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ORIGINAL PAPER

Granulated copper oxide nanocatalyst: a mild and efficient reusable catalyst for the one-pot synthesis of 4-amino-5-pyrimidinecarbonitriles under aqueous conditions

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Abstract An efficient method for the synthesis of 4-amino-5-pyrimidinecarbonitriles by the three-component reaction of malononitrile, aldehydes, and N-unsubstituted amidines under aqueous conditions using CuO microspheres as catalyst is reported. The catalyst exhibited remarkable reusable activity.

Keywords CuO microspheres · Malononitrile · Aldehydes · Amidines · 4-Amino-5-pyrimidinecarbonitriles

Introduction

Heterocyclic compounds occur very widely in nature and are essential to life. Nitrogen-containing heterocyclic molecules constitute the largest portion of chemical entities, which are part of many natural products, fine chemicals, and biologically active pharmaceuticals vital for enhancing the quality of life [1, 2]. Pyrimidine is one of the most common N-heteroaromatic compounds incorporated into the structures of many pharmaceuticals, including analgesics [3], antihypertensives, antipyretics, and anti-inflammatory drugs [4]. Pyrimidines also occur in some pesticides [5], herbicides, and plant growth regulators [6].

Organic reactions in aqueous media have attracted much attention in synthetic organic chemistry, not only because water is the most abundant, cheap, and environmentally friendly solvent but also because water exhibits unique reactivity and selectivity, which are different from those obtained in conventional organic solvents. Thus, elements of novel reactivity as well as selectivity that cannot be attained in conventional organic solvents are challenging goals in aqueous chemistry [7]. The significant enhancement in the rate of reaction has been attributed to hydrophobic packing, solvent polarity, hydration, and hydrogen bonding [8–10]. Thus, the use of water instead of organic solvents has gained importance as an essential component of the development of sustainable chemistry [11].

Very recently, the employment of nanocrystalline metal oxides as catalysts in organic synthesis has attracted much attention [12]. Nanocatalysts in general and nano metal oxides in particular, despite having a greater chemical reactivity, suffer from inappropriate physical forms that make their practical applications often unfeasible or at least formidable. Industrial processes, especially fixed bed operations, often require casting of powdery nanocatalysts into a granulated structure.

We herein describe a practical, inexpensive method for the preparation of spherical granules of CuO catalyst. The prepared catalysts were then used in the synthesis of 4-amino-5-pyrimidinecarbonitriles **4** via multi-component reactions of aldehydes **1**, malononitrile (**2**), and amidines **3** under aqueous conditions (Scheme 1).

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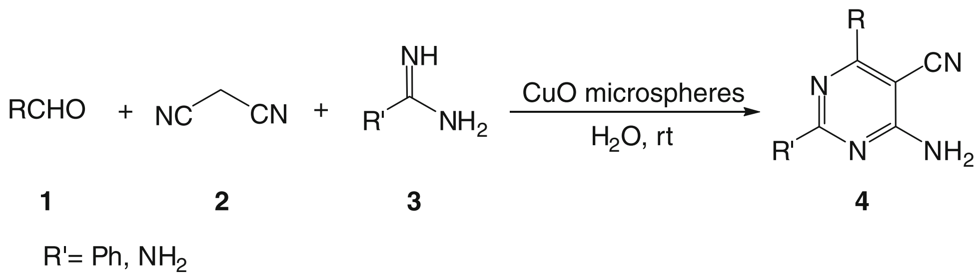
Scheme 1



Results and discussion

Granulated copper oxide nanocatalyst was prepared via a three-step procedure. In the first step, copper oxide nanoparticles were synthesized by hydrothermal decomposition of copper nitrate under supercritical water conditions. Then, they were immobilized in the polymeric matrix of sodium alginate. High temperature calcination in an air stream was the third step, which entirely removed the carbonaceous materials and resulted in a pebble-type catalyst of high porosity.

The X-ray diffraction (XRD) patterns of nano-sized and bulk CuO are shown in Fig. 1. All XRD peaks are indexed to the monoclinic crystal system of CuO. The average size of the obtained CuO particles shown in Fig. 2 is 5 nm. The crystallite size was also calculated by X-ray line-broadening analysis using the Scherrer equation: the average CuO crystallite size was found to be 8 nm. The mean surface area of the CuO catalyst was 32.457 $m^2\ g^{-1}$ from Brunauer–Emmett–Teller (BET) analysis.

