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Microwave Assisted and Solvent-Free Synthesis Of 2,4,5,6-Tetrasubstituted Pyrimidines Using Nano Silica Catalyst

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ABSTRACT

Simple and efficient synthesis of 2,4,5,6-tetrasubstituted pyrimidines in the presence of nano-SiO_2 is described via a four component reaction between aromatic nitriles, hydroxylamine, arylaldehydes and malonitrile under microwave irradiation and solvent-free conditions in good to excellent yields.
KEYWORDS: nanosilica; solvent free; pyrimidine; microwave; catalysis.

1. INTRODUCTION

Multicomponent reactions (MCRs), by virtue of their convergence, productivity, facile execution, and generally high yields of products have received a great deal of attention in organic and medicinal chemistry (Domling, 2000). Pyrimidines are of chemical and pharmacological interest **(**Brown, et al, 1994, Undheim, et al, 1996). Derivatives containing pyrimidine ring system have been shown to possess antitumor, antibacterial, antifungal, antimalarial, and anticonvulsant activities**(**Johar, et al, 2005, Agarwal, et al, 2005). Some examples are valuable drugs in treatment of hyperthyroidism, acute leukemis of childhood, and adult granulocytic leukemia **(**Undheim, et al, 1996). 4-amino-5-pyrimidinecarbonitrile has been used as a kit for the detection of larginine (a substrate for nitric oxide syntheses and a precursor of nitric oxid) and its derivatives in body samples, conjugated molecules which have a pyrimidine core as the key unit have recently received much attention and they are prospective candidates for light emitting devices**(**Wong, et al, 2002) and molecular wires **(**Harriman, et al, 1996). Tetra substituted pyrimidines have been synthesized using various methods and procedures including condensation of 1,2,3-trisubstituted enones with guanidies (Agarwal, et al, 2005).

Due to the unique properties of pyrimidine derivatives, developments of synthetic methods which enable facile access to this heterocycle are desirable. As part of our continuing efforts on the development of efficient methods for the preparation of widely used organic compounds from readily available building blocks, we describe here a simple, one pot, four-component synthesis of tetra substituted pyrimidines under solvent free conditions using raw materials, where possible to adapting the principles of green chemistry in order to reducing the use of organic solvent as potentially toxic and hazardousmaterials, as well as its simplicity and mild conditions, and inherent lower costs, with more likely industrial application. Thus, aromaticnitriles **2**, Hydroxylami, arylaldehyde **1**, malononitrile undergo a one-pot four-component reaction under solvent-freeconditions and to produce 2,4,5,6-tetrasubstituted pyrimidines in 86-95%yields (*Table 1*).

High-speed synthesis by microwaves has attracted a considerable amount of attention in recent years. Using a microwave oven in microwave-assisted organic synthesis (MAOS), not only reduces chemical reactions times from hours to minutes, but also reduces side reactions, increases the yield, and improves reproducibility. Therefore, many academic and industrial research groups are already using MAOS as a forefront technology for rapid optimization of reactions, for the efficient synthesis of new chemical entities, and for discovering and probing new chemical reactivity.

Recently, solid-supported reagents, such as nano silica have gained considerable interest in organic synthesis because of their unique properties of the reagents such as high efficiency due to more surface area, more stability and reusability, low toxicity, greater selectivity and ease of handling. Although, the catalytic applications of silica supported reagents for organic synthesis have been established, to the best of our knowledge, there is no report in the literature on the use of nano silica in the synthesis of tetrasubstituted pyrimidines.

