One-Pot-Multicomponent Synthesis of 2,6-Diamino-4-arylpyridine-3,5-dicarbonitrile Derivatives Using Nanomagnetic Fe_3O_4@SiO_2@$ZnCl_2$

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ABSTRACT

Nanomagnetic Fe_3O_4@SiO_2@$ZnCl_2$ was used as a simple, cost-effective, and reusable heterogeneous catalyst for the synthesis of 2,6-diamino-4-arylpyridine-3,5-dicarbonitriles by a one-pot-three-component condensation reaction of malononitrile, ammonium acetate, and aldehydes under solvent-free conditions at 110 °C. Simple and mild reaction conditions, facile preparation of the catalyst, the use of a cheap catalyst and easy workup and isolation are notable features of this method.

***Keywords**: 2,6-diamino-4-arylpyridine-3,5-dicarbonitriles; nano magnetic Fe_3O_4@SiO_2@$ZnCl_2$; green chemistry; multicomponent reaction*

ABSTRAK

Nanomagnetik Fe_3O_4@SiO_2@$ZnCl_2$ digunakan sebagai katalis sederhana, hemat biaya, dan merupakan katalis heterogen yang dapat digunakan kembali untuk sintesis 2,6-diamino-4-arilpiridin-3,5-dikarbonitril melalui reaksi kondensasi tiga komponen one-pot *antara malononitril, amonium asetat, dan aldehida dengan kondisi tanpa pelarut pada temperatur 110 °C. Kondisi reaksi yang sederhana dan ringan, persiapan katalis yang mudah, penggunaan katalis yang murah dan mudah dilakukan serta mudah diisolasi adalah aspek yang penting dari metode ini.*

***Kata Kunci**: 2,6-diamino-4-arilpiridin-3,5-dikarbonitril; nano magnetik Fe_3O_4@SiO_2@$ZnCl_2$; kimia hijau; reaksi multi-komponen*

INTRODUCTION

In recent years, magnetic nanoparticles (MNPs), have proven to be valuable assets in organic chemistry. In this field of research, several studies have been carried out on their biological and technological applications such as drug delivery [1-2], magnetic resonance imaging (MRI) [3], bioseparation [4-5] bimolecular sensors [6-7] and magneto-thermal therapy [8-9]. Recent reports show that magnetic nanoparticles are efficient supports which can facilitate the isolation and recycling of expensive catalysts from the reaction media [10-12].

Construction of functionalized *N*-heterocycles utilizing Multicomponent reaction (MCR) strategy has evolved as a new synthetic tool [13-15]. *N*-containing heterocycles show a vast abundance of numerous natural products and several biologically active pharmaceuticals. Among the all heteroaromatic compounds, polysubstituted pyridines are unrivaled and also considered as “privileged medicinal scaffolds” because they are partial structures of many natural products, pharmaceuticals, and synthetic organic moieties [16-21].

Recently, pyridine-3,5-dicarbonitriles have displayed several applications in medicinal fields. 2,6-Diamino-4-arylpyridine-3,5-dicarbonitrile derivatives present cytotoxic properties against A-549, P-388, HT-29, and MEL-28 tumoral cell lines, the capability of very potent inhibitors of histamine release [22]. Their applications as electrical materials [23], nonlinear optical materials [24], fluorescent liquid crystals [25], and chelating agents in metal-ligand chemistry [26] are considered very important. On the other hand, the 2-aminopyridine structural motif exists in several significant biologically active compounds [27-30].

Preparation of 2,6-diamino-4-arylpyridine-3,5-dicarbonitriles can be carried out by multicomponent reaction of aldehydes, malononitrile, and amines or ammonia [31-35] such as the reaction of amines with a 6-chloro substituent of 2-amino-4-phenyl-pyridine-3,5-dicarbonitrile [36-37], usage of 3-amino-3-ethoxyacrylo nitrile (ethyl 2-cyanoacetimidate) [38-39] and (trimethoxy methyl)benzene [40]. Accordingly, discovery and development of an efficient process to obtain new derivatives of these compounds are still desirable for the

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purposes of drug discovery. However, some of these catalysts suffer from the drawbacks of the perspective of green chemistry such as prolonged reaction times, toxic and corrosive solvent, non-reusable catalyst, unsatisfactory yields, expensive catalysts, and the need to use the microwave or ultrasonic irradiation in some cases. Therefore, it seemed desirable to develop greener and milder methods for the 2,6-diamino-4-arylpyridine-3,5-carbonitrile. Green chemistry approaches are most important due to the reduction in byproducts, a reduction in produced waste, and reduction of energy cost [41-48].

