

Nano-TiO₂: An efficient and useful catalyst for the synthesis of 3-cyano-2(1H)-pyridone derivatives

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A highly efficient procedure for the synthesis of 3-cyano-2(1H)-pyridones and their 2-imino isosteres *via* a one-pot multicomponent reaction of 3,4-dimethoxyacetophenone, malonitrile or ethyl cyanoacetate, an aldehyde and ammonium acetate in the presence of nano-TiO₂ is achieved in good yields. Short reaction times, simple work-up, isolation of the products in high yields with high purity, mild reaction conditions are features of this new procedure.

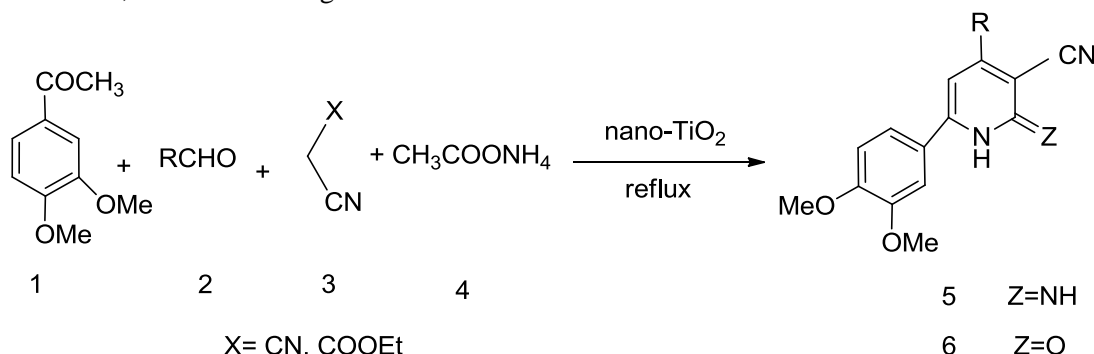
Keywords: 3-Cyano-2(1H)-pyridones, 2-Imino, Cardiotoxic, nano-TiO₂

INTRODUCTION

Among the various classes of nitrogen containing heterocyclic compounds, pyridine derivatives display a broad spectrum of biological activities. Substituted 3-cyano pyridines are important intermediates in pharmaceuticals, anti-inflammatory and dyes and therefore development of efficient procedures towards functionalized pyridines is an attractive target for organic synthesis.

Cardiac glycosides (digoxin and digitoxin), discovered in the 18th century, still represent the corner stone of therapy for congestive heart failure (CHF), despite their low therapeutic index and their propensity to cause life-threatening arrhythmia [1-3]. The newer sympathomimetic agents (dobutamine, dopamine) are orally inactive and may lead to tachyphylaxis due to β -receptor down regulation [4, 5]. Because of the need for safer and orally effective drugs, the synthesis of milrinone analogues as a series of nonglycosidic, non-sympathomimetic, cardiotoxic agents has been

developed [6]. 3-cyano-2(1H)-pyridinones and their 2-imino isosteres are milrinone analogues which also can be used as nonsteroidal cardiotoxic agents [7] and their syntheses are categorized by the following three types: (i) Knoevenagel and Hantzsch condensation chemistry from β -keto esters [8-10] (ii) pyridine synthesis from α , β -unsaturated ketones [11, 12] (iii) Krohnke type cyclization with 1,5-diketone and ammonium acetate [13], but many of reported methods have drawbacks such long reaction times, harsh reaction conditions, the use of stoichiometric reagents or of toxic and inflammable solvents, difficult work-ups or low yields of products. Consequently, there is a need to develop new methods for the synthesis of these compounds. In this communication we wish to report the application of nano-TiO₂ in the synthesis of 3-cyano-2(1H)-pyridones and their 2-imino isosteres. (Scheme 1)



Scheme 1.