Due to the interesting chemistry of tetrasubstituted pyrimidines, the development of synthetic methods easily accessible to these useful compounds is desirable. As part of our studies on the development of efficient and straightforward methods to prepare organic compounds from readily available building

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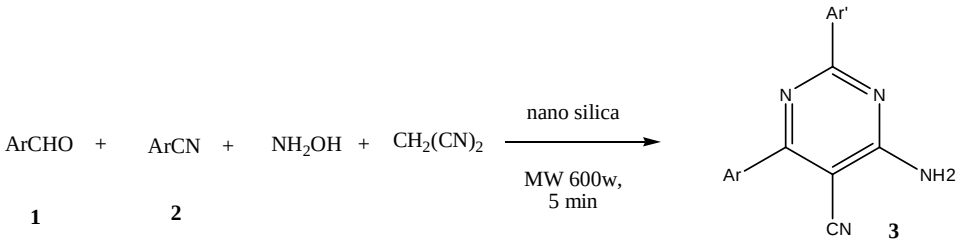
blocks (Adib, et al., 2006), a simple and efficient method to synthesize of tetrasubstituted pyrimidines by Microwave assisted, simple reaction of aromatic nitriles, hydroxylamine, arylaldehydes and malonitrile using nano-SiO_2 as a solid catalyst under solvent-free conditions is reported here. We found that a mixture of aromatic nitriles, hydroxylamine, arylaldehydes and malonitrile in the presence of nano silica as a catalyst in microwave irradiation and solvent free conditions, affords tetrasubstituted pyrimidines **3** in good to excellent yields (*Scheme 1, Table 1*).



Scheme1. Synthesis of 2,4,5,6-tetrasubstituted pyrimidines **3** catalyzed by nano-SiO_2.

EXPERIMENTAL

All starting materials and solvents were obtained from Merck (Germany) and Fluka (Switzerland) and were used without further purification. The methods used to monitor the reactions are TLC and NMR. Melting points were measured on an Electrothermal 9100 apparatus and are uncorrected. IR spectra were measured on a Jasco 6300 FTIR spectrometer. ^{1}H and ^{13}C NMR spectra ($CDCl_3$) were recorded on a BRUKER DRX-300 AVANCE spectrometer at 300.1 and 75.5 MHz, respectively. Elemental analyses were performed using a Heraeus CHN-O-Rapid analyzer. Mass spectra were recorded on a FINNIGAN-MATT 8430 mass spectrometer operating at an ionization potential of 70 eV. Chromatography columns were prepared from Merck silica gel 60 mesh.

The reaction were carried out by first mixing the nitrile **2** and hydroxylamine, proceeding in the presence of a catalytic amount of acetic acid under solvent free condition and irradiate in microwave oven at 600 w for 2 minutes. After nearly complete conversion to the corresponding amidoxime **5**, as indicated by TLC monitoring, the arylaldehyde **1**, malononitrile and catalytic amount of nano-SiO_2 (0.1 mmol) was added and irradiate in the microwave oven 600 w for 3 min. During the procedure, the reaction was monitored by TLC. Upon completion, the reaction mixture was cooled to room temperature and then boiling ethanol was added. The catalyst was removed. The residue was purified by column chromatography using n-hexane-EtOAc (3:1) as eluent. The solvent was removed and the product was recrystallized from 1:1 n-hexane-EtOAc. TLC and ^{1}HNMR analysis of the reactionmixture clearly indicated formation of the corresponding 2,4,5,6-tetrasubstituted pyrimidines **3a-f** in 85-96%yields (*Table 1*).The structures of the isolated products were corroborated by the comparison of their m.p. values and their spectral data (high-field ^{1}Hand ^{13}C NMR spectra)with those of authentic samples.

RESULTS AND DISCUSSION

The structure of compounds **2**a-f was deduced from their elemental analysis, and high-field ^{1}H and ^{13}C NMR spectra.

In conclusion, we have developed a simple, microwave assisted, one pot, four-component, and solvent-free procedure for the preparation of tetrasubstituted pyrimidines of potential synthetic and pharmacological interest. Using raw materials, one-pot and solvent-free condition are the main advantages of this method. This method appears to have broad scope with respect to variation in the pyrimidines 2-,4-, and 6-positions and presents a straightforward procedure for the synthesis of 2,4,6-triarylpyrimidines. The corresponding data for compounds **3**a and **3**b are given below:

4-amino-2,6-diphenyl-5-pyrimidinecarbonitrile (3a)

Colorless crystals. ^{1}H NMR (500.1 MHz, DMSO. d_6): δ 5.74 (2H, br. s, NH_2), 7.40-7.60 (6H, m, 6 CH), 8.13 (2 H, d, J = 7.7 Hz, 2 CH), 8.51 (2 H, d, J = 7.2 Hz, 2 CH). ^{13}C NMR (125.8 MHz, DMSO - d_6): δ = 85.77 (CN), 117.11 (C), 129.08, 129.29, 129.39, 129.63, 131.97, and 132.39(6 CH), 136.93 and 137.17 (2 C), 165.36, 165.94, and 168.71 (3 C-N).