With these precedents in mind, along with the understanding of the 4*H*-thiopyrans formation mechanism through 2-arylpropane-1,1,3,3-tetracarbonitrile intermediates [49], we report the one-pot multicomponent synthesis of 2,6-diamino-3,5-dicarbonitrile pyridine derivatives from reactions of aldehydes (1), malononitrile (2), and ammonium acetate (3) using nanomagnetic Fe_3O_4@SiO_2@$ZnCl_2$ as a catalyst under solvent-free conditions.

EXPERIMENTAL SECTION

Materials

Chemicals (malononitrile, aldehydes, ammonium acetate, $FeCl_3.6H_2O$, $FeCl_2.4H_2O$, NH_3, tetraethyl orthosilicate, $ZnCl_2$, and ethanol) were purchased from Fluka, Merck, and Sigma-Aldrich chemical companies.

Instrumentation

IR spectra were recorded on a Shimadzu 435-U-04 spectrophotometer (KBr pellets). ^{1}H NMR spectra were obtained using a Bruker 300 MHz spectrometer in DMSO-d_6 using TMS as an internal reference. Melting points were determined in open capillary tubes in a Stuart BI Brønstead Electrothermal Cat No: IA9200 apparatus and are uncorrected.

Procedure

General procedure for the preparation of 2,6-diamino-4-arylpyridine-3,5-dicarbonitriles (4a-k)

First, a mixture of aldehyde (1 mmol), ammonium acetate (3 mmol) with malononitrile (1.5 mmol), and nanomagnetic Fe_3O_4@SiO_2@$ZnCl_2$ (0.04 g) was stirred magnetically under solvent-free for an appropriate time as mentioned in Table 2. After completion of the reaction (monitored by TLC), the reaction mixture was diluted with hot ethanol (96%, 3 mL). Next, the nanomagnetic catalyst was separated from the reaction mixture by employing an external magnet. Then, the resulting crude product was poured into crushed ice and the solid product, which separated, was filtered. After that, the catalyst was dried in an oven at 70 °C for 6 h. Recovered catalyst was reused in subsequent reactions. Finally, the solid product was recrystallized from ethanol (96%, 5 mL) to get pure 4a-k derivatives.

Spectroscopic data for representative compounds

2,6-Diamino-4-phenylpyridine-3,5-dicarbonitrile (4a). Yellow solid; m.p. > 300 °C; IR (KBr, *v*, cm^{-1}): 3475, 3425, 3363, 3220, 3158, 2205, 1674, 1624, 1586, 1558, 1540, 1458, 760; ^{1}H-NMR (400 MHz, DMSO-*d6*) δ: 7.55-7.54 (m, 3H), 7.48-7.47 (m, 2H), 7.27 (s, 4H) ppm; ^{13}C-NMR (100 MHz, DMSO-*d6*), δ = 165, 161, 128.6, 128.3, 138, 116,5, 111.4, 79.8 ppm.

2,6-Diamino-4-(4-chlorophenyl)pyridine-3,5-dicarbonitrile (4c). White solid; m.p. >300 °C; IR (KBr, *v*, cm^{-1}): 3478, 3419, 3364, 3173, 2209, 1622, 1573, 1558, 1541, 1453, 1313, 1035, 764; ^{1}H-NMR (400 MHz, DMSO-*d*6) *δ*: 7.65 (m, 1H), 7.55-7.47 (m, 3H), 7.35 (m, 4H) ppm; ^{13}C-NMR (100 MHz, DMSO-*d*6), δ = 165, 160, 138.9, 132.1, 131.4, 130.1, 129.72, 127.7, 115.7, 80.4 ppm.