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RESULTS AND DISCUSSION

As part of our program aimed at developing new selective and environmental friendly methodologies for the preparation of fine chemicals, we performed the synthesis of 3-cyano-2(1H)-pyridones and their 2-imino isosteres through one-pot multi-component reaction of 3,4-dimethoxyacetophenone, malonitrile or ethyl cyanoacetate, an aldehyde and ammonium acetate in the presence of nano-TiO₂.


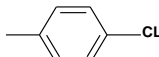
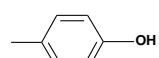
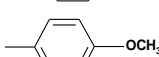

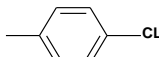
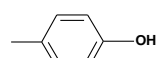
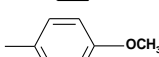
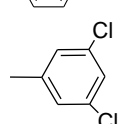
This reaction proceeded smoothly and rapidly to give the corresponding pyridones and 2-imino analogues in good yields (Table 1). Initially, we examined the effect of varying the solvent on the synthesis of 5b. This reaction was carried out in various solvents such as water, DMF, chloroform, ethanol, CH₂Cl₂ and toluene. As shown in Table 2, the best results in terms of yield and time are obtained in ethanol.

By carrying out reactions with different amounts of ammonium acetate, it was found that 8 mmol of ammonium acetate furnished the maximum yield for 1 mmol of the reactants. When ethyl cyanoacetate was used instead of malonitrile, the corresponding 2-pyridone was obtained in good yield (Table 1, entries 6-10).

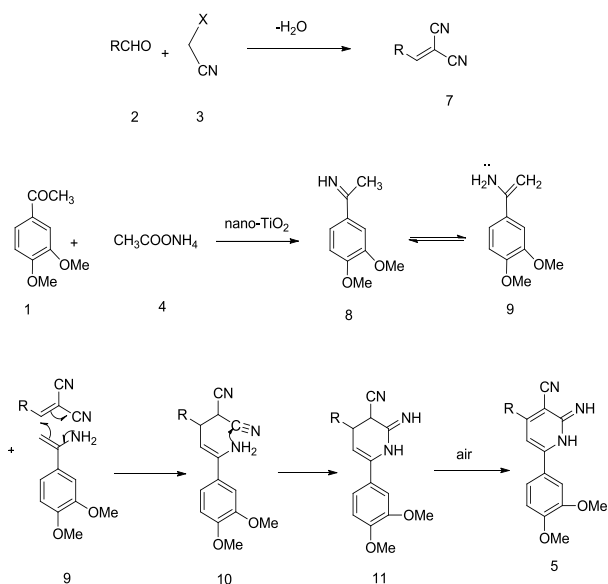
Under optimized reaction conditions, various aromatic aldehydes reacted very well with malonitrile and ethyl cyanoacetate as the active methylene compounds to give the corresponding 2(1H)-pyridones and their 2-imino isosteres in good yields (Table 1). The effect of temperature in ethanol as a solvent was studied by carrying out the reactions at different temperatures [room temperature (25 °C), 45 °C and under refluxing temperature (78 °C)]. As it is shown in Table 1, the yields of the reactions increased as the reaction temperature was raised. From these results it was decided that refluxing temperature would be the best temperature for all reactions. The reaction proceeds very cleanly under reflux and is free from side products.

A reasonable mechanism for this reaction is shown in Scheme 2. The enamine formed from dimethoxyacetophenone and ammonia adds to the aldol condensation product of the aldehyde and malonitrile. Subsequent addition to a cyano group followed by dehydrogenation affords the desired product 5.

Table 1. Synthesis of 3-cyano-2(1H)-pyridones with nano-TiO₂

Entry	R	X	Z	Product	Time (h)	Yield(%) ^a		
						25°C	45°C	78°C
1	-CH ₃	CN	NH	5a	3	45	65	83
2		CN	NH	5b	3	45	70	85
3		CN	NH	5c	3	40	68	87
4		CN	NH	5d	3	45	72	84
5		CN	NH	5e	3	50	71	84
6	-CH ₃	COOEt	O	6a	3	45	65	85
7		COOEt	O	6b	3	45	72	86
8		COOEt	O	6c	3	40	70	86
9		COOEt	O	6d	3	45	72	85
10		COOEt	O	6e	3	50	75	83
11		COOEt	O	6f	3	45	70	89

^aYield of isolated products.



