

SHORT COMMUNICATION

NANO-TiO₂ AS A NOVEL AND EFFICIENT CATALYST FOR THE SYNTHESIS OF PYRIDINE DICARBONITRILES

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ABSTRACT. Pyridine dicarbonitriles have been synthesized in good yields via a one-pot multi-component reaction of aldehyde, malononitrile, and thiol in the presence of nano-TiO₂ as a catalyst in ethanol.

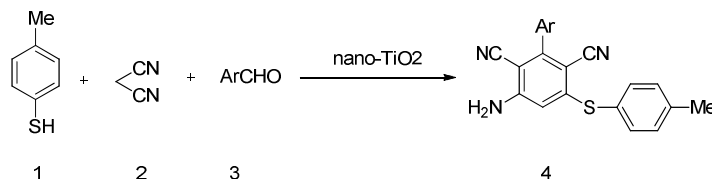
KEY WORDS: Pyridine dicarbonitriles, Multi-component reaction, One-pot, Nano-TiO₂

INTRODUCTION

In recent years, multicomponent reactions (MCRs) have become important tools in modern preparative synthetic chemistry because these reactions increase the efficiency by combining several operational steps without any isolation of intermediates or change of the conditions [1, 2] and MCRs have recently emerged as valuable tools in the preparation of structurally diverse chemical libraries of drug-like heterocyclic compounds [3-5].

The pyridine nucleus is of considerable interest as this ring is the key constituent in a range of bioactive compounds, both naturally occurring and synthetic, and often of considerable complexity [6]. The pyridine dicarbonitrile substructure was therefore chosen as a basic structural scaffold for the design of a reaction-based library [7]. Thus, the synthesis of highly substituted pyridines has attracted much attention, and a number of procedures have been developed using a variety of protocols, such as hetero-Diels-Alder reaction of 3-siloxy-1-aza-1,3-butadienes with electron-deficient acetylenes [8], three-component condensation of aldehyde, malononitrile, and thiol [9], ruthenium-catalyzed cycloisomerization of 3-azadienynes [10], Mannich reaction of aldehydes and iminium salts [11] and Vilsmeier-Haack reaction of R-hydroxyketenedithioacetals [12]. Among these, one of the very convenient approaches which attracted our attention is the three-component condensation of aldehyde, malononitrile, and thiol to the highly substituted pyridines developed by Evdokimov *et al.* [9]. Herein, we report a mild, practical and highly efficient procedure for the preparation of the title compounds using nano-TiO₂ catalyst at room temperature (Scheme 1).

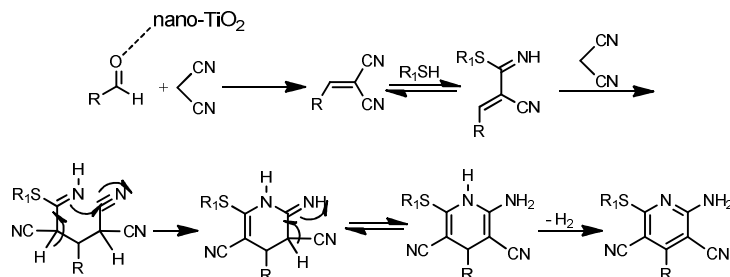
To the best of our knowledge there are no reports on the synthesis of these compounds with 4-methyl thiophenol using nano-TiO₂ as the catalyst.



Scheme 1. Synthesis of pyridine dicarbonitriles.

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A plausible mechanism for this reaction is suggested in Scheme 2.



Scheme 2. Mechanism for the synthesis of pyridine dicarbonitriles.

RESULT AND DISCUSSION

It is known that the specific surface area and surface-to-volume ratio increase dramatically as the size of a material decreases. The high surface area brought about by nanoparticle size is beneficial to many TiO_2 -based devices, as it facilitates reaction/interaction between the devices and the interacting media [13]. TiO_2 nanoparticle has been widely investigated in the past decades due to its multiple potential catalytic activity for esterification [14], degradation of methyl parathion [15], photodecomposition of methylene-blue [16], rhodamine B degradation [17], synthesis of β -acetamido ketones [18], 2-alkylbenzimidazoles and indazole [19], β -amino ketones [20], bis(indolyl)methanes [21], 2-indolyl-1-nitroalkane [22], selective oxidation of sulfides [23], Friedel–Crafts alkylation of indoles [24] and photocatalytic synthesis of quinaldines [25].

The investigation on nano- TiO_2 catalytic activity for the synthesis of many organic molecules is current work in our laboratory. The dimensions of applied TiO_2 nanoparticles were determined with SEM and are 38 nm (Figure 1).

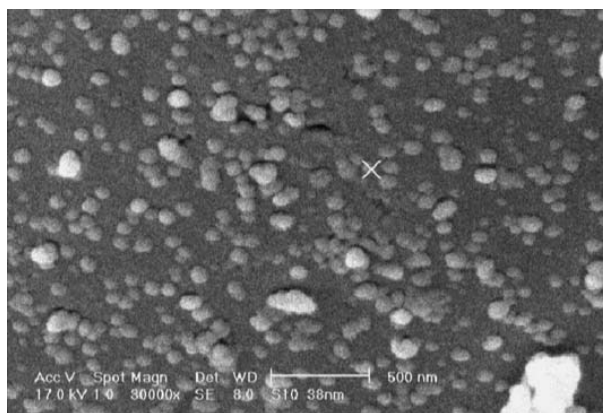


Figure 1. SEM photograph of nano- TiO_2 .

