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An Efficient NiO-ZrO_2 Catalyzed One-Pot Synthesis of Pentasubstitutedthiopyridines

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Abstract: Here we report aNiO-ZrO_2catalyzed one pot cyclocondensation, performed at room temperature in ethanol for obtaining high yields of polyfunctionalized pyridines, 2-amino-4-aryl-3,5-dicyano-6-phenylthiopyridines. The developed protocol obeys certain green principles and is scalable and cost effective. The method offered several advantages, such as operational simplicity, easy work-up procedure, shorter reaction time, and high yields of the products (82–93%). This protocol is user-friendly and could be an attractive tool for the synthesis of highly functionalized bioactive 2-amino-4-aryl-3,5-dicyano-6-phenyl thiopyridines.

Keywords: 2-Amino-4-aryl-3,5-dicyano-6-phenylthiopyridines; NiO-ZrO_2; multi component reaction

I. Introduction

Nickel oxide (NiO) is an significant inorganic material having applications in solar cells, capacitors and rechargeable lithium ion batteries [1-4]. Nickel nanoparticles are significant for catalysis [5]. Zirconium oxide (ZrO2) is an important transition metal oxide which shows promising optical and electrical properties [6] and has several applications in catalysts, coatings, fuel cells and sensors [7-10].

Heterocycles exhibit significant diverse medicinal properties. Among the nitrogen heterocycles, [8] functionalized pyridines, isolated from nature and syntheses are found to display wide range of therapeutic activities. [9–18] They are systematically reviewed by Khan et al.[19]Taking into consideration the various applications in the field of medicinal and supramolecular chemistry, attempts are found to be directed on designing and development of novel methodologies for synthesis of polyfunctionalized pyridines. First time Evdokimov et al.[20] have reported one pot cyclo condensation of aldehydes, thiophenol, and malononitrile, using Et3N or1,4-diazabicyclo[2.2.2]octane (DABCO) as a catalyst and obtained 20–48% yield of2-amino-3,5-dicyano-6-sulfanyl pyridines along with by-products (enaminonitriles). These are the main limitations of this method.

Prompted by the above observations and in continuation of our earlier interest inbiocatalysis[21–25] here in the present work, an alternative NiO-ZrO_2catalyzed protocol has been developed by optimizing the reaction conditions for getting enhanced yields of the titled products using scalable conditions.

II. Experimental Section

General experimental procedure for the synthesis of 2-amino-4-aryl-3,5-dicyano-6- phenyl thiopyridines (4a–j)

NiO-ZrO_2(1 g) was added in ethanol (15 mL) and mass was sonicated at 35 kHz at RT for 30 min. To this then aryl aldehydes (9.4 mmol), Malanonitrile (18.8 mmol), Thiophenol (9.4 mmol), were added. Then the reaction mass was stirred at room temperature. The progress of the reaction was monitored by thin layer chromatography using ethyl acetate: pet ether (2:8) as eluent. After 45 min, ethyl acetate (30 mL) was added to the reaction mass. Then the reaction mixture was filtered through the bed of celite (1 g). From the filtrate, the solvents were removed under reduced pressure and the crude solid product isolated was crystallized from ethanol. The melting points and the yields of the derivatives are recorded in Table 2. Melting points and spectral data of the 2-amino-4-aryl-3,5-dicyano-6-phenyl-thiopyridines (4a–j) are in good agreement with those reported in the literature. [26]

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2-Amino-4-(4-chlorophenyl)-6-phenylsulfanylpyridine-3,5-dicarbonitrile (4f)

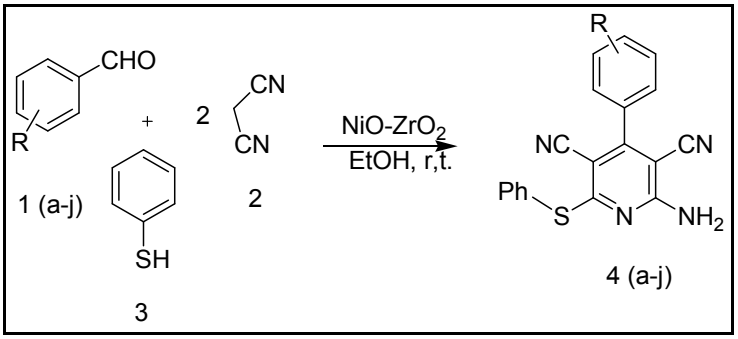
^{1}H NMR (300 MHz, $CDCl_3$) δ ppm: 5.53 (s, 2H, NH2), 7.26 (s, 2H, Ar-H), 7.42–7.58 (m,5H, Ar-H); ^{13}C NMR (75 MHz, $CDCl_3$) δ ppm = 87.39, 115.23, 114.80, 127.22, 129.69,129.59, 130.10, 130.24, 131.73, 136.01, 137.66, 157.34, 159.47, 169.58; HRMS (ESI+): Anal.Calcd. for $C_{19}H_{11}ClN_4S$ $[M+H]^+$: 363 · 0426; Found: 363 · 0464.

