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A CATALYTIC METHOD FOR THE SYNTHESIS OF 4-ALKYL(ARYL)-6-ARYL-3-CYANO-2(1*H*)-PYRIDINONES AND THEIR 2-IMINO ISOSTERES AS NONSTEROIDAL CARDIOTONIC AGENTS

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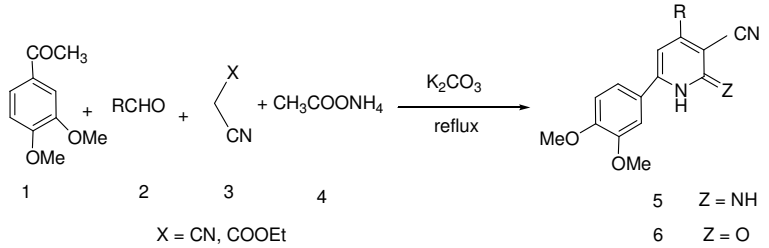
ABSTRACT. A highly efficient procedure for the synthesis of 4-alkyl(aryl)-6-aryl-3-cyano-2(1*H*)-pyridinones and their 2-imino isosteres via a one-pot multicomponent reaction of 3,4-dimethoxyacetophenone, malonitrile or ethyl cyanoacetate, an aldehyde and ammonium acetate in the presence of K_2CO_3 is achieved in good yields.

KEY WORDS: 3-Cyano-2(1*H*)-pyridinones, 2-Imino, Cardiotonic, Dimethoxyacetophenone

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 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, cardiotonic agents has been developed [6]. 4-Alkyl(aryl)-6-aryl-3-cyano-2(1*H*)-pyridinones and their 2-imino isosteres are milrinone analogues which can also be used as as nonsteroidal cardiotonic agents [7] and their syntheses are categorized by the following three types: (i) Knoevenagel and Hantzsh condensation chemistry from β-keto esters [8-10], (ii) pyridine synthesis from α,β-unsaturated ketones [11, 12] and (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 K_2CO_3 in the synthesis of 4-alkyl(aryl)-6-aryl-3-cyano-2(1*H*)-pyridinones and their 2-imino isosteres. (Scheme 1)



Scheme 1

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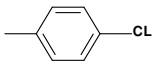
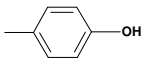
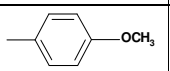
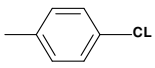
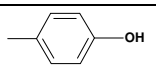
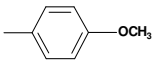
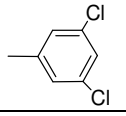
RESULTS AND DISCUSSION

As part of our program aimed at developing new selective and environmental friendly methodologies for the preparation of fine chemicals [14], we performed the synthesis of 4-alkyl(aryl)-6-aryl-3-cyano-2(1*H*)-pyridinones 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 K_2CO_3.

This reaction proceeded smoothly and rapidly to give the corresponding pyridinones 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, CH_2Cl_2 and toluene. As shown in Table 2, the best results in terms of yield and time were obtained in ethanol.

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

Table 1. Synthesis of 3-cyanopyridines derivatives with K_2CO_3.

Entry	R	X	Z	Product	Time (h)	Yield (%)[a]		
						25 °C	45 °C	78 °C
1	-CH_3	CN	NH	**5a**	3	45	65	81
2		CN	NH	**5b**	3	45	70	82
3		CN	NH	**5c**	3	40	68	85
4		CN	NH	**5d**	3	45	72	82
5		CN	NH	**5e**	3	50	71	83
6	-CH_3	COOEt	O	**6a**	3	45	65	82
7		COOEt	O	**6b**	3	45	72	82
8		COOEt	O	**6c**	3	40	70	84
9		COOEt	O	**6d**	3	45	72	82
10		COOEt	O	**6e**	3	50	75	82
11		COOEt	O	**6f**	3	45	70	86

[a]Yield of isolated products.

Table 2. Synthesis of **5b** with K_2CO_3 in the presence of different solvent.

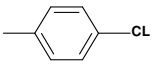
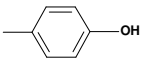
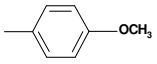
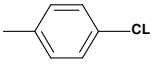
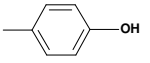
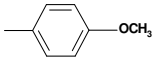
Entry	Solvent	Temperature	Time (h)	Yield (%)[a]
1	Ethanol	Reflux	3	82
2	Acetonitrile	Reflux	3	80
3	Ethyl acetate	Reflux	4	78
4	THF	Reflux	4	75
5	Dichloromethane	Reflux	6	65

[a]Yield of isolated products.

After optimizing the reaction condition, various aromatic aldehydes reacted very well with malononitrile and ethyl cyanoacetate as the active methylene compounds to give the corresponding 2(1*H*)-pyridinones 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 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.