In connection with our recent interested aimed at the development of efficient protocols for the preparation of biologically active heterocycles [26-29], herein, we selected nano-TiO₂ as a new catalyst to synthesise of pyridine dicarbonitriles. The reaction of various aldehydes, 4-methyl thiophenol, malononitrile in the presence of nano-TiO₂ in ethanol afforded pyridine dicarbonitriles at room temperature in good yields (Table 1). We performed the effect of various solvents on the synthesis of **4a**. This reaction was carried out in various solvents and the best results in terms of yield and time obtained in ethanol (Table 2).

Table 1. Synthesis of pyridine dicarbonitriles with deifferent aldehydes

Entry	Ar	Product	Yield (%) ^a
1	C ₆ H ₅	4a	82
2	4-Cl-C ₆ H ₄	4b	87
3	3-Cl-C ₆ H ₄	4c	85
4	4-Br-C ₆ H ₄	4d	83
5	3-Br-C ₆ H ₄	4e	83
6	3-NO ₂ -C ₆ H ₄	4f	81
7	4-NO ₂ -C ₆ H ₄	4g	82
8	4-CH ₃ O-C ₆ H ₄	4h	85

^aYields were analyzed by GC.

Table 2. Synthesis of **4a** in the presence of different solvents using Nano-TiO₂ as a catalyst.

Entry	Solvent	Yield (%) ^a
1	THF	68
2	CH ₃ OH	72
3	CH ₃ CN	76
4	CHCl ₃	71
5	C ₂ H ₅ OH	82

^aYields were analyzed by GC.

In each reaction, the yield is a function of the reaction time and the best time for all reactions was completed after 1 h. The reactions proceeded well with 5 mol% of catalyst and use of an increased amount of catalyst does not make much difference. In order to show the merit of the present work, we compared the result of the synthesis of these compounds in the presence of various catalysts but the best results obtained with nano-TiO₂ (Table 3).

Table 3. Synthesis of **4a** using various catalysts.

Entry	Catalyst	Yield (%) ^a	Ref.
1	H ₆ [P ₂ W ₁₈ O ₆₂]	10	This work
2	P-TSA	50	This work
3	KHSO ₄	30	This work
4	Na ₂ SiO ₃	80	[30]
5	Bulk TiO ₂	70	This work
6	Nano-TiO ₂	82	This work

^aYields were analyzed by GC.

CONCLUSION

In conclusion, we have described a highly efficient procedure for the preparation of pyridine dicarbonitriles via a condensation reaction of various aldehydes, malononitrile, and thiol using

nano-TiO₂ as a catalyst. The procedure offers several advantages including high yields, operational simplicity, cleaner reaction, minimal environmental impact and low cost, which make it a useful and attractive process for the synthesis of these compounds.

EXPERIMENTAL

All products were characterized by m.p., IR, ¹H NMR and GC/MS. Melting points were measured by using the capillary tube method with an electrothermal 9200 apparatus. ¹H and ¹³C NMR spectra were recorded on a Bruker DRX Avance spectrometer at 500 and 125 MHz, respectively, with CDCl₃ as solvent. IR spectra were recorded from KBr disk on the FT-IR Bruker Tensor 27. GC/MS spectra were recorded on an Agilent Technologies 6890 network GC system and an Agilent 5973 network Mass selective detector. Thin layer chromatography (TLC) on commercial aluminum-backed plates of silica gel, 60 F254 was used to monitor the progress of reactions. All products were characterized by spectra and physical data.

Synthesis of nano-TiO₂. A 500 mL three-necked flask containing 5 mL of titanium tetrachloride was equipped with a condenser, a gas trap and a water steam producer. The titanium tetrachloride was heated to 130 °C. By adding water steam to hot titanium tetrachloride for 15 min, a milky solution was formed. After washing the condenser, the milky solution was filtered to obtain a white solid. By heating of the white solid in oven at 400 °C for 7 h, the TiO₂ nanoparticle as a white crystalline powder was formed.

Typical procedure for preparation of pyridine dicarbonitriles. To a magnetically stirred solution of aldehyde (1 mmol), 4-methyl thiophenol (1 mmol) and nano-TiO₂ (5 mol%) in ethanol (5 mL) was added malononitrile (2 mmol) and stirring was continued for 1 h. The precipitate was filtered and washed with ethanol to give product.

4a. IR (KBr) (ν_{\max} , cm⁻¹): 3451, 3323, 2215, 1618, 1548, 1574; ¹H NMR (DMSO, 500 MHz) δ_{H} (ppm): 2.38 (s, 3H, CH₃), 7.31- 7.59 (m, 9H), 7.78 (br, s, 2H) ppm; ¹³C NMR (DMSO, 125 MHz) δ_{C} (ppm): 167.48, 160.56, 159.46, 140.44, 135.84, 134.83, 134.58, 131.24, 131.03, 129.58, 129.30, 124.37, 116.18, 115.90, 94.08, 87.84, 21.80; GC/MS: 341 (M⁺).