2,6-Diamino-4-(4-hydroxyphenyl)pyridine-3,5-dicarbonitrile (4d). White solid; m.p. >300 °C; IR (KBr, *v*, cm^{-1}): 3416, 3368, 3166, 2205, 1626, 1565, 1539, 1302, 1173, 841; ^{1}H-NMR (400 MHz, DMSO-*d*6) *δ*: 9.97 (s, 1H), 7.33-7.30 (m, 2H), 7.19 (m, 4H), 6.90-6.88 (m, 2H) ppm; ^{13}C-NMR (100 MHz, DMSO-*d6*), δ = 161.6, 160.2, 159.4, 130.4, 125.9, 117.3, 115.7, 80.1 ppm.

RESULT AND DISCUSSION

In continuation of our efforts to develop new green chemistry methods as well as our interest in applications of heterogeneous-catalyzed organic reactions [50-56], we designed a simple and facile synthesis of 4a-k by a three-component condensation reaction of aromatic aldehydes (1), malononitrile (2), and ammonium acetate (3), and under solvent-free conditions in the presence of nanomagnetic Fe_3O_4@SiO_2@$ZnCl_2$ as a core-shell and heterogeneous reusable nanocatalyst (Fig. 1). Because nanoparticle materials have enormously large and highly reactive surface area, they exhibit unique properties in comparison to bulk materials. For our investigations, nanomagnetic Fe_3O_4@SiO_2@$ZnCl_2$ was prepared according to the literature procedure [57].

To optimize the reaction conditions, the condensation reaction of ammonium acetate (3 mmol), benzaldehyde (1 mmol) and malononitrile (1.5 mmol) were chosen, and different amounts of Fe_3O_4@SiO_2@$ZnCl_2$ as a heterogeneous catalyst in the range room temperature to 120 °C were examined under solvent-free conditions (Table 1). As showed in Table 1, the best results were achieved when the reaction was done in the presence of 0.04 g of the catalyst at 110 °C (Table 1, entry 1). No improvement was seen in the yield

Table 1. Effect of temperature and amount catalyst on the synthesis of 4a

Entry	$Fe_3O_4@SiO_2@ZnCl_2$ (g)	Temp. (°C)	Time (min)	Yield (%)
1	0.04	110	120	86
2	0.04	100	120	80
3	0.04	120	120	87
4	0.03	110	120	82
6	0.05	110	120	87
7	0.04	rt	120	Trace
8	-[a]	100	120	46

[a]In absence of a catalyst

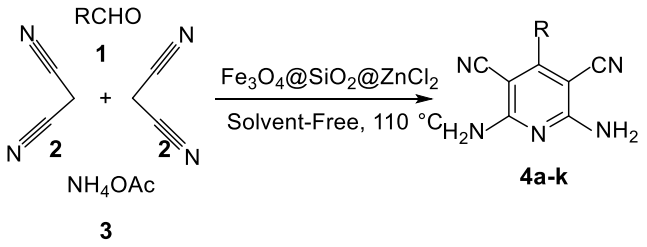


Fig 1. Synthesis of 2,6-diamino-4-arylpyridine-3,5-dicarbonitriles (4a-k) using nanomagnetic $Fe_3O_4@SiO_2@ZnCl_2$

Table 2. One-pot synthesis of 4a-k derivatives using nanomagnetic $Fe_3O_4@SiO_2@ZnCl_2$