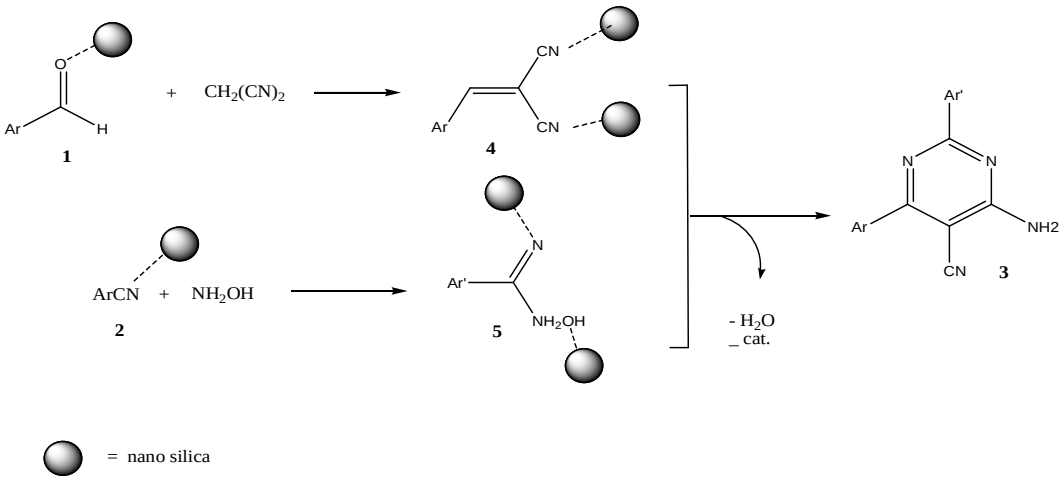
4-amini-2,6-bis(4-methylphenyl)-5-pyrimidinecarbonitrile (3b)

Colorless crystals. ^{1}HNMR(300.1MHz,DMSO - d_6): δ = 2.36 (3 H, s, CH3), 7.31 (2 H, d, *J* = 8.0 Hz, 2 CH), 7.52-7.59 (3 H, m, 3 CH), 7.82-8.05 (2 H, br. s, NH_2), 7.96 (2 H, d, *J* = 7.6 Hz, 2 CH), 8.29 (2 H, d, *J* = 8.1Hz, 2 CH). ^{13}C NMR (75.5MHz, DMSO - d_6): δ = 20.97 and 21.05 (2 CH_3), 83.74 (CN), 116.64 (C), 128.45, 128.56, 129.02 and 129.09 (4 CH),

Table 1. Synthesis of compounds **3**a-f

Product	Ar	Ar'	Mp °C	Yield (%)a
3a	Ph	Ph	153-155	96
3b	4-MeC_6H_4	4-MeC_6H_4	145-147	93
3c	4-$MeOC_6H_4$	4-MeC_6H_4	134-136	92
3d	4-MeC_6H_4	Ph	168-170	91
3e	Ph	4-MeC_6H_4	173-175	87
3f	4-$MeOC_6H_4$	Ph	134-136	85

[a] Isolated yields



Scheme 2. A possible path for synthesis of 2,4,5,6-tetrasubstituted pyrimidines **3**a-f.

In conclusion, we have developed a simple, microwave assisted synthesis of 2,4,5,6-tetrasubstituted pyrimidines of potential synthetic interest. Solvent-free conditions, excellent yields, and a simplified purification process, fairly fast reaction times, mild reaction conditions, use of simple, inexpensive and readily available catalyst, and high atom economy are the main advantages of this method.

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