Short communication

ZnO Nanoparticles as New and Efficient Catalyst for the One-pot Synthesis of Polyfunctionalized Pyridines

Javad Safaei-Ghomi* and Mohammad Ali Ghasemzadeh

Department of Organic Chemistry, Faculty of Chemistry, University of Kashan, 51167, Kashan, I. R. Iran

** Corresponding author: E-mail: safaei@kashanu.ac.ir*

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Abstract

In this research, an efficient one-pot synthesis of 2-amino-3,5-dicyano-4-phenyl-6-(phenylthio)pyridines has been developed via multi-component reaction of aldehydes, thiols and malononitrile in the presence of ZnO nanoparticles. Polysubstituted pyridines as heterocyclic privileged medicinal scaffolds are prepared via carbon-carbon and carbon-heteroatom bond formation. The present methodology provides a novel and efficient method for the synthesis of pyridine derivatives with some advantages such as short reaction times, excellent yields, recoverability and low catalyst loading.

Keywords: ZnO, highly substituted pyridines, multi-component reactions, heterogeneous catalysis, nanoparticles.

1. Introduction

During the last decades, nanocrystalline metal oxides have received significant attention as efficient catalysts in many organic reactions due to their high surface-to-volume ratio and coordinated parts which provide a larger number of active sites per unit area in comparison with their heterogeneous counter sites. In recent years, ZnO nanoparticles (ZnO NPs) have been of considerable interest because of the role of ZnO in solar cells,[1] catalysts,[2] antibacterial materials,[3] gas sensors,[4] luminescent materials[5] and photocatalysts.[6] ZnO nanoparticles have been used as an efficient heterogeneous catalyst in various organic transformations such as Mannich reaction,[7] and the Knoevenagel condensation reaction,[8] in the synthesis of coumarins,[9] β-phosphono malonates,[10] benzimidazole,[11] β-acetamido ketones/esters,[12] 4-amino-5-pyrimidinecarbonitriles,[13] polyhydroquinoline[14] and 2,3-disubstituted quinalolin-4(1H)-ones.[15]

In recent times, multi-component reactions (MCRs) have become progressively attractive tools for the fast preparation of compound libraries of small molecules.[16,17] A large number of products achieved via MCRs have useful biological, pharmaceutical, or materials properties.[18,19]

The three-component coupling of aldehydes, thiols and malononitrile is one of the best examples of MCRs, and has received great attention in recent years.[20] Because of significant biological and physiological activities, synthesis of pyridines has attracted much attention in recent years.[21–23] Polyfunctionalized pyridine derivatives known as medicinally privileged scaffolds can inhibit MAPK-activated PK-26[24] and modulate androgen receptor functions.[25] Among them, 2-amino-3,5-dicyano-6-sulfanyl pyridine, in particular, serves as žprivileged scaffold' due to its potential therapeutic applications in the treatment of urinary incontinence,[26] HBF infections,[27] Creutzfeldt-Jacob disease, Parkinson's disease, hypoxia/ischemia, asthma, kidney disease, epilepsy and cancer.[28–30] Also 2-amino-3,5-dicyano-4-phenyl-6-(phenylthio)pyridine skeleton is often used as anti-prion,[31] anti-hepatitis B virus and antibacterial agent.[32] Consequently, synthesis of highly functionalized pyridine derivatives, with the aim of developing new drug molecules has been an active area of research. The synthetic routes for the preparation of substituted pyridines mainly involve: the Mannich reaction of iminium salts and aldehydes,[33] conversion of ketene dithioacetals to substituted pyridines,[34] reaction of 3-siloxy-1-aza-1,3-butadiens and 2*H*-1,4- oxazinones with acetylenes,[35] conversion of conjugated oximes under Vilsmeier conditions,[36] cycloisomerization of 3-azadienynes,[37] Vilsmeier-Haack reaction of α-hydroxyketenedithioacetals,[38] the Diels-Alder cycloadditions of oximinosulfonates[39] and other classical methods.[40–42] One of the most attractive routes for the

synthesis of these compounds involves the cyclocondensation of aldehydes, malononitrile and thiols. Generally, this method has been carried out under basic conditions using various bases such as: Et_3N, DABCO, piperidine, morpholine, thiomorpholine, pyrrolidine, *N,N*-DIPEA, pyridine, 2,4,6-collidine, DMAP, aniline, *N*-methylaniline, *N,N*-dimethylaniline and *N,N*-diethylaniline.[20] Furthermore, the preparation of pyridines has been also achieved in the presence of [bmim]OH,[43] KF/alumina,[44] DBU,[45] TBAH,[46] $ZnCl_2$,[47] microporous molecular sieves[48] and boric acid.[49] Moreover, some heterogeneous nanocatalysts such as silica nanoparticles[50] and magnesium oxide nanoparticles[51] have been used in the synthesis of polyfunctionalized pyridine derivatives.

