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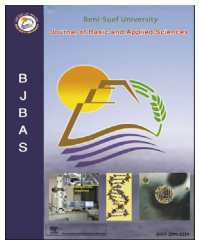

Full Length Article

Efficient synthesis of a novel series of indeno fused pyrido[2,3-*d*]pyrimidines using β-cyclodextrin-propyl sulfonic acid as an eco-friendly catalyst

Prasanna Nithiya Sudhan [a], *Majid Ghashang* [b], *Syed Sheik Mansoor* [a,*]

[a] *Research Department of Chemistry, Bioactive Organic Molecule Synthetic Unit, C. Abdul Hakeem College (Autonomous), Melvisharam, Tamil Nadu 632 509, India*

[b] *Faculty of Sciences, Najafabad Branch, Islamic Azad University, Najafabad, Esfahan, Iran*

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ABSTRACT

A simple and facile synthesis of 5-aryl-5,11-dihydro-1*H*-indeno[2′,1′:5,6]pyrido[2,3-d]pyrimidine-2,4,6-trione derivatives was accomplished by the one-pot condensation of aromatic aldehydes, 1,3-indandione and 6-amino uracil under solvent-free conditions in the presence of the catalyst, β-cyclodextrin-propyl sulfonic acid (β-CD-PSA). This method has the advantages of high yield, clean reaction, simple methodology, and short reaction time. The catalyst could be recycled and reused four times without significant loss of activity.

1. Introduction

The elimination of volatile and toxic organic solvents in chemical processes represents very powerful procedures for green chemical technology from both the economic and synthetic points of view (Kiyani and Ghiasi, 2015; Shaterian and Rigi, 2014; Shirini et al., 2015). They have many advantages, such as reduced pollution, lower cost, and simplicity in processing, which are beneficial to the industry as well as to the environment.

Pyrido[2,3-*d*]pyrimidines are annulated uracil which have received considerable attention over the past years due to their wide range of biological and pharmacological activities, which include anticancer agents inhibiting dihydrofolate reductases or tyrosine kinases (Gangjee et al., 1996), cytotoxic (Moreno

* *Corresponding author.* Research Department of Chemistry, Bioactive Organic Molecule Synthetic Unit, C. Abdul Hakeem College (Autonomous), Melvisharam, Tamil Nadu 632 509, India.
E-mail address: smansoors2000@yahoo.co.in (S.S. Mansoor).

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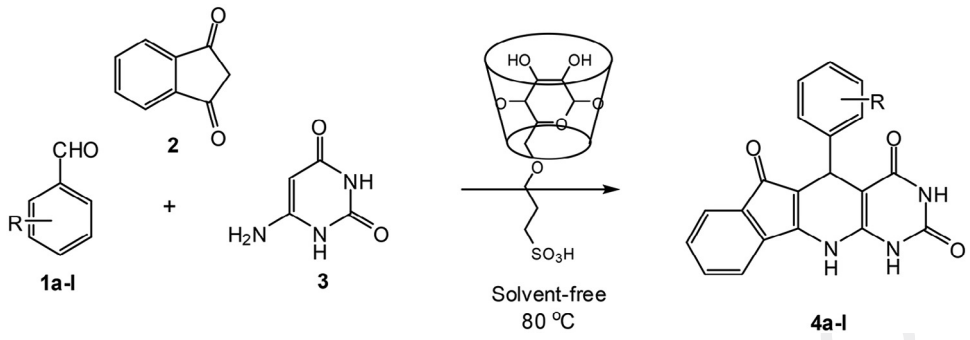

Scheme 1 – Synthesis of 5-aryl-5,11-dihydro-1*H*-indeno[2′,1′:5,6]pyrido[2,3-*d*]pyrimidine-2,4,6-trione.

et al., 2012), antitumor (Broom et al., 1976; Grivsky et al., 1980), anti-proliferative CDK2 inhibitor (Ibrahim and Ismail, 2011), antihistaminic (Quintela et al., 1997), anti-inflammatory (El-Gazzar and Hafez, 2009), antibacterial (Degraw et al., 1974; Matsumoto and Minami, 1975), inhibitors of cyclin-dependent kinases (Barvian et al., 2000), anti-allergic (Hermecz et al., 1984), analgesic (Awoutters et al., 1986), calcium channel antagonists (Pastor et al., 1994), antihypertensive (Bennett et al., 1981) and CNS depressant activity (Hasan et al., 1994). As a result, the compounds of this class have attracted considerable interests for research. Several methods have already been reported for the synthesis of pyrido[2,3-*d*]pyrimidines (Abdolmohammadi and Afsharpour, 2012; Baharfar and Azimi, 2011; Nemati and Saeedirad, 2013; Nia et al., 2013; Quiroga et al., 1998; Rad and Mokhtary, 2015; Sarmah et al., 2013; Wang et al., 2004, 2005; Youssif et al., 1999; Ziarani et al., 2014).