Scheme 2.

Table 2. Synthesis of 5b with nano-TiO₂ in the presence of different solvents

Entry	Solvent	Temperature	Time(h)	Yield (%) ^a
1	Ethanol	Reflux	3	82
2	Acetonitrile	Reflux	3	80
3	Ethyl acetate	Reflux	4	78
4	THF	Reflux	4	75
5	Dichloromethane	Reflux	6	65

^aYield of isolated products.

It is known that the specific surface area and the 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 TiO₂-based devices, as it facilitates reaction/interaction between the devices and the interacting media [14]. TiO₂ nanoparticles have been widely investigated in the past decades due to their multiple potential catalytic activity for esterification [15], degradation of methyl parathion [16], photodecomposition of methylene blue [17], rhodamine B degradation [18], synthesis of β -acetamido ketones [19], 2-alkylbenzimidazoles and indazole [20], β -amino ketones [21], bis(indolyl)methanes [22], 2-indolyl-1-nitroalkane [23], selective oxidation of sulphides [24], Friedel-Crafts alkylation of indoles [25] and photocatalytic synthesis of quinaldines [26].

The investigation on nano-TiO₂ catalytic activity for the synthesis of many organic molecules is a current work in our laboratory. The dimensions of the applied TiO₂ nanoparticles were determined with SEM and are 38 nm (Fig. 1).

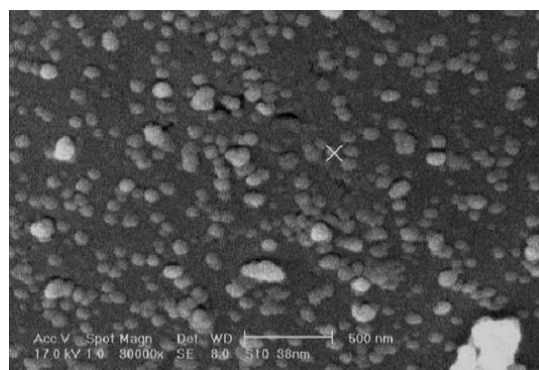


Fig.1. SEM photograph of nano-TiO₂

EXPERIMENTAL

All products are known compounds and were characterized by m.p., IR, ¹HNMR and GC/MS. Melting points were measured by the capillary tube method with an Electrothermal 9200 apparatus (Germany). ¹HNMR spectra were recorded on a Bruker AQS AVANCE-500 MHz spectrometer (Germany) using TMS as an internal standard (CDCl₃ solution). IR spectra were recorded from KBr disks on the FT-IR Bruker Tensor 27 (Germany). GC/MS spectra were recorded on an Agilent Technologies 6890 network GC system supplied with an Agilent 5973 network mass selective detector (United States). 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 spectral and physical data.

Typical procedure for preparation of 4-aryl(alkyl)-3-cyano-6-(3,4-dimethoxyphenyl)-2(1H)-iminopyridines (5a-e):

A mixture of 3,4-dimethoxyacetophenone (1 mmol), malononitrile (1 mmol), the appropriate aldehyde (1 mmol), ammonium acetate (8 mmol) and nano-TiO₂ (5 mol%) in ethanol (5 mL) was refluxed for 3 h. The progress of the reaction was monitored by TLC (hexane-ethylacetate (2:1)). After completion of the reaction, the solvent was evaporated and the mixture was washed with chloroform and filtered to recover the catalyst. The filtrate was evaporated and the crude product was recrystallized from ethanol.

Typical procedure for preparation of 4-aryl(alkyl)-6-(3,4-dimethoxyphenyl)-3-cyano-2(1H)-pyridinones (6a-e):

The foregoing method was carried out except that malononitrile was replaced by ethyl cyanoacetate (Table 1, entries 6-10).

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 the white solid in an oven at 400 °C for 7 h, the TiO₂ nanoparticles formed a white crystalline powder.