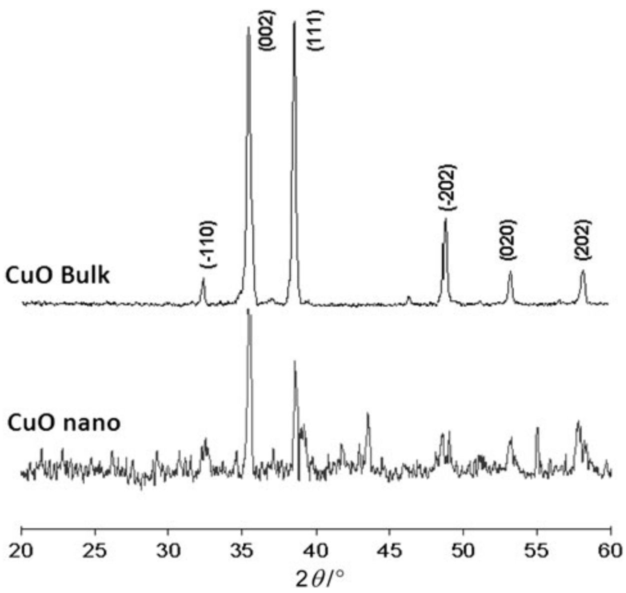


Fig. 1 XRD patterns of CuO particles prepared under supercritical conditions and bulk CuO

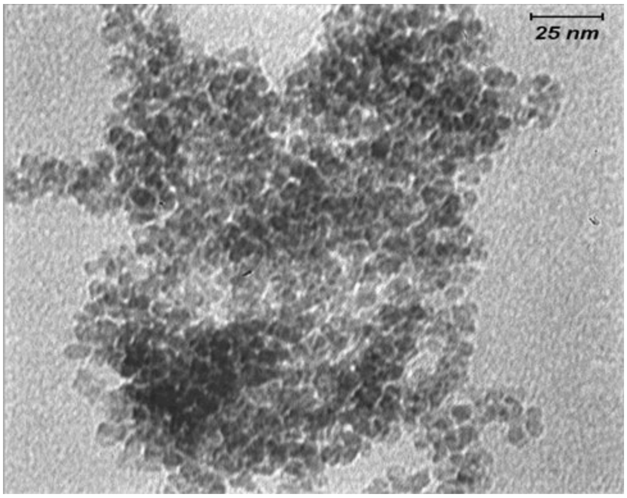


Fig. 2 Transmission electron micrographs of CuO nanoparticles

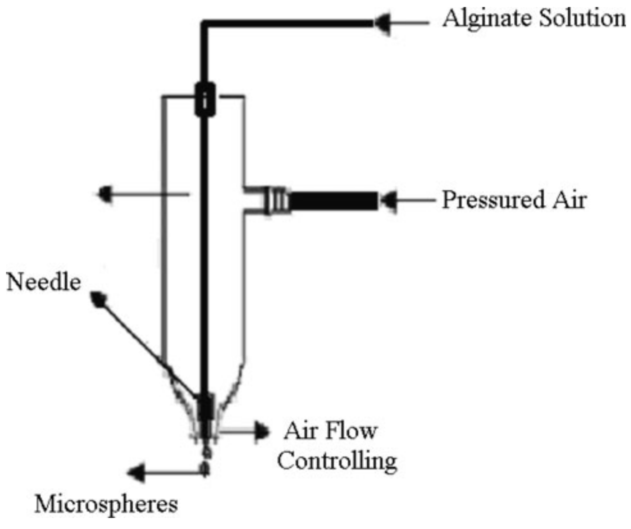


Fig. 3 Schematic diagram of the apparatus for preparation of granulated CuO microspheres

The first step in the synthesis of CuO microspheres was preparation of the aqueous CuO nanoparticle suspension. Fabrication of the microspheres (MSs) was then effected by mixing of the CuO suspension with sodium alginate solution, and dropwise injection of the obtained sol into $BaCl_2$ solution through a 0.50-mm medical needle to gelify and form microspheres (Fig. 3). The size of the droplets and thus microspheres was adjusted by means of a pneumatic

Table 1 Surface area of microspheres at different conditions

Entry	Temperature/°C	Time/h	BET/m^2 g^{-1}
MS_1	600	6	18.74
MS_2	700	6	9.16
MS_3	800	6	5.65