4b. IR (KBr) (ν_{\max} , cm⁻¹): 3477, 3345, 2216, 1633, 1595, 1574; ¹H NMR (CDCl₃, 500 MHz) δ_{H} (ppm): 2.47 (s, 3H, CH₃), 7.30- 7.58 (m, 8H), 7.80 (br, s, 2H) ppm; ¹³C NMR (CDCl₃, 125 MHz) δ_{C} (ppm): 170.19, 159.68, 157.49, 140.84, 137.82, 136.07, 131.99, 130.62, 130.32, 129.89, 123.80, 115.49, 115.07, 96.07, 87.45, 21.85; GC/MS: 375 (M⁺).

4c. IR (KBr) (ν_{\max} , cm⁻¹): 3477, 3345, 2216, 1633, 1595, 1574; ¹H NMR (CDCl₃, 500 MHz) δ_{H} (ppm): 2.47 (s, 3H, CH₃), 7.30- 7.58 (m, 8H), 7.80 (br, s, 2H) ppm; ¹³C NMR (CDCl₃, 125 MHz) δ_{C} (ppm): 170.19, 159.68, 157.49, 140.84, 141.50, 139.85, 137.82, 136.07, 131.99, 130.62, 130.32, 129.89, 123.80, 115.49, 115.07, 96.07, 87.45, 21.85; GC/MS: 375 (M⁺).

4d. IR (KBr) (ν_{\max} , cm⁻¹): 3471, 3346, 2215, 1631, 1591, 1570; ¹H NMR (DMSO, 500 MHz) δ_{H} (ppm): 2.37 (s, 3H, CH₃), 7.30- 7.80 (m, 8H), 7.81 (br, s, 2H) ppm; ¹³C NMR (DMSO, 125 MHz) δ_{C} (ppm): 167.47, 160.46, 158.37, 140.48, 135.82, 134.05, 132.68, 131.49, 131.04, 124.98, 124.29, 116.08, 115.77, 93.92, 87.74, 21.80; GC/MS: 420 (M⁺).

4e. IR (KBr) (ν_{\max} , cm⁻¹): 3471, 3346, 2215, 1631, 1591, 1570; ¹H NMR (DMSO, 500 MHz) δ_{H} (ppm): 2.37 (s, 3H, CH₃), 7.30- 7.80 (m, 8H), 7.81 (br, s, 2H) ppm; ¹³C NMR (DMSO, 125 MHz) δ_{C} (ppm): 167.47, 160.46, 158.37, 141.20, 140.48, 137.50, 135.82, 134.05, 132.68, 131.49, 131.04, 124.98, 124.29, 116.08, 115.77, 93.92, 87.74, 21.80; GC/MS: 420 (M⁺).

4f. IR (KBr) (ν_{\max} , cm^{-1}): 3417, 3331, 2217, 1642, 1554, 1348; ^1H NMR (DMSO, 500 MHz) δ_{H} (ppm): 2.24 (s, 3H, CH_3), 6.54- 7.56 (m, 8H), 8.22 (br, s, 2H) ppm; ^{13}C NMR (DMSO, 125 MHz) δ_{C} (ppm): 165.70, 159.60, 157.50, 141.20, 137.50, 136.7, 135.4, 134.80, 132.7, 130.4, 129.5, 128.9, 125.9, 115.1, 114.8, 93.2, 87.2, 21.85; GC/MS: 386 (M^+).

4g. IR (KBr) (ν_{\max} , cm^{-1}): 3417, 3331, 2217, 1642, 1554, 1348, 1321, 1238; ^1H NMR (DMSO, 500 MHz) δ_{H} (ppm): 2.24 (s, 3H, CH_3), 6.54- 7.56 (m, 8H), 8.22 (br, s, 2H) ppm; ^{13}C NMR (DMSO, 125 MHz) δ_{C} (ppm): 165.70, 159.60, 157.50, 136.7, 135.4, 134.80, 132.7, 130.4, 129.5, 128.9, 125.9, 115.1, 114.8, 93.2, 87.2, 21.85; GC/MS: 386 (M^+).

4h. IR (KBr) (ν_{\max} , cm^{-1}): 3410, 3322, 2216, 1637, 1607, 1575, 1545, 1510, 1459, 1420, 1371; ^1H NMR (CDCl_3 , 500 MHz) δ_{H} (ppm): 2.37 (s, 3H, CH_3), 3.85 (s, 3H, OCH_3), 7.12-7.52 (m, 8H), 7.72 (br, s, 2H) ppm; ^{13}C NMR (CDCl_3 , 125 MHz) δ_{C} (ppm): 167.48, 160.67, 159.10, 140.37, 135.81, 134.24, 131.16, 130.98, 126.69, 125, 124.49, 116.42, 115.67, 94.10, 87.71, 21.79; GC/MS: 371 (M^+).

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