

MCM-41-nPrNH₂ as a Recoverable Nanocatalyst for the Synthesis of New Phenylpyrido[4,3-d]pyrimidin-2-amine Derivatives

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MCM-41 anchored *n*-propylamine (MCM-41-nPrNH₂) was found to be a highly efficient and recoverable nanocatalyst for the synthesis of new class of phenylpyrido[4,3-d]pyrimidin-2-amine derivatives under solvent free conditions in high to quantitative yields. All the structures of title compounds 3a-j were elucidated by comprehensive ¹H NMR, ¹³C NMR, IR and Mass spectra

Keywords: Phenylpyrido[4,3-d]pyrimidin-2-amine derivatives, Solvent free conditions, MCM-41-nPrNH₂, Recoverable nanocatalyst.

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1. INTRODUCTION

MCM-41 (Mobil Composition of Matter No. 41) is a mesoporous material and consists of a hexagonal array of unidirectional pore structures which has been synthesized under basic condition using cationic surfactants as a structure-directing agent. Pure MCM-41 is neutral in charge and exhibits only weak hydrogen-bonding type sites which limit its application in catalysis [1-5]. An additional possibility to develop basic catalysts is modification of supports, as the chemical functionalities of these materials can be uniformly achieved by covalent anchoring of different organic moieties [6]. One of the modified organic-inorganic hybrid materials that have been applied as effective solid base catalyst in organic transformations is 3-aminopropylated silica (MCM-41-nPrNH₂) [7-10]. The functional aminopropyl group was anchored on MCM-41 silica by the post-modification which was prepared according to the method reported in the literature from the reaction of MCM-41 with 3-aminopropyltriethoxysilane in refluxing toluene [11].

The use of heterogeneous solid base catalysts is of current interest in chemistry and industry because solid bases offer many advantages such as simplicity in handling, more environmentally safe disposal and less corrosion problems.

Pyrido[4,3-d]pyrimidines display various remarkable biological activities such as antibacterial [12], antiallergic [13], fungicidal, antiviral, anti-inflammatory, and antimicrobial properties [14-19]. Inhibition of the adenosine kinase enzyme [20], or dihydrofolate reductase, and irreversible inhibition of epidermal growth factor receptor [21], stimulated our interest immensely. Also, 5, 6, 7, 8-tetrahydropyrido[4,3-d]pyrimidine and related compounds have been used as starting materials for the multi-step synthesis of tetrahydroptericoic acid derivatives [22].

In view of the useful properties of pyrido[4,3-d]pyrimidines and to the best of our knowledge there are no reports for the synthesis of phenylpyrido[4,3-d]pyrimidin-2-amines in the literature. Hence, following our immense desire to adopt rather greener and economical reaction conditions [23], herein, we report an efficient synthesis of 3 and its derivatives through the two component reactions between (*E*)-3,5-bis(benzyl-

idene)-4-piperidones (1) and benzamidine hydrochloride (2) in the presence of recoverable catalyst (MCM-41-nPrNH₂) under solvent free conditions (Fig. 1).

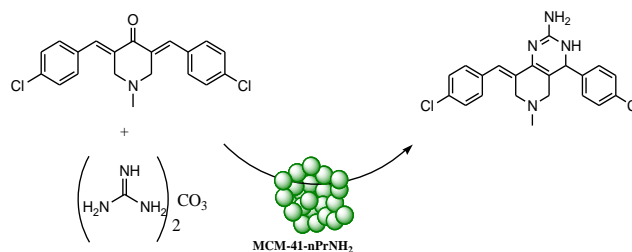


Fig. 1 – Synthesis of phenylpyrido[4,3-d]pyrimidin-2-amine derivatives in the presence of MCM-41-nPrNH₂

2. RESULTS AND DISCUSSIONS

After optimization of the reaction condition, a variety of aromatic aldehydes, possessing both electron-donating and electron-withdrawing groups were employed for phenylpyrido[4,3-d]pyrimidin-2-amine formation and the results indicated that for 3,5-dibenzylidenepiperidin-4-one bearing different functional groups, the reaction proceeded smoothly in all cases. It is worth mentioning that 3,5-dibenzylidenepiperidin-4-one with electron-withdrawing groups reacted rapidly whereas with those having electron-rich groups, longer reaction times were required. Electron-withdrawing groups on the phenyl rings induce greater electronic positive charge on the corresponding β -atoms than electron donating moieties.

3. EXPERIMENTALS

3.1 General remarks

Melting points were recorded on a Buchi B-540 apparatus. IR spectra were recorded on an ABB Bomem Model FTLA200-100 instrument. ¹H and ¹³C NMR spectra were measured on a Bruker DRX-300 spectrometer, at 300 and 75MHz, using TMS as an internal standard. Chemical shifts (δ) were reported relative to TMS, and coupling constants (*J*) were reported in hertz (Hz). Mass spectra were recorded on a Shimadzu QP 1100 EX mass spectrometer with 70-eV ionization potential.