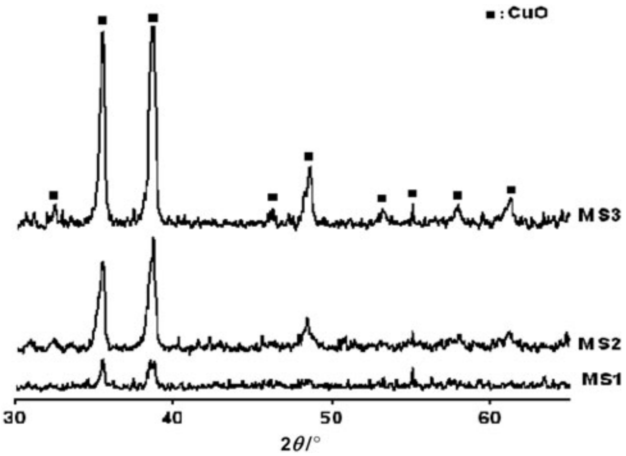


Fig. 4 XRD patterns of CuO microspheres: **a** MS_1, **b** MS_2, **c** MS_3

cutting system which provided an air stream blown around the injecting needle.

Particles obtained by the dripping method were calcined at different temperature [600 °C (MS_1), 700 °C (MS_2), 800 °C (MS_3)]. With respect to particle morphology, the calcination temperature played an important role in the surface characteristics of the microspheres.

Table 1 presents the results of BET tests of the final granulated products. Maximum surface area was shown by MS_1 that was calcined at the lowest temperature.

The XRD patterns of CuO microspheres are shown in Fig. 4. All XRD peaks are indexed to the monoclinic crystal system of CuO. The XRD pattern of the copper oxide microspheres formed at 800 °C shows a relatively sharp peak with the highest intensity as shown in Fig. 4. This is mainly due to the growth of crystallite size.

Scanning electron microscope (SEM) images in Fig. 5a–c show the size and morphology of different microspheres that have undergone different thermal treatments. The size of all microspheres is in the range of 300–500 μm.

Our catalytic strategy was first evaluated by treating benzaldehyde and malononitrile with guanidinum carbonate in water for 15 min at room temperature using catalytic amounts (10 mol%) of CuO microspheres. This reaction successfully afforded the desired 4-amino-5-pyrimidinecarbonitrile in moderate to good yield (78–93%).