Reusability of nano-TiO₂

Next, we investigated the reusability and recycling of nano-TiO₂. At the end of the reaction, the catalyst could be recovered by a simple filtration. The recycled catalyst was washed with methanol and subjected to a second run of the reaction process. To assure that catalysts were not dissolved in methanol, they were weighed after filtration and before using and reusing for the next reaction. The results show that these catalysts are not soluble in methanol. In Table 3, the comparison of the efficiency of nano-TiO₂ in the synthesis of 5a after five runs is reported. As it is shown in Table 3, the first reaction using recovered nano-TiO₂ afforded a similar yield to that obtained in the first run. In the following runs the yield gradually decreased.

Table 3. Reuse of nano-TiO₂ for the synthesis of 5a

Entry	Time/h	Yield/% ^a
1	3	83
2	3	81
3	3	80
4	3	75
5	3	70

(a) Isolated yields

Selected physical data

5c: Mp: 207 °C (lit.203-207[21]). IR (KBr) (ν_{\max} , cm⁻¹): 2225, 3340. ¹H NMR (DMSO-D₆, 500 MHz) δ H (ppm): 3.75 (s, 3H, 3-OCH₃), 3.89 (s, 3H, 4-OCH₃), 7.12–7.58 (m, 8H, aromatic), 10.51 (brs, 1H, NH), 10.62 (brs, 1H, NH). GC/MS: 365 (M⁺).

5d: Mp: 202 °C (lit.205-207 [21]). IR (KBr) (ν_{\max} , cm⁻¹): 2246, 3345. ¹H NMR (DMSO-D₆, 500 MHz) δ H (ppm): 3.85 (s, 3H, 3-OCH₃), 3.91 (s, 3H, 4-OCH₃), 7.12–7.58 (m, 8H, aromatic), 9.86 (brs, 1H, NH), 9.98 (brs, 1H, NH), 10.65 (1H, OH), GC/MS: 347 (M⁺).

6a: Mp: 255 °C (lit.255-257 [21]). IR (KBr) (ν_{\max} , cm⁻¹): 1670, 2220, 3320. ¹H NMR (DMSO-D₆, 500 MHz) δ H (ppm): 2.43 (s, 3H, CH₃), 3.75 (s, 3H, 3-OCH₃), 3.89 (s, 3H, 4-OCH₃), 7.01–7.49 (m, 4H, aromatic), 12.05 (brs, 1H, NH). GC/MS: 270 (M⁺).

6b: Mp: 285 °C (lit.287-289 [21]). IR (KBr) (ν_{\max} , cm⁻¹): 1641, 2228, 3330. ¹H NMR (DMSO-500

D₆, 500 MHz) δ H (ppm): 3.89 (s, 3H, 3-OCH₃), 4.01 (s, 3H, 4-OCH₃), 7.09–7.52 (m, 9H, aromatic), 12.51 (brs, 1H, NH). GC/MS: 332 (M⁺).

CONCLUSION

In summary, we have developed a simple and efficient protocol for the synthesis of 3-cyano-2(1H)-pyridones and their 2-imino isosteres with nano-TiO₂. Short reaction times, simple work-up, isolation of the products in high yields with high purity, mild reaction conditions are features of this new procedure.

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НАНО-TiO₂: ЕФЕКТИВЕН И ПОЛЕЗЕН КАТАЛИЗАТОР ЗА СИНТЕЗА НА 3-ЦИАНО-2 (1H) -ПИРИДОНИ ПРОИЗВОДНИ

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(Резюме)

Постигната е високо ефективна процедура за синтез на 3-циано-2 (1H) -пиридони и техните 2-имино изостери чрез едностодийна многокомпонентна реакция на 3,4-диметоксиацетофенон, малонитрил или етил цианоацетат, алдехид и амониев ацетат в присъствие на нано-TiO₂ с добри добиви. Характеристика на тази нова процедура са кратки реакционни времена, проста работа, изолиране на продуктите с високи добиви и висока степен на чистота, меки реакционни условия.