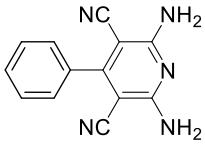
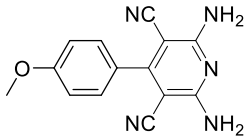
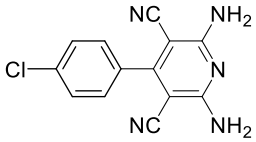
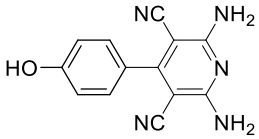
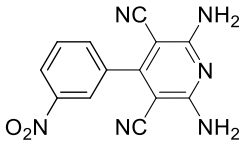
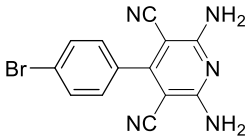
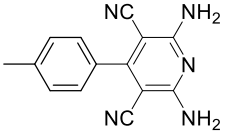
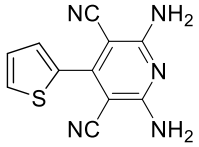
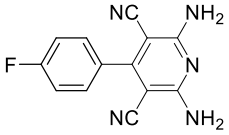
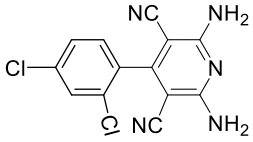
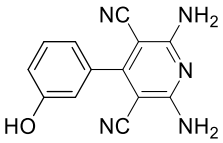
Entry	Products (4a-k)[a]	Time (min)	Yield (%)	Mp °C (Lit.)
4a		120	86	>300[33]
4b		120	88	>300[33]
4c		160	83	>300[33]
4d		160	79	>300[33]
4e		160	82	>300[33]
4f		120	83	>300[33]
4g		120	85	>300[33]
4h		160	84	>300[33]

Table 2. Continued

Entry	Products (4a-k)[a]	Time (min)	Yield (%)	Mp °C (Lit.)
4i		150	85	>300[33]
4j		120	82	>300[33]
4k		160	86	>300[33]

[a]All known products have been reported previously in the literature and were characterized by comparison of IR and NMR spectra with authentic samples.

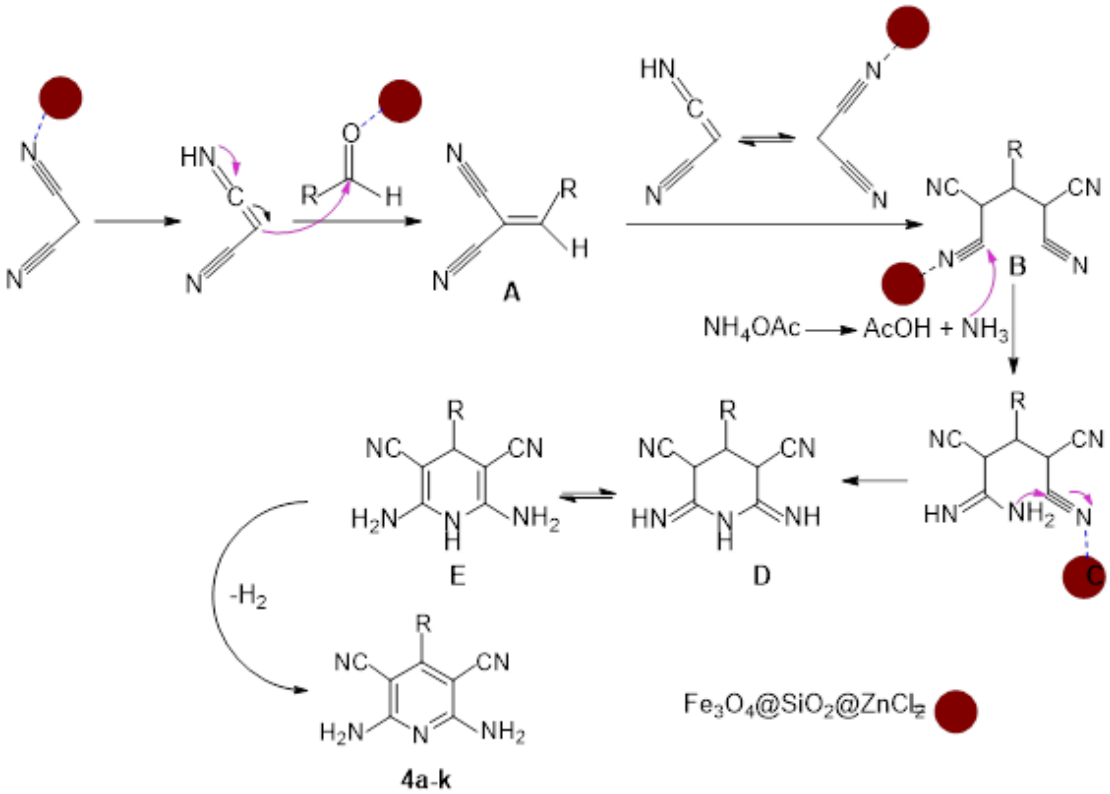


Fig 2. The proposed mechanism for the synthesis of 2,6-diamino-4-arylpyridine-3,5-dicarbonitrile (4a-k)