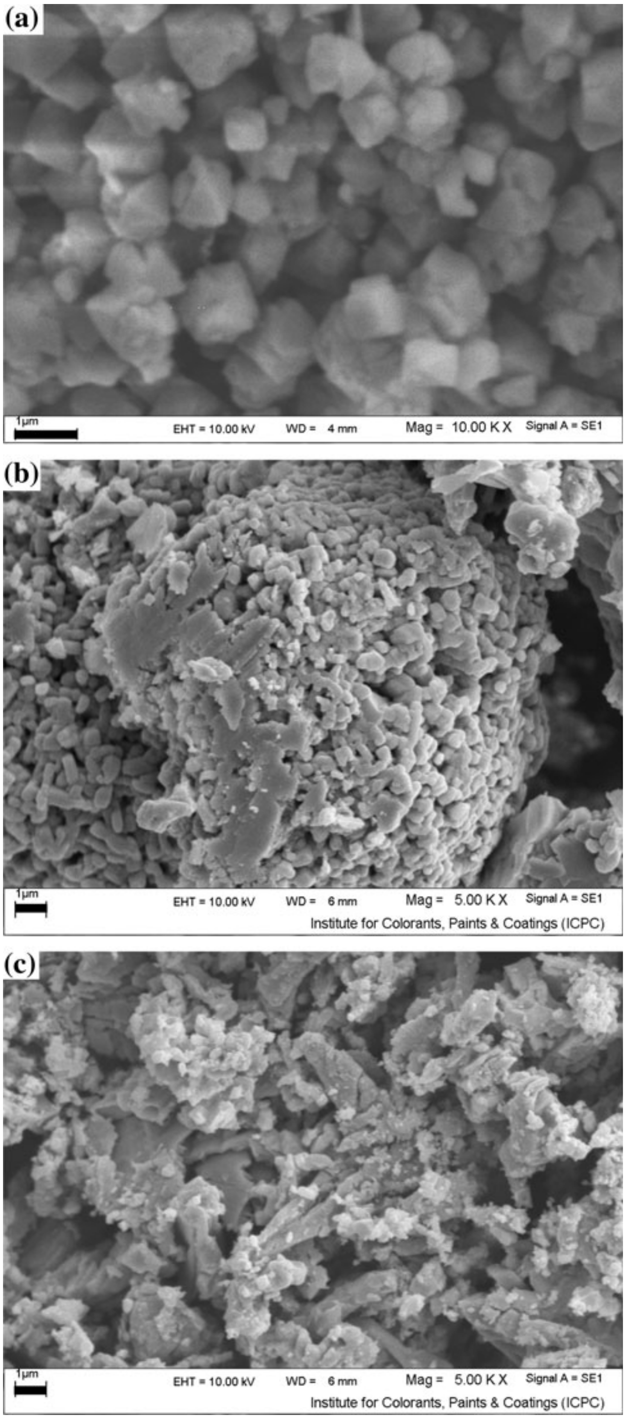


Fig. 5 SEM images of **a** MS_1, **b** MS_2, **c** MS_3 (*scale bar* 1 μm)

The size of CuO plays an important role in terms of yields and reaction times. When the reaction was conducted with bulk CuO, a poor yield of the product was obtained (Table 2).

We compared the catalytic activity of CuO nanoparticles with CuO microspheres (MS_1, MS_2, and MS_3). The highest yield was obtained with CuO nanoparticles and surprisingly CuO microspheres (MS_1) gave comparable yields to CuO

Table 2 Synthesis of 2,4-diamino-6-phenyl-5-pyrimidinecarbonitrile with different copper oxide catalysts

Entry	Catalyst	Time/min	Yield/%
1	CuO bulk	45	59
2	Nano-CuO	15	96
3	MS_1	15	93
4	MS_2	30	84
5	MS_3	30	78

Reaction conditions: benzaldehyde (1 mmol), malononitrile (1 mmol), guanidinum carbonate (1 mmol), and catalyst (10 mol%), H_2O, room temperature

nanoparticles (Table 2). The high surface area of the copper oxides is supposed to be important for the catalytic performance. Granulation of nanoparticles by the immobilization–calcination method reduces the specific surface area from 32.5 to 18.74 $m^2\ g^{-1}$, but the value of surface area is still much larger than that of bulk CuO (0.49 $m^2\ g^{-1}$).

Although it is possible to slightly increase the yield of the reaction by using CuO nanoparticles, the CuO microsphere-catalyzed reaction has the advantages of easy product purification, efficient recycling of the catalyst, and minimization of metal oxide traces in the product. Thus, we chose CuO microspheres (MS_1) as catalyst for this reaction.

To investigate the advantageous role of water as a solvent for this method, comparative reactions were carried out in other solvents. The reaction of benzaldehyde, guanidinum carbonate, and malononitrile was carried out in $CHCl_3$ and CH_2Cl_2 under similar reaction conditions to furnish 2,4-diamino-6-phenyl-5-pyrimidinecarbonitrile (**4b**) in yields of only 48 and 53%, respectively. When the same reaction was carried out in more polar solvents such as tetrahydrofuran (THF), MeCN, and EtOH under otherwise identical conditions, **4b** was obtained in yields of 68, 73, and 78%, respectively (Table 3). It is remarkable that the reaction carried out in water afforded **4b** in excellent yield (93%), which is significantly higher than those obtained for the volatile/toxic/polar organic solvents.

Table 3 Solvent effect for synthesis of 2,4-diamino-6-phenyl-5-pyrimidinecarbonitrile

Entry	Solvent	Time/min	Yield/%
1	CH_2Cl_2	60	53
2	THF	30	68
3	$CHCl_3$	60	48
4	EtOH	30	78
5	MeCN	30	73
6	H_2O	15	93

Reaction conditions: benzaldehyde (1 mmol), malononitrile (1 mmol), guanidinum carbonate (1 mmol), and CuO microspheres (MS_1, 10 mol%), room temperature

The role of water as the reaction medium and its mechanism are still not clear. Recently, it was reported that some organic molecules can react on the surface of water. Often a very strong enhancement of reaction rates was noticed in this case, particularly when at least one component involved in this reaction bore a polar group, enabling some degree of solubility [13].

