (C-14), 155.61 (CNH_2), 153.38 (CONH), 152.72 (C=O), 129.32-129.20 (C-12 & C-16), 118.20 (C≡N), 115.16 (C-13), 97.22 (C-5), 58.65 (C-9), 54.87 (C-10) ppm; Ms (*m/z*): 298.06 [M+H$^+$].

2.3.5. 7-Amino-5-(3-hydroxyphenyl)-2,4-dioxo-2,3,4,5-tetrahydro-1H-pyrano[2,3-d]pyrimidine-6-carbonitrile (**4e**)

Yellow powder, IR (KBr, υ cm^{-1}): 3439 (OH), 3337 (NH_2), 3193, 3028 (NH), 2206 (C-H), 2131(C≡N), 1677 (C=O), 1625 (C=O), 14741(C=C); ^{1}H NMR (400 MHz, DMSO-d_6): δ = 12.04 (s, 1H, NH), 10.62 (s, 1H, NH), 6.97-6.83 (m, 3H, Ar-H), 6.61 (s, 2H, NH_2), 6.09 (s, 1H, OH), 3.94 (s, 1H, CH);^{13}C NMR (100 MHz, DMSO-d_6): δ = 179.43 (C=O), 170.23 (C-14), 159.49 (CNH_2), 157.19 (CONH), 155.08 (C=O), 129.31 (C-16), 129.20 (C≡N), 115.15 (C-13), 93.41 (C-5), 84.21 (C-9), 52.03 (C-10); Ms (*m/z*): 299.02 [M+H$^+$].

2.3.6. 7-Amino-5-(4-bromophenyl)-2,4-dioxo-2,3,4,5-tetrahydro-1H-pyrano[2,3-d]pyrimidine-6-carbonitrile (**4f**)

White powder, IR (KBr, υ cm^{-1}): 3370 (NH_2), 3340, 3189 (NH), 3080 (C-H), 2220 (C≡N), 1684 (C=O), 1567 (C=C). ^{1}H NMR (400 MHz, DMSO-d_6): δ = 14.10 (s, 1H, NH), 13.01 (s, 1H, NH), 7.75 (d, J = 7.1 Hz, 2H, Ar-H), 7.33 (d, J = 7.1 Hz, 2H, Ar-H), 6.82 (s, 2H, NH_2), 3.90 (s, 1H, CH) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ = 173.47 (C=O), 160.34 (CNH_2), 153.89 (CONH), 145.91 (C=O), 138.53 (C-11), 131.97 (C-13 & C-15), 129.69 (C-12 & C-16), 124.03 (C-14), 121.28 (C≡N), 105.25 (C-5), 69.60 (C-9), 50.10 (C-10) ppm;Ms (*m/z*): 384.12 [M+Na$^+$].

2.3.7. 7-Amino-2,4-dioxo-5-phenyl-2,3,4,5-tetrahydro-1H-pyrano[2,3-d]pyrimidine-6-carbonitrile (**4g**)

Yellow powder, IR (KBr, υcm^{-1}): 3371 (NH_2), 3301, 3212 (NH), 3114 (C-H), 2129 (C≡N), 1694 (C=O), 1572 (C=C). ^{1}H NMR (400 MHz, DMSO-d_6): δ = 10.98 (s, 1H, NH), 10.80 (s, 1H, NH), 7.31 (t, J = 7.3 Hz, 2H, Ar-H), 7.14 – 7.06 (m, 3H, Ar-H), 6.82 (s, 2H, NH_2), 4.29 (s, 1H, CH) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ =160.39 (C=O), 155.61 (CNH_2), 153.91 (CONH), 151.36 (C=O), 145.92 (C-11), 128.68 (C-12), 128.49 (C-13), 127.61 (C-14), 118.21 (C≡N), 93.41 (C-5), 58.66 (C-9), 50.89 (C-10) ppm;Ms (*m/z*): 283.08 [M+H$^+$].