According to the aforementioned importance of nanocatalysts and substituted pyridines as privileged medicinal scaffolds, herein we report a novel, green and mild method for the synthesis of 2-amino-3,5-dicyano-4-phenyl-6-(phenylthio)pyridines via the multi-component coupling reaction in the presence of ZnO nanoparticles.

2. Results and Discussion

To optimize the reaction conditions, the condensation reaction of benzaldehyde, malononitrile and thiophenol was selected as a model study to examine the effects of the catalyst, solvent and reactants for the synthesis of pyridine derivatives (Scheme 1). The model reaction was carried out in the presence of various nanocatalysts such as Fe_3O_4, Mn_3O_4, MgO, SiO_2 and ZnO using 30 mol% of each catalyst separately. The results shown in Table 1 indicated that the best result was obtained when we used zinc oxide nanoparticles as the catalyst for this condensation reaction. The use of 20 mol% of this catalyst was sufficient to progress the reaction and an increase in the amount of the catalyst did not change the yield and the reaction time.

Table 2 shows that, the solvent has a great effect on the accelerating of the reaction. The best results (90% yield) were obtained in ethanol at reflux for these multicomponent reaction (Table 2, entry 5).

Table 1: Preparation of 2-amino-4-phenyl-6-(phenylsulfanyl)-3,5-pyridinedicarbonitrile(**4a**) with different nano-catalysts.[a]

Entrry	Catalyst	Time (min)	Yields(%)[b]
1	Fe_3O_4	130	40
2	Mn_3O_4	160	35
3	MgO	120	70
4	SiO_2	150	75
5	ZnO	90	90

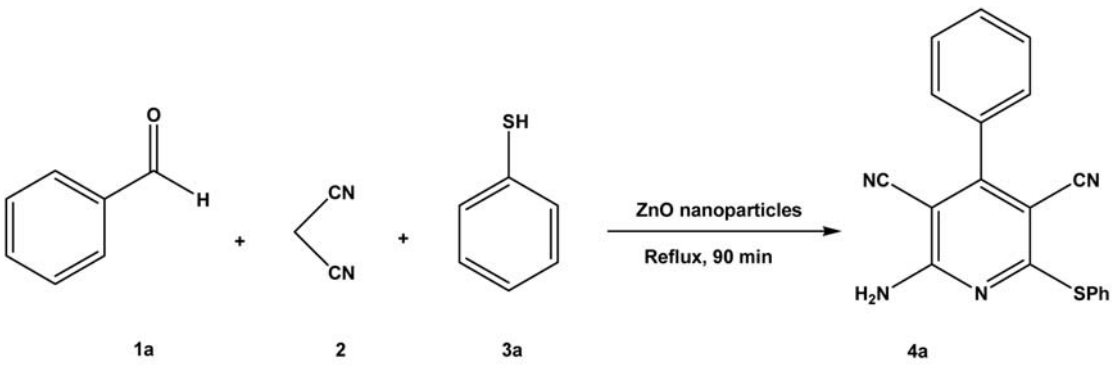
[a] 1mmol of benzaldehyde, 2.2 mmol of malononitrile and 1 mmol of thiophenol in ethanol under reflux conditions. [b] Isolated yields.