The generality of this process was demonstrated by the wide range of substituted aldehydes and N-unsubstituted amidines used to synthesize the corresponding products in high to excellent yields (Table 4). The results in Table 4 indicate that aromatic aldehydes bearing different functional groups such as chloro, nitro, methyl, or methoxy were able to undergo the condensation reaction.

A mechanism for the reaction is outlined in Scheme 2. The reaction occurs via initial formation of the cyano olefin **3** from the condensation of aryl aldehyde **1** and malononitrile. The second step is followed by Michael addition, cycloaddition, isomerization, and aromatization of the unstable intermediate via facile aerial oxidation to afford the 4-amino-5-pyrimidinecarbonitriles **4**.

The insolubility of CuO microspheres in different organic solvents and water provided an easy method for their separation from the product. Recycling experiments were performed using the CuO microsphere (MS_1) catalyst for the synthesis of 2,4-diamino-6-phenyl-5-pyrimidinecarbonitrile (**4b**). After each cycle, the catalyst was recovered by simple filtration, washed with deionized water and ethanol, and dried in vacuo. The recovered CuO microspheres were used directly in the next cycle. The recycling results are listed in Table 5 and show that the catalyst was still highly efficient after the fifth cycle.

Finally, the efficiency of the present method for the synthesis of **4b** was compared with other reported procedures (Table 6) [14]. CuO microspheres (MS_1) are therefore an efficient, environmentally benign catalyst in the synthesis of 2,4-diamino-6-phenyl-5-pyrimidinecarbonitrile.

Table 4 Synthesis of 4-amino-5-pyrimidinecarbonitriles **4**

4	R	R′	Yield/%	M.p./°C	Lit. m.p./°C [14]
a	C_6H_5	Ph	98	212–213	212
b	C_6H_5	NH_2	93	229–230	228–230
c	4-MeC_6H_4	Ph	91	208–210	210
d	4-MeC_6H_4	NH_2	96	129–130	130
e	4-ClC_6H_4	Ph	93	221–222	222
f	4-ClC_6H_4	NH_2	98	229–230	229–231
g	4-$MeOC_6H_4$	Ph	82	211–213	213
h	4-BrC_6H_4	Ph	88	234–236	235–238
i	4-$Me_2NC_6H_4$	Ph	86	160–162	162

Reaction conditions: aldehyde **1** (1 mmol), malononitrile (1 mmol), N-unsubstituted amidines **3** (1 mmol), and CuO microspheres (MS_1, 10 mol%), H_2O, room temperature, 15 min

Scheme 2

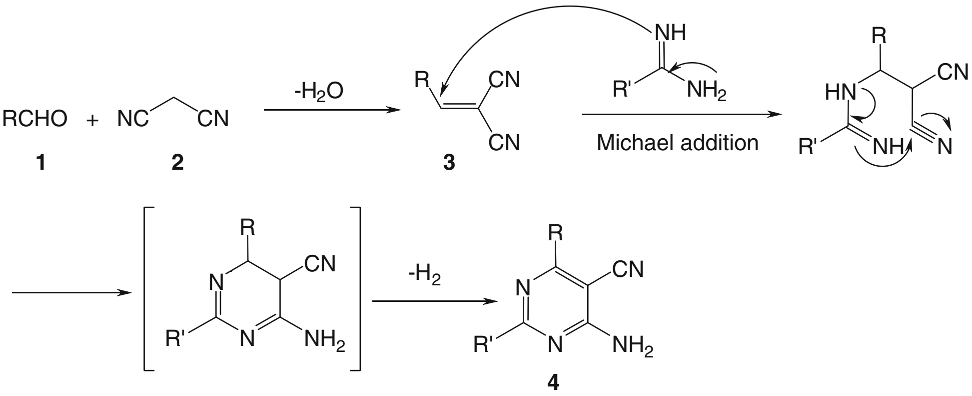


Table 5 Recycling of CuO microspheres

Run	1	2	3	4	5
Time/min	15	15	20	23	27
Yield/%	93	91	86	83	81

In conclusion, we have reported herein several noteworthy features of a new catalyst for the synthesis of 4-amino-5-pyrimidinecarbonitriles through the three-component reaction of malononitrile, aldehydes, and N-unsubstituted amidines using CuO microspheres. This protocol offers many attractive features such as reduced reaction times, higher yields, and economic viability of the catalyst. The reaction proceeds under aqueous conditions and isolation of the catalyst is easily achieved. The catalyst is recoverable and reusable in several runs without loss of catalytic activity. This makes the method an economic, benign, simple, and convenient process for the synthesis of 4-amino-5-pyrimidinecarbonitriles.