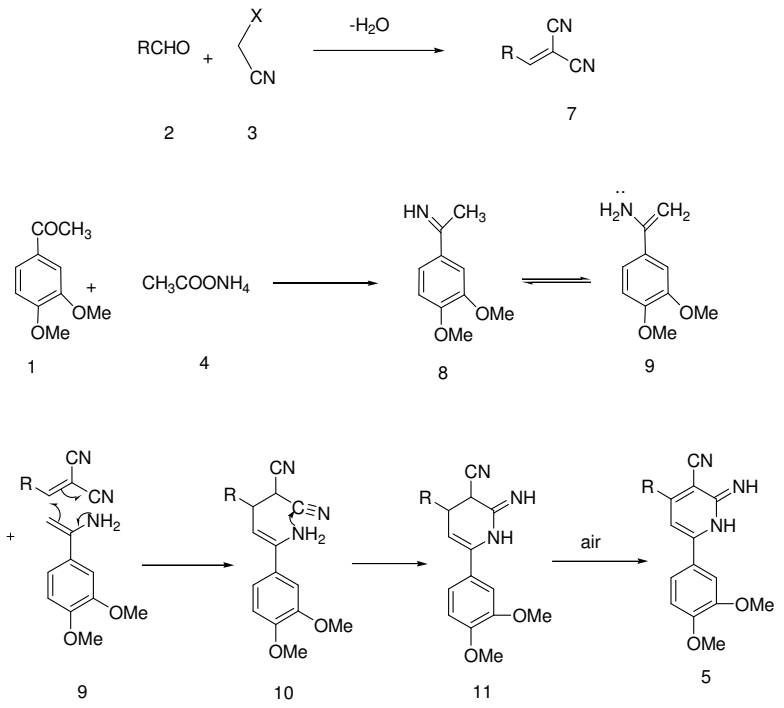
We have used Et_3N instead of K_2CO_3 in these reactions, but K_2CO_3 affords better yields. (Table 1, 3). In addition, the time required for completion of the reaction was found to be less with K_2CO_3.

Table 3. Synthesis of 3-cyanopyridines derivatives with ET_3N.

Entry	R	X	Z	Product	Time (h)	Yield (%)[a]		
						25 ˚C	45 ˚C	78 ˚C
1	$-CH_3$	CN	NH	**5a**	4	25	45	55
2		CN	NH	**5b**	4	25	40	57
3		CN	NH	**5c**	4	20	48	55
4		CN	NH	**5d**	4	25	42	57
5		CN	NH	**5e**	4	20	41	58
6	$-CH_3$	COOEt	O	**6a**	4	25	45	56
7		COOEt	O	**6b**	4	25	42	58
8		COOEt	O	**6c**	4	20	40	59
9		COOEt	O	**6d**	4	25	42	57
10		COOEt	O	**6e**	4	20	45	57

[a]Yield of isolated products.

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



Scheme 2

In summary, we have developed a simple and efficient protocol for the synthesis of 4-alkyl(aryl)-6-aryl-3-cyano-2(1*H*)-pyridinones and their 2-imino isosteres with K_2CO_3. The 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.

EXPERIMENTAL

All the products are known compounds and were characterized by mp, IR, ^{1}H NMR and GC/MS. Melting points were measured by using the capillary tube method with an Electrothermal 9200 apparatus (Germany). ^{1}H NMR spectra were recorded on a Bruker AQS AVANCE-500 MHz spectrometer (Germany) using TMS as an internal standard ($CDCl_3$ solution). IR spectra were recorded from KBr disk on the FT-IR Bruker Tensor 27 (Germany). GC/MS spectra were recorded on an Agilent Technologies 6890 network GC system and an Agilent 5973 network mass selective detector (USA). Thin layer chromatography (TLC) on commercial aluminum-backed plates of silica gel, 60 F254 was used to monitor the progress of reactions. All the products were characterized by spectra 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 K_2CO_3 (0.5 mmol) in ethanol (5 mL) was refluxed for 3 h. The mixture was cooled to room temperature and the precipitated products were separated by filtration then washed successively with water, dried and crystallized.

*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).

Selected physical data

5c. Mp: 207 ºC (lit. 203-207 ºC [15]). IR (KBr) (ν_{max}, cm^{-1}): 2225, 3340. ^{1}H NMR (DMSO-D_6, 500 MHz) δ_H (ppm): 3.75 (s, 3H, 3-OCH_3), 3.89 (s, 3H, 4-OCH_3), 7.12-7.58 (m, 8H, aromatic), 10.51 (brs, 1H, NH), 10.62 (brs, 1H, NH). GC/MS: 365 (M^+).

5d. Mp: 202 ºC (lit. 205-207 ºC [15]). IR (KBr) (ν_{max}, cm^{-1}): 2246, 3345. ^{1}H NMR (DMSO-D_6, 500 MHz) δ_H (ppm): 3.85 (s, 3H, 3-OCH_3), 3.91 (s, 3H, 4-OCH_3), 7.12-7.58 (m, 8H, aromatic), 9.86 (brs, 1H, NH), 9.98 (brs, 1H, NH), 10.65 (1H, OH), 10. GC/MS: 347 (M^+).

6a. Mp: 255 ºC (lit. 255-257 ºC [15]). IR (KBr) (ν_{max}, cm^{-1}): 1670, 2220, 3320.^{1}H NMR (DMSO-D_6, 500 MHz) δ_H (ppm): 2.43 (s, 3H, CH_3), 3.75