Table 2. The model reaction was carried out in various solvents [a]

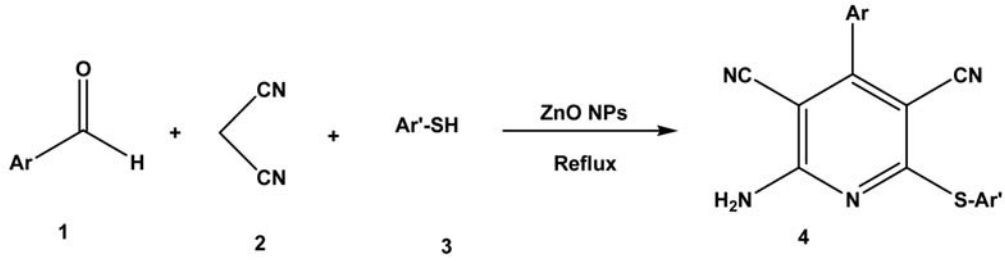
Entry	Solvent	Time (min)	Yield (%)[b]
1	Toluene	220	40
2	Acetonitrile	160	55
3	DMF	130	60
4	Water	140	50
5	Ethanol	90	90

[a] Reflux conditions. [b] Isolated yields.

In order to optimize the ratio of reactants, the model reaction was carried out several times in the presence of zinc oxide nanoparticles. The best results were obtained when benzaldehyde, malononitrile and thiophenol were employed as substrates in a 1:2.2:1 molar ratio. To study the scope of this reaction, we next utilized various aldehydes and thiols in three-component reactions under the optimal conditions (Scheme 2 and Table 3). The data of Table 3 show that aryl aldehydes with electron-withdrawing group such as NO_2, CN, Cl and Br react with malononotrile very smoothly to produce 2-amino-3,5-dicyano-4-phenyl-6-(phenylthio)pyridines in relatively short reaction times. In addition, sterically hindered aldehydes reacted more slowly in comparison with unhindered aldehydes.



Scheme 1. The model reaction for the preparation of highly substituted pyridines.



Scheme 2. Synthesis of polyfunctionalized pyridine derivatives using ZnO nanoparticles.

Table 3. One-pot synthesis of pyridines catalyzed with ZnO nanoparticles.

Entry	Ar	Ar'	Product	Time (min)	Yield (%)	m.p. (°C)	Lit. m.p (°C)
1	Ph	Ph	4a	90	90	218–220	(220–221)[45]
2	*m*-MeC_6H_4	Ph	4b	120	82	277–279	(278–280)[45]
3	*p*-MeC_6H_4	Ph	4c	140	92	208–210	(206–207)[48]
4	*m*-OHC_6H_4	Ph	4d	130	84	265–267	–
5	*p*-OHC_6H_4	Ph	4e	145	82	314–316	(315–317)[48]
6	*p*-$OMeC_6H_4$	Ph	4f	150	94	240–242	(241–244)[45]
7	*m*-$NO_2C_6H_4$	Ph	4g	110	75	218–220	(219–220)[45]
8	*p*-$NO_2C_6H_4$	Ph	4h	85	78	288–290	(289–290)[48]
9	*p*-ClC_6H_4	Ph	4i	80	85	221–223	(221–222)[48]
10	*p*-BrC_6H_4	Ph	4j	90	82	254–256	(255–257)[45]
11	Ph	*p*-MeC_6H_4	4k	110	84	248–250	(246–249)[51]
12	*p*-MeC_6H_4	*p*-MeC_6H_4	4l	115	85	222–224	–
13	*p*-$OMeC_6H_4$	*p*-MeC_6H_4	4m	130	90	229–231	(230–233)[51]
14	*p*-$NO_2C_6H_4$	*p*-MeC_6H_4	4n	80	75	301–303	–
15	*p*-CNC_6H_4	*p*-MeC_6H_4	4o	95	80	272–274	–

3. Experimental

3. 1. General

Chemicals were purchased from the Sigma-Aldrich and Merck and were used without further purification. All of the materials were of commercial reagent grade and were used without further purification. Zinc oxide nanoparticles were prepared according to the procedure reported by Shen et al.[52] All melting points are uncorrected and were determined in capillary tubes on Boetius melting point microscope. ^1H and ^{13}C NMR spectra were obtained on Bruker 400 MHz spectrometer with $CDCl_3$ as solvent using tetramethylsilane (TMS) as an internal standard. Chemical shift values are in δ. FT-IR spectrum was recorded on Magna-IR, Nicolet 550 spectrometer in KBr pellets in the range of 400–4000 cm^{-1}. The elemental analyses (C, H, N) were obtained from a Carlo ERBA Model EA 1108 analyzer. Powder X-ray diffraction (XRD) was carried out on a Philips diffractometer of X'pert Company with monochromatized Cu Kα radiation (λ = 1.5406 Å). Microscopic morphology of products was visualized by SEM (LEO 1455VP). The mass spectra were recorded on a Joel D-30 instrument at an ionization potential of 70 eV. The compositional analysis was done by energy dispersive analysis of X-ray (EDAX, Kevex, Delta Class I).

3. 2. Preparation of Zinc Oxide Nanoparticles

In a typical procedure zinc acetate (9.10 g, 0.05 mol) and oxalic acid (5.4 g, 0.06 mol) were combined by grinding in an agate mortar for 1h at room temperature. Afterwards, the prepared ZnC_2O_4 $2H_2O$ nanoparticles were calcinated at 450 C for 30 min to produce 3.2 g of ZnO nanoparticles under thermal decomposition conditions. The prepared ZnO NPs have been structurally characterized by SEM, XRD and EDAX analysis.

3. 3. Catalyst Recovery

After completion of the reaction, the mixture was centrifuged and the ZnO NPs catalyst was filtered. Nanoparticles were then washed three to four times with dichloromethane and methanol and dried at 150 C for 4 h. The recovered catalyst was used for five times with a slightly decreased activity (Figure 1).

In order to study the morphology and particle size of ZnO nanoparticles, SEM image of ZnO nanoparticles was performed (Figure 2). These results show that spherical ZnO NPs were obtained from $Zn(CH_3COO)_2$ and $H_2C_2O_4$ $2H_2O$ with particle size between 20–30 nm under solvent-free conditions.

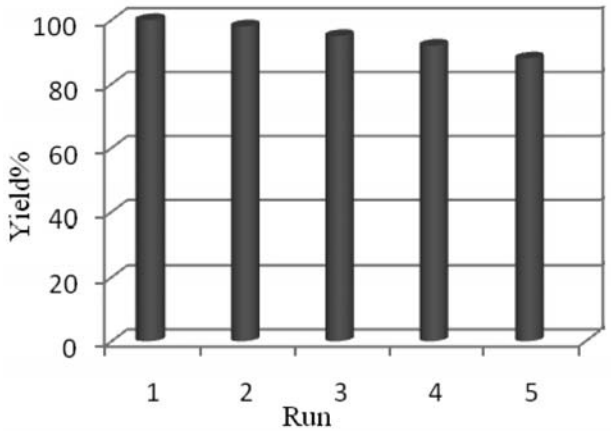


Figure 1. Recoverability of ZnO nanoparticles.

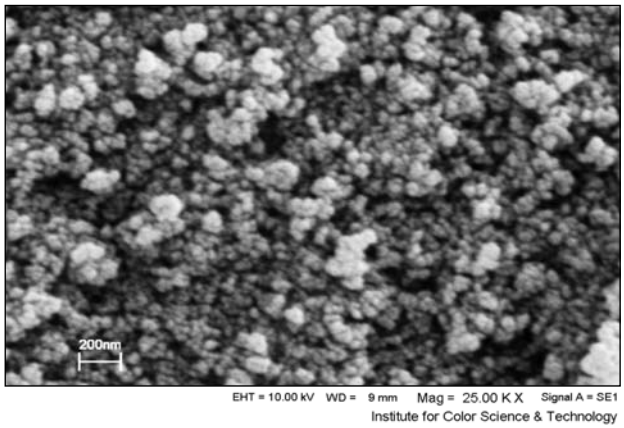


Figure 2. SEM images of ZnO nanoparticles.

The XRD pattern of ZnO nanoparticles was shown in Figure 3. All reflection peaks can be easily indexed to pure hexagonal phase of ZnO with P63mc group (JCDPS No. 36-1451). The crystallite size diameter (D) of the Zn-O nanoparticles has been calculated by Debye–Scherrer equation ($D = K\lambda/\beta\cos\theta$), where β FWHM (full-width at half-maximum or half-width) is in radian and θ is the position of the maximum of diffraction peak, K is the so-called shape factor, which usually takes a value of about 0.9, and k is the X-ray wavelength (1.5406 Å for Cu Kα). Crystallite size of ZnO has been found to be 24 nm.

The chemical purity of the samples as well as their stoichiometry was tested by EDAX studies. The EDAX spectra show the presence of zinc and oxygen as the only elementary components (Figure 4).

3. 4. Typical Procedure for the Synthesis of 2-amino-3,5-dicyano-4-phenyl-6-(phenylthio)pyridines (4a-o)

ZnO nanoparticles (0.015 gr, 0.2 mmol, 20 mmol%) was added to a mixture of aldehyde (1mmol) and malono-

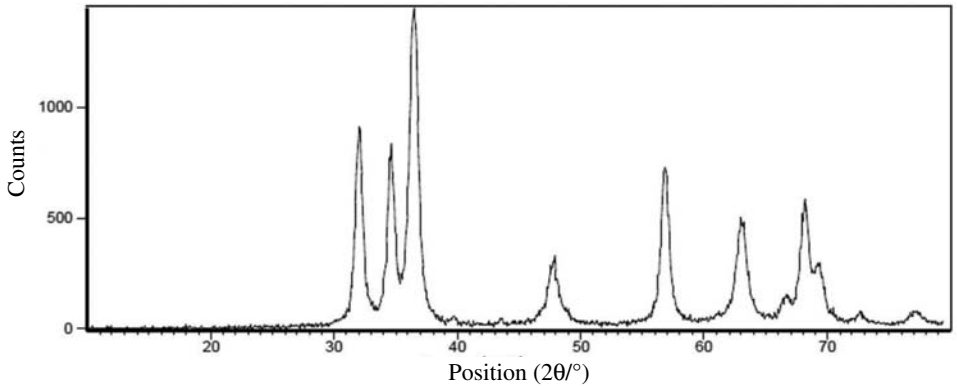


Figure 3. The XRD pattern of ZnO nanoparticles.

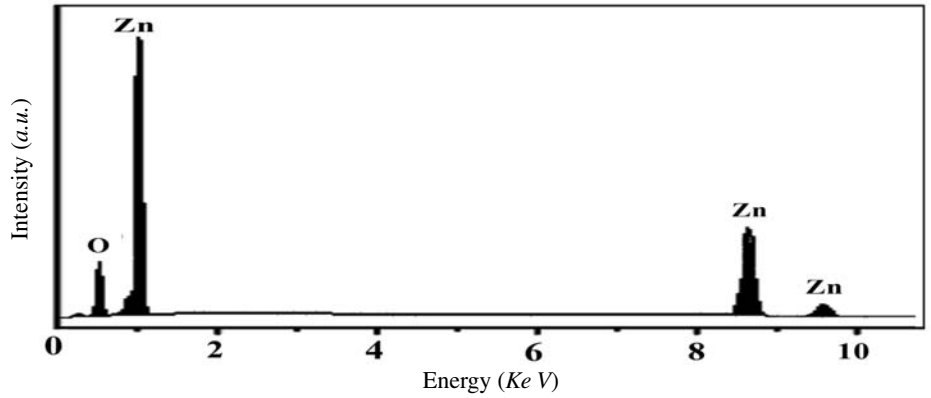


Figure 4. EDAX spectrum of ZnO nanoparticles.

nitrile (2.2 mmol) in 5 ml ethanol and the reaction mixture was stirred for 10 min at 50 °C. Afterwards the desired thiol (1 mmol) was added to the solution and refluxed. Progress of the reaction was continuously monitored by TLC. After the reaction completion, the mixture was cooled to the room temperature and centrifuged to separate the catalyst. The solvent was evaporated under vacuum and the solid obtained was recrystallized from ethanol to afford the pure pyridines. Spectral data of the new products are given below.

2-Amino-4-(3-hydroxyphenyl)-6-(phenylthio)pyridine-3,5-dicarbonitrile (4d).

White solid; mp 265–267 C; IR (KBr) *v* 3445, 3366, 3211, 2213, 1622, 1575, 1536, 1483, 1255 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 5.42 (s, 2H, NH_2), 7.05 (s, 1H, Ar-H), 7.23–7.25 (m, 3H, Ar-H), 7.48–7.53 (m, 3H, Ar-H), 7.57–7.59 (m, 2H, Ar-H), 10.51 (bs, 1H, OH); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 87.8, 94.2, 113.1, 115.3, 127.2, 129.1, 129.8, 130.7, 132.1,133.5, 134.1, 135.8, 136.6, 157.1, 161.8, 164.5, 168.2; MS (EI) (*m/z*) 344 (M^+). Anal. Calcd. for $C_{19}H_{12}N_4OS$: C 66.26, H 3.51, N 16.27; Found C 66.52, H 3.42, N 16.08.