2.3.8. 7-Amino-5-(4-methoxyphenyl)-2,4-dioxo-1,3,4,5-tetrahydro-2H-pyrano[2,3-d] pyrimidine- 6-carbonitrile (**4h**)

Dark yellow powder, IR (KBr, υ cm^{-1}): 3317 (NH_2), 3282, 3145 (NH), 3063 (C-H), 2215(C≡N), 1743 (C=O), 1668(C=C). ^{1}H NMR (400 MHz, DMSO-d_6): δ = 10.98 (s, 1H, NH), 10.80 (s, 1H, NH), 7.14 (d, J = 7.5 Hz, 2H, Ar-H), 6.86-6.82 (m, 4H, Ar-H & NH_2), 4.16 (s, 1H, CH), 3.81 (s, 3H, OCH_3) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ = 161.99 (C=O), 159.11 (C-14), 155.61 (CNH_2), 151.97 (CONH), 151.36 (C=O), 130.34 (C-11), 129.50 (C-12), 123.56 (C≡N), 113.14 (C-13), 93.41 (C-5), 58.66 (C-9), 57.46 (CH_3), 53.46 (C-10) ppm;Ms (*m/z*): 313.01 [M+H$^+$].

2.3.9. 7-Amino-5-(2-methoxyphenyl)-2,4-dioxo-1,3,4,5-tetrahydro-2H-pyrano[2,3-d] pyrimidine- 6-carbonitrile (**4i**)

Yellow powder, IR (KBr, υ cm^{-1}): 3419 (NH_2), 3202, 3137 (NH), 3016 (C-H), 2272(C≡N), 1765 (C=O), 1609 (C=C). ^{1}H NMR (400 MHz, DMSO-d_6): δ =10.93 (s, 1H, NH), 10.71 (s, 1H, NH), 7.44 (d, J = 4.6 Hz, 1H, Ar-H), 7.14-7.7.11 (m, 4H, Ar-H & NH_2), 4.16 (s, 1H, CH), 3.73 (s, 3H, OCH_3) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ =169.87 (C=O), 161.02 (C-14), 158.21 (CNH_2), 152.46 (CONH), 151.82 (C=O), 131.15 (C-11), 129.09 (C-12), 124.02 (C≡N), 113.18 (C-13), 94.39 (C-5), 58.93 (C-9), 57.41 (CH_3), 53.57 (C-10) ppm; Ms (*m/z*): 313.05 [M+H$^+$].

2.3.10. 7-Amino-5-(3,4-dimethoxyphenyl)-2,4-dioxo-1,3,4,5-tetrahydro-2H-pyrano[2,3-d]pyrimidine-6-carbonitrile (**4j**)

Yellow powder, IR (KBr, υ cm^{-1}): 3194 (NH_2), 3103, 2223 (NH), 1734 (C-H), 2609 (C≡N), 1662 (C=O), 1262 (C=C). ^{1}H NMR (400 MHz, DMSO-d_6): δ = 10.98 (s, 1H, NH), 10.80 (s, 1H, NH), 6.83 – 6.80 (m, 5H, Ar-H & NH_2), 4.29 (s, 1H, CH), 3.83 (s, 3H, OCH_3), 3.75 (s, 3H, OCH_3) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ = 164.65 (C=O), 155.61 (CNH_2), 153.94 (CONH), 151.97 (C=O), 149.25 (C-14), 148.54 (C-13), 131.34 (C-11), 126.92 (C-16), 119.53 (C≡N), 116.52 (C-12), 114.27 (C-15), 93.40

(C-5), 58.66 (C-9), 57.91 (CH_3), 56.78 (CH_3), 51.23 (C-10) ppm; Ms (*m/z*): 343[M+H^+].

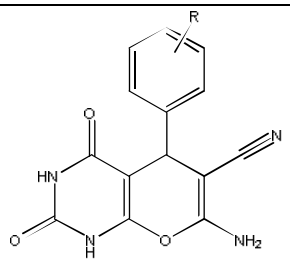
Results and discussion:

Herein we report the synthesis of pyrano[2,3-*d*]pyrimidinones (**4a–j**) as a domino Knoevenagel–Michael condensation pathways (**Table 1**). In initial studies, hydroxybenzaldehyde**1** (1.0 mmol), malononitrile**2** (1.0 mmol) and barbituric acid **3** (1.0 mmol) were refluxed in aqueous ethanol using different catalysts for synthesis of model product **4d**. We found the base catalysts such as N-methylamidazole, triethylamine, piperidine, morpholine and dibutylamine (**Table 2**), were equally competent in furnishing the desired model product **4d** in good yields. Among these basic catalysts, 20mol % of dibutylamine(DBA) gave the best result in terms of time of completion and the product yields **94%**. In the absence of catalyst, the reaction was completed under reflux condition after 189 minutes and the yield of product was obtained 37% (**Table 2**). Therefore, dibutylamine(DBA) catalyst appears to be Superior to any of the other tested catalysts. **Table 3** shows the comparative results of the different catalyst with the catalytic activity of DBU for the synthesis of Pyrano[2,3-*d*]pyrimidine derivatives.

