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Dibutylamine (DBA): A highly efficient catalyst for the synthesis of pyrano[2,3-*d*]pyrimidine derivatives in aqueous media

Ajmal R. Bhat [a], Aabid H. Shalla [b], Rajendra S. Dongre [a,*]

[a] *Department of Chemistry, R.T.M. Nagpur University, Nagpur 440033, India*
[b] *Islamic University of Science and Technology, Jammu Kashmir 192122, India*

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Abstract

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

Keywords: Annulated pyrano[2,3-*d*]pyrimidines; Barbituric acid; Knoevenagel–Michael addition reaction; Spectral analysis; Aromatic aldehydes; DBA catalyst

1. Introduction

Heterocyclic compounds have received considerable attention in recent years due to their variety of biological activities, especially as inhibitors of PDE5 extracted from human platelets [1], HIV-1 reverse transcriptase [2], human EPK2 [3] and cyclin-dependent kinase [4]. The study of aromatic six membered N-heterocyclic rings is of great importance in the pharmaceutical sector due to bio-isosteric factors, which are of theoretical and practical importance. Pyrimidine rings have significant pharmacological importance as an integral part of DNA and RNA in several biological processes [5–7]. Therefore, the chemotherapeutic efficacy of annulated pyrano[2,3-*d*]pyrimidines is related to their ability to inhibit enzyme action for DNA biosynthesis, such as dihydrofolate reductase (DHFR), thymidylate synthetase (TSase), thymidine phosphorylase (TPase) and reverse transcriptase (RTase). When pyrano[2,3-*d*]pyrimidine moieties are annulated into one molecule, the resultant derivative has enhanced pharmaceutical activity, such as, antitumor [8], antihypertensive [9], antibacterial [10] and antileishmanial activity [11]. Therefore, for the preparation of these complex molecules, large efforts have been made towards the synthetic manipulation of annulated uracils, which occupy a distinct and unique place in medicinal chemistry. Annulated pyrano[2,3-*d*]pyrimidine derivatives are unsaturated N-heterocyclics formed as a fusion of pyran

* Corresponding author. Tel.: +91 08087723120; fax: +91 07122500429.
E-mail address: rsdongre@hotmail.com (R.S. Dongre).
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and pyrimidine rings, consisting of one oxygen atom at 8 and two nitrogen atoms at the 1 and 3 positions. They are synthesized by various procedures based on multicomponent reactions, such as Knoevenagel condensation, Michael addition followed by cyclodehydration and finally heterocyclization.

Multicomponent reactions (MCRs) have gained significant interest from modern medicinal and combinatorial chemists [12,13] due to the 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 [14,15]. Pyrano[2,3-*d*]pyrimidine derivatives have been reported using different catalysts, such as Zn[(L)proline]$_2$ [16], [BMIm]BF_4 [17], N-methylmorpholine [18], DAHP [19], SBA-Pr-SO_3H [20], $H_{14}[NaP_5W_{30}O_{110}]$ [21], 1,4-dioxane [22], L-proline [23] and [K $Al(SO4)_2$] [24]. Et_3N was used as a catalyst for the synthesis of pyrano[2,3-*d*]pyrimidine derivatives under microwave irradiation [25]. A catalyst-free procedure was also examined for the preparation of pyrano[2,3-*d*]pyrimidine derivatives [26]. In addition, ultrasonic irradiation [27] and ball-milling techniques [28] were used for the synthesis of pyrano[2,3-*d*]pyrimidine derivatives. The solvent and the inexpensive, mild and reusable catalyst for MCRs play an important role in the synthesis and its selectivity of targeted products. One of these catalysts is dibutylamine (DBA), which has received significant interest as a high reactive, eco-friendly, inexpensive, readily available and non-toxic catalyst to obtain corresponding products in excellent yields with high selectivity [29].

In continuation of the current research from our laboratory to develop efficient multicomponent reactions (MCRs) for the preparation of pyrimidine-annulated bioactive molecules [30], we report here, the dibutylamine (DBA) catalyzed efficient, simple and fast synthesis of pyrano[2,3-*d*]pyrimidine derivatives via one-pot, three-component domino Knoevenagel–Michael addition reaction in aqueous media (Scheme 1).

2. Experimental

2.1. Apparatus and analysis

All chemicals were obtained from Merck and S.D. Fine Chem. Co. and were used without further purification. Melting points were determined by the open capillary method and were uncorrected. IR spectra were recorded on a Perkin–Elmer 298 spectrophotometer using KBr pellets. ^{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 with tetramethylsilane as the internal standard. Chemical shifts are reported in ppm. Mass spectra were recorded on a Shimadzu GC-MS-QP-2010 model using the direct injection probe technique. Reactions were 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)*

Substituted aromatic aldehydes **1** (1 mmol), malononitrile **2** (1 mmol), barbituric acid **3** (1 mmol) and 20 mol% dibutylamine (DBA) were added to an RB flask with 16 ml aqueous media (1:1 ratio) and were stirred for 43–129 min at room temperature. The progress of the 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. Spectral data for the synthesized pyrano[2,3-d]pyrimidine derivatives *4(a–j)*

2.3.1. 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, ν 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 ν 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