by increasing the amount of catalyst and temperature (Table 1, entries 6 and 3).

To investigate the efficacy and the generality of the catalyst, different aldehydes were reacted with ammonium acetate and malononitrile under the optimized reaction conditions. The results are presented in Table 2. All reactions proceeded efficiently to give 4a-k in high yields and in short reaction times. The structures of the products were established from their spectral properties (^{1}H-NMR, ^{13}C-NMR, and elemental analysis) and also by comparison with available literature data (see experimental section).

The formation of 2,6-diamino-4-arylpyridine-3,5-dicarbonitriles could be explained by a proposed tentative mechanism (Fig. 2). Our proposed mechanism for the one-pot-three-components synthesis of 2,6-diamino-4-arylpyridine-3,5-dicarbonitriles in the presence of nanomagnetic $Fe_3O_4@SiO_2@ZnCl_2$ consists

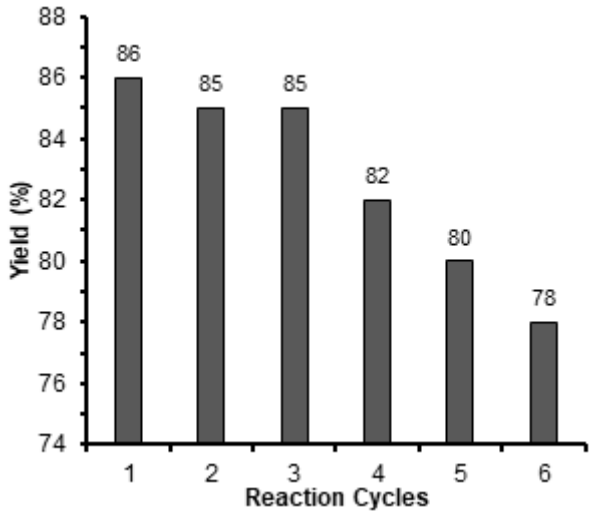


Fig 3. Reusability of nanomagnetic Fe_3O_4@SiO_2@$ZnCl_2$ for the model reaction

of the standard Knoevenagel condensation of aldehyde and malononitrile in the presence of nanomagnetic Fe_3O_4@SiO_2@$ZnCl_2$, which would lead to the formation of arylidene-malononitrile A as an intermediate. Michael-type addition of the malononitrile 2 would provide the adduct B. Then, a nucleophilic attack of ammonium acetate on a cyanide group of B gives the intermediate C. The structure D that is in equilibration with E tautomer would be produced by cycloaddition of C. Consequently, dehydrogenation to yield the product 4a-k would be undergone by this tautomer.

The lifetime of the catalyst and its level of reusability are important factors in practical applications of heterogeneous systems. To simplify this issue, we established a set of experiments using the recycled catalyst for the synthesis of 4a. After the completion of the reaction, the catalyst was dried at 70 °C for 6 h. As shown in Fig. 3, the recovered catalyst was re-used six times to afford 86, 85, 85, 82, 80 and 78% yields for 120 min, respectively, without significant loss of its activity. In addition, the weight of the recovered catalyst is the same as the amount of the fresh catalyst used the first time in the reaction.

CONCLUSION

In conclusion, an efficient protocol for the one-pot synthesis of 4a-k derivatives has been described under thermal solvent-free conditions using inexpensive starting materials. To the best of our knowledge, this new procedure represents the first example of a heterogeneous and reusable nanomagnetic Fe_3o_4@SiO_2@$ZnCl_2$ catalyst for these three-component reactions.

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