The structural assignment of model product **4d**was confirmed by IR, ^{1}HNMR, ^{13}CNMR and mass spectrometric analysis. The IR spectra exhibited sharp absorption bands at 3457, 3260 3131–3088, 2293, 1729, 1678 and 1555 cm^{-1}, which are attributed to OH, NH_2, NH, C-H, C≡N, C=O and C=C stretching vibrations, respectively. In the ^{1}H NMR spectrum of compound **4d,** it showed the peaks at δ 10.87 (s, 1H, NH), δ 10.79 (s, 1H, NH), δ 6.98 (d, *J* = 7.5 Hz, 2H, Ar-H), δ 6.82 (s, 2H, NH_2), δ 6.61 (d, *J* = 7.6 Hz, 2H, Ar-H), δ 6.05 (s, 1H, OH) and δ 4.31 (s, 1H, CH) ppm (Figure 1). In the ^{13}CNMR spectrum of the compound **4d**, the 12 significant signals were recorded at 168.93, 157.19, 155.61, 153.38, 152.72, 129.32-129.20, 118.20, 115.16, 97.22, 58.65 and 54.87 ppm (Figure 2). Molecular ion peak was observed in agreement with molecular weight of compound. Results indicated that a series of substituted aromatic aldehydes were successfully employed to prepare the corresponding product in excellent yields (**83–94%**) and there is no major effect on the yield of product by electron donating/withdrawing substituents.

Dibutylamine(DBA) is an amine basic in character, so facilitates proton removal from active methylene compounds thereby increases reaction rate yields of desired products. Mechanistically, DBA is an effective catalyst for the formation of the higher reactive iminium group which is utilized to facilitate Knoevenagel condensation of malononitrile witharomatic aldehydes by loss of water molecule, followed by Michael addition of barbituricacid on electron deficient C-atom and an intra molecularheterocyclization that leads to theformation of the pyrano[2,3-*d*]pyrimidine derivatives.

Table. 1- Physical properties of the pyrano[2,3-*d*] pyrimidine derivatives **4(a-j)**



4 (a-j)

Product	Time (mins)	Yield (%)[a]	M.P (°C) Found
4a	103	83	235-236
4b	110	86	239-241
4c	101	84	231-234
4d	53	94	158-160
4e	67	91	169-171
4f	72	89	228-232
4g	58	94	236-238
4h	67	91	289-293
4i	59	87	301-303
4j	78	93	312-314

[a]Isolated yields

Table. 2-Effect of catalysts for the synthesis of model product **4d**

Entry	Catalyst	Catalyst (mol %)	Time (mins)	Yield (%)[a]
1	N-methylamidazole	20mol	114	79
2	Triethylamine	20mol	83	90
3	Piperidine	20mol	110	71
4	Morpholine	20mol	140	68
5	Dibutylamine	5mole	105	74
6	Dibutylamine	10moe	68	86
7	Dibutylamine	15mole	53	87
8	Dibutylamine	20mol	53	94
9	Catalyst free	—	189	37

[a]Isolated yields

Table. 3- DBA comparison with different catalysts for the synthesis of pyrano[2,3-*d*]pyrimidine derivatives

Entry	Catalyst	Solvent	Condition	Time	Yield	Lit. Ref.
1	Zn[(L)proline]$_2$	EtOH	Reflux	30 min-12 h	80-92	[16]
2	[BMIm]BF4	[BMIm]BF_4	90^{0}C	3-5 h	82-95	[17]
3	N-methylmorpholine	[bmim][PF_6]	70^{0}C	15 min	85-89	[18]
4	DAHP	EtOH	r.t	2 h	71-81	[19]
5	SBA-Pr-SO3H	Solvent free	140^{0}C	5-45 min	91	[20]
6	Et3N	DMF	MW	10-12 min	65-70	[25]
7	DBA	aq.EtOH	Reflux	43-129 min	83–94	Present work

Conclusion:

In conclusion, we have synthesised annulated pyrimidine derivatives like pyrano[2,3-*d*]pyrimidines via one-pot three-component domino Knoevenagel-Michael addition reaction using dibutylamine (DBA) as new efficient catalyst in aqueous media. The synthetic method is simple as no special apparatus for work up are required, and the compound formed is filtered and purified just by simple crystallization. This synthesis is also advantageous in terms of atom economy as well as is devoid of any hazardous chemicals.

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