The unique supramolecular property due to the hydrophobic cavity of CDs, enable the wide application of CDs in many fields of science and technology (Harada et al., 1993, 2009). *β*-Cyclodextrin based polyurethane has been reported as a phase-transfer catalyst for the preparation of benzyl cyanides and azides in water (Kiasat and Nazari, 2012a), synthesis of benzyl thiocyanates and acetates (Kiasat and Nazari, 2012b) and for the synthesis of 1,4-dihydropyridine and polyhydroquinoline derivatives *via* the Hantzsch reaction (Kiasat et al., 2014). *β*-Cyclodextrin-butane sulfonic acid has been reported as an efficient and reusable catalyst for the multicomponent synthesis of 1-amidoalkyl-2-naphthols under solvent-free conditions (Gong et al., 2015a) and synthesis of 1,8-dioxo-octahydroxanthenes (Gong et al., 2015b). Synthesis of 3,4-dihydropyrimidones *via* Biginelli reaction (Gong et al., 2015c) and 1,2,4,5-tetrasubstituted imidazoles (Ran et al., 2015) have been achieved by using *β*-Cyclodextrin-propyl sulfonic acid.

The above mentioned observations led us to attempt the synthesis of some indeno fused pyrido[2,3-*d*]pyrimidine derivatives in the presence of *β*-cyclodextrin-propyl sulfonic acid (*β*-CD-PSA). Furthermore, *β*-CD-PSA is inexpensive, biodegradable, and can be reusable. In a continuation of our interest in the synthesis of biologically active organic compounds by multicomponent reactions (Ghashang et al., 2013, 2014a, 2014b, 2014c), we have developed an efficient synthesis of 5-aryl-5,11-dihydro-1H-indeno[2′,1′:5,6]pyrido[2,3-d]pyrimidine-2,4,6-trione derivatives using *β*-CD-PSA as an efficient catalyst *via* the cyclocondensation reaction of aromatic aldehydes, 1,3-indandione and 6-amino uracil under solvent-free conditions at 80 °C (Scheme 1).

2. Materials and methods

2.1. *Chemicals and analysis*

Chemicals were purchased from Merck, Fluka and Aldrich Chemical Companies. Analytical thin-layer chromatography was performed with E. Merck silica gel 60F glass plates. Visualization of the developed chromatogram was performed by UV light (254 nm). Column chromatography was performed on silica gel 90, 200–300 mesh. Melting points were determined with Shimadzu DS-50 thermal analyzer. The products were characterized by comparison of their physical data with those of known samples or by their spectral data. ^{1}H NMR (500 MHz) and ^{13}C NMR (125 MHz) spectra were obtained using Bruker DRX-500 Avance at ambient temperature, using TMS as internal standard. FT-IR spectra were obtained as KBr discs on Shimadzu spectrometer. Mass spectra were determined on a Varion – Saturn 2000 GC/MS instrument. Elemental analysis was measured by means of Perkin Elmer 2400 CHN elemental analyzer flowchart.

2.2. *Preparation of β-CD-PSA*

β-CD-PSA is prepared from *β*-CD and 1,3-propane sultone as reported previously (Gong et al., 2015c) (Scheme 2).

2.3. *General procedure for preparation of (4a-l)*

A mixture of equimolar amounts of aryl aldehyde **1** (1 mmol), 1,3-indandione **2** (1 mmol) and 6-amino uracil **3** (1 mmol) was heated at 80 °C under solvent-free condition in the presence of *β*-CD-PSA (1 mol %). The progress of the reaction was monitored by TLC (EtOAc/petroleum ether:1/9). Stirring at 80 °C was continued until disappearance of the starting materials (monitored by TLC). The reaction mixture was cooled and washed with water. The solid obtained was recrystallized from MeOH to furnish the desired pure product (Table 2).

2.4. *Spectral data for the synthesized compounds are presented below (4a-l)*

2.4.1. *5-Phenyl-5,11-dihydro-1H-indeno[2′,1′:5,6]pyrido [2,3-d]pyrimidine-2,4,6-trione (4a)*

IR (KBr, cm^{-1}): 3370, 3288, 3077, 2822, 1700, 1644, 1629, 1545, 1503, 1011, 852, 773; ^{1}H NMR (500 MHz, DMSO-d_6) *δ*: 4.77 (s, 1H, CH),

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