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3.2 Preparation of MCM-41-nPrNH₂

Functionalized catalyst (MCM-41-nPrNH₂) was prepared according to the method reported in the literature from the reaction of MCM-41 with 3-aminopropyltriethoxysilane in refluxing toluene [11] (Fig. 2)

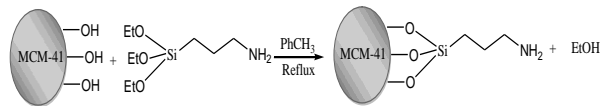


Fig. 2 – Functionalization of the MCM-41 with 3-aminopropyltriethoxysilane

3.3 General procedure for the synthesis of 3,5-dibenzylidenepiperidin-4-one

In a 50-mL reaction vial, a mixture of the 4-piperidone (10 mmol), the appropriate aldehyde (20 mmol), 10% NaOH (1 mL) and 95% EtOH (30 mL) was stirred at room temperature for 0.5-2 h. The separated solid was collected by filtration and for further purification was recrystallized from ethanol [19].

Table 1 – The reaction time (min) and the yield (%) of phenylpyrido[4,3-d]pyrimidin-2-amine product in the present of MCM-41-nPrNH₂

Entry	Product	Time (min)	Yield* (%)	M.P (°C) Found
3a	4Cl-C ₆ H ₄ -	30	8	240-242
3b	2,4diCl-C ₆ H ₃ -	30	80	206-208
3c	2Cl-C ₆ H ₄ -	30	98	146-148
3d	2,3diCl-C ₆ H ₃ -	30	89	156-158
3e	3-NO ₂ -C ₆ H ₄ -	30	95	228-230
3f	4-NO ₂ -C ₆ H ₄ -	20	98	>300

3.4 General procedure for the synthesis of 4-phenylpyrido[4,3-d]pyrimidin-2-amine derivatives

A mixture of 3,5-dibenzylidenepiperidin-4-one (0.33 mmol), and guanidine carbonate (0.33 mmol) was add-

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ed to MCM-41-nPrNH₂ (30 mg); it was then stirred at 130 °C for an appropriate period of time (Table 1). After completion of the reaction (monitored by thin-layer chromatography, TLC; petroleum ether and EtOAc, 1:1), the reaction mixture was cooled to room temperature a minimum amount of ethylacetate was added, and the nanocatalyst recovered. The extract was concentrated under reduced pressure and purified by recrystallization in 1:1 EtOH/H₂O.

(8E)-8-(4-chlorobenzylidene)-4-(4-chlorophenyl)-3,4,5,6,7,8-hexahydro-6-methylpyrido[4,3-d]pyrimidin-2-amine (3a)

IR (KBr, cm⁻¹) V_{max}: 3381, 3251, 3154, 2970, 1646, 1458; ¹HNMR (300 MHz; DMSO- d₆): 2.06 (3H, s, N-CH₃), 2.42 (1H, d, J=16.0 Hz), 2.80 (1H, d, J=16.0 Hz), 3.00 (1H, d, J=13.5 Hz), 3.37 (1H, d, J=14.1 Hz), 4.51 (1H, s), 7.23-7.56 (12H, m); ¹³CNMR (75 MHz, DMSO- d₆): 44.8, 109.6, 119.2, 128.3, 128.8, 129.0, 130.6, 132.8.

(8E)-8-(2,4-dichlorobenzylidene)-4-(2,4-dichlorophenyl)-3,4,5,6,7,8-hexahydro-6-methylpyrido[4,3-d]pyrimidin-2-amine (3b)

IR (KBr, cm⁻¹) V_{max}: 3383, 3255, 3157, 2972, 1647, 1452; ¹HNMR (300 MHz; DMSO- d₆): 2.11 (3H, s, N-CH₃), 2.55 (1H, d, J=16.0 Hz), 2.85 (1H, d, J=16.0 Hz), 3.00-3.24 (2H, m), 4.35 (1H, s), 5.28 (1H, s), 5.38 (1H, s), 6.64 (1H, brs), 7.20 (1H, s), 7.23 (1H, d, J=8.4 Hz), 7.38 (2H, dd, J₁=8.1, J₂=3.1 Hz), 7.50 (1H, dd, J₁=8.3, J₂=2.0 Hz), 7.59 (2H, dd, J₁=8.3, J₂=2.0 Hz); ¹³CNMR (75 MHz, DMSO- d₆): 45.1, 52.3, 55.1, 56.0, 107.9, 117.3, 127.0, 128.3, 128.6, 128.7, 130.9, 131.6, 131.9, 132.0, 132.8, 133.7, 134.4, 134.6, 135.5, 140.4, 152.3; MS (EI): m/e = 57 (4), 258 (19), 292 (60), 309 (17), 366 (17), 366 (23), 431 (55), 465 (100), 468 (38).

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