Experimental

Batchwise supercritical hydrothermal synthesis of CuO nanoparticles

Copper(II) nitrate trihydrate (Merck AG, for synthesis) was used as the precursor for synthesis of nano copper oxide. Preparation of CuO took place in a stainless steel autoclave that was able to endure a working temperature and pressure of 550 °C and 610 atm. The concentration of $Cu(NO_3)_2$ was 0.05 mol dm^{-3}, and the heating period was about 2 h. Synthesis was carried out at 500 °C to accelerate the hydrolysis reactions and thus shorten the fabrication period. In order to maintain the safety margin, the 200-cm^3 stainless steel autoclave was loaded with only 60–80 cm^3 of the solution.

After removing from the furnace, the autoclave was quenched with cold water and CuO nanoparticles were recovered from the discharged solution by high speed centrifugation at 14,000 rpm for about 60 min. The produced nanoparticles were then washed in the same centrifuge with ultra-pure water three times, and then dried at ambient temperature.

Preparation of granulated CuO microspheres

CuO nanoparticles (2 g) were dispersed in 5 cm^3 deionized water and the mixture was stirred to form an aqueous CuO suspension, and the reaction mixture was exposed to ultrasonic irradiation for 30 min. Then 14 cm^3 of gelatin aqueous solution (sodium alginate, 3.6 wt.%) was added into the above solution, and the mixture was mechanically stirred for 2 h. An alginate–CuO nanoparticle solution was sprayed through a thin inner nozzle (∅ = 0.5 mm) into a

Table 6 Synthesis of **4b** under different reaction conditions [14]

Entry	Method	Catalyst	Solvent	Time/min	Yield/%
1	Microwave-assisted conditions	Sodium acetate	Solvent-free	5	70
2	Microwave-assisted conditions	Without catalyst	Solvent-free	10	52
3	Microwave-assisted conditions	Sodium acetate	Toluene	1.5	74
4	Microwave-assisted conditions	Triethylamine	Toluene	0.5	90
5	Microwave-assisted conditions	Sodium acetate	Water	0.5	73
6	Reflux	Sodium acetate	Water/ethanol (1:1)	360	78
7	Stirring at room temperature	CuO microspheres (MS_1)	Water	15	93

All reactions were carried out under 300-W microwave irradiation

0.1 mol dm^{-3} barium chloride solution with pressured air blown through an outer aperture in the nozzle (Fig. 3). The resultant beads were allowed to stand in the solution for 3 h at room temperature on a magnetic stirrer, and then they were washed with pure water three times and eventually dried at 400 °C for 10 h. The dried microspheres were transferred into a muffle furnace and calcined at 600 °C (MS_1), 700 °C (MS_2), and 800 °C (MS_3) for 6 h to decompose and burn all of the organic material.

Characterization

The crystal structure of the prepared CuO nanoparticles and final microspheres was analyzed by using Cu Kα radiation (Philips PW 1800). The particle size and morphology of the nanocrystalline particles were examined using a transmission electron microscope (TEM, LEO 912AB). In the case of microspheres, a SEM (LEO1 455VP) was used for the same purpose. The surface area of the CuO nanoparticles and the granular microspheres was determined by the nitrogen adsorption BET method (Quantachrome Instruments, Nova 2000e).

General procedure for the preparation of 4-amino-5-pyrimidinecarbonitriles

A mixture of aldehyde **1** (1 mmol), malononitrile (1 mmol), amidine hydrochloride or guanidinum carbonate **3** (1 mmol), and CuO microspheres (0.1 mmol) in 5 cm^3 H_2O was stirred for 15 min, the progress of the reaction being monitored by TLC using *n*-hexane/ethyl acetate (2:3) as eluent. Upon completion of the reaction, the reaction mixture was filtered to isolate the solid product. The solid product was dissolved in chloroform and the catalyst was then removed by simple filtration. After evaporation of the solvent, the products were purified by recrystallization from ethanol.

The spectral data of 4-amino-5-pyrimidinecarbonitriles described in this article agree with those reported in a previously published paper [14].

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