2-Amino-4-(p-tolyl)-6-(p-tolylthio)pyridine-3,5-dicarbonitrile (4l).

Colorless solid; mp 222–224 C; IR (KBr) *v* 3442, 3357, 3198, 2211, 1616, 1572, 1533, 1481, 1252 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 2.11 (s, 3H, CH_3), 2.41 (s, 3H, CH_3), 5.44 (s, 2H, NH_2), 7.25–7.36 (m, 4H, Ar-H), 7.41–7.59 (m, 4H, Ar-H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 15.7, 17.1, 86.1, 96.3, 114.2, 115.5, 126.6, 129.1, 129.2, 129.7, 131.4, 134.6, 135.2, 136.1, 156.2, 158.9, 167.6; MS (EI) (*m/z*) 356 (M^+). Anal. Calcd. for $C_{21}H_{16}N_4S$: C 70.76, H 4.52, N 15.72; Found C 70.52, H 4.65, N 15.84.

2-Amino-4-(4-nitrophenyl)-6-(p-tolylthio)pyridine-3,5-dicarbonitrile (4n).

Yellow solid; mp 301–303 C; IR (KBr) *v* 3472, 3332, 3218, 2215, 1626, 1541, 1509, 1344, 1262 cm^{-1} ; ^1H NMR ($CDCl_3$, 400 MHz) δ 2.40 (s, 3H, CH_3), 5.50 (s, 2H, NH_2), 7.26–7.28 (d, *J* = 7.6, 2H , Ar-H), 7.43–7.45 (d, *J* = 7.8, 2H, Ar-H), 7.66–7.68 (d, *J* = 7.6, 2H , Ar-H), 8.39–8.41 (d, *J* = 7.8, 2H , Ar-H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 18.9, 86.8, 96.2, 115.1, 116.9, 125.3, 131.3, 132.9, 134.1, 134.9, 135.5, 136.2, 137.3, 156.1, 158.2, 165.1; MS (EI) (*m/z*) 387 (M^+). Anal. Calcd. for $C_{20}H_{13}N_5O_2S$: C 62.01, H 3.38, N 18.08; Found C 61.85, H 3.26, N 18.16.

2-Amino-4-(4-cyanophenyl)-6-(p-tolylthio)pyridine-3,5-dicarbonitrile (4o).

White solid; mp 272–274 C; IR (KBr) *v* 3479, 3352, 3215, 2218, 1634, 1551, 1498, 1256 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 2.41 (s, 3H, CH_3), 5.50 (s, 2H, NH_2), 7.28–7.30 (d, *J* = 7.8, 2H, Ar-H), 7.37–7.51 (m, 4H, Ar-H), 7.71–7.73 (d, *J* = 7.8, 2H, Ar-H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 87.2, 94.5, 114.9, 115.8, 128.1, 130.5, 131.5, 133.8, 134.1, 134.4, 135.7, 136.5, 155.4, 156.3, 165.1; MS (EI) (*m/z*) 367 (M^+). Anal. Calcd. for $C_{21}H_{13}N_5S$: C 68.65, H 3.57, N 19.06; Found C 68.78, H 3.44, N 18.95.

4. Conclusions

The present protocol represents a simple, efficient and economic method for the three-component reaction of aldehydes, thiols and malononitrile in order to prepare polyfunctionalized pyridine derivatives in the presence of ZnO nanoparticles as a novel, efficient and reusable catalyst in green media. The products were obtained in excellent yields within significantly reduced reaction time.

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6. References

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Povzetek

Avtorji v prispevku poročajo o razvoju učinkovite enostopenjske sinteze 2-amino-3,5-diciano-4-fenil-6-(feniltio)piridinov s pomočjo večkomponentne reakcije med aldehidi, tioli in malononitrilom v prisotnosti ZnO nanodelcev. Na ta način so s tvorbo vezi ogljik-ogljik in ogljik-heteroatom pripravili vrsto poli-substituiranih piridinov, ki so osnova mnogim medicinsko pomembnim spojinam. Predstavljena metodologija uvaja novo in učinkovito metodo za sintezo derivatov piridina z majhno količino lahko obnovljivega katalizatorja, kratkim reakcijskim časom in dobrim izkoristkom.