III. Results and Discussion

One-pot multicomponent cyclocondensation protocol has been developed for 2-amino-4- aryl 3,5-dicyano-6-phenyl thiopyridines (4a–j) by performing cyclocondensation of aryl aldehydes, (1a–j) malononitrile (2), and thiophenol (3) in ethanol in presence of using NiO-ZrO_2(Scheme 1). To set the best experimental conditions, the cyclocondensation of 4-chlorobenzaldehyde (1a), malononitrile (2), and thiophenol (3) has been practiced as a standard model reaction. To screen the suitable medium, we performed the model reaction in different solvents, viz. water, ethanol, methanol, acetonitrile, N,N-dimethyl formamide and dichloromethane in the presence of NiO-ZrO_2under identical conditions.

The performance of these solvents are recorded in Table 1. It seems that aprotic organic solvents viz. dichloromethane, and acetonitrile when used to perform model reaction yield of the titled pyridine is moderate. Protic solvents viz. methanol, H2O, and EtOH are found to be relatively accelerating rates and hence yield of the product. Ethanol was found to be better solventand gave high yield of 2-amino-4-aryl-3,5-dicyano-6-phenylthiopyridine (4a). Hence, ethanol was selected as a solvent for this cyclocondensation.

To optimize the amount of NiO-ZrO_2, required for accelerating the cyclocondensation the above standard reaction was performed in ethanol at RT by varying amount of baker yeast from o to 1 g for 9.4 mmol of benzaldehyde, 18.8 mmol of malononitrile, and 9.4 mmol of thiophenol. It was found that when 1 g of NiO-$ZrO_2$was incorporated, while performing the above cyclocondensation it gave better yield of(4a) within 40 min at RT.



Scheme 1: Synthesis of 2-amino 4-aryl-3,5-dicyano-6-phenyl thiopyridines (4a–j).

Then using the above optimized conditions, cyclocondensation of various aryl aldehydes (1b–j), malononitrile (2), and thiophenol (3) using NiO-ZrO_2at room temperature has been performed and obtained substituted 2-amino-4-aryl-3,5-dicyano-6-phenylthiopyridines (4b–j) with better to excellent yields.

Table 1: Screening of reaction media for the synthesis of compound (4a)

Entry	Solvent	Yield (%)
1	Ethanol	93
2	DCM	68
3	MeOH	70
4	MeOH:H_2O	69
5	CH_3CN	65
6	H_2O	58

Reaction conditions: benzaldehyde (9.4 mmol), malanonitrile (18.8 mmol), thiophenol (9.4 mmol), NiO-ZrO_2(1 g), solvent (15 ml), and stirred for 40 min at RT.

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Table 2: Physical data of 2-amino-4-aryl-3,5-dicyano 6-phenyl thiopyridines

Entry	Compound	R	Yield (%)[a]	MP (°C)[b]
1	4a	-H	93	216-218
2	4b	2-NO_2	92	288-290
3	4c	4-F	90	235-236
4	4d	4-OMe	93	272-274
5	4e	4-OH	85	265-266
6	4f	4-Cl	87	230-232
7	4g	4-NMe_2	82	168-170
8	4h	4-Br	84	212-213
9	4i	3,4-$(OMe)_2$	90	226-228
10	4j	4-Me	82	208-210

Reaction conditions: Benzaldehydes (9.4 mmol), malanonitrile (18.8 mmol), thiophenol (9.4 mmol), NiO-ZrO_2(1 g), ethanol (15 mL), stirred at RT for 40 min.

[a]Isolated yields.

[b]Melting points are in good agreement with those reported in the literature. [26]

Under optimized condition when standard reaction was performed in the absence of NiO-ZrO_2, keeping stirring more than 24 h at RT there was negligible conversion of reactants to product (4a). Hence it seems that NiO-$ZrO_2$is displaying its role as a catalyst.

IV. Conclusion

An efficient, cost effective, and environmentally friendly protocol has been developed for the synthesis of 2-amino-4-aryl-3,5-dicyano-6-phenyl thiopyridines (4a–j) for the first time by using catalyst, NiO-ZrO_2. The method offered several advantages, such as operational simplicity, easy work-up procedure, shorter reaction time, and high yields of the products (82–93%). This protocol is user-friendly and could be an attractive tool for the synthesis of highly functionalized bioactive 2-amino-4-aryl-3,5-dicyano-6-phenyl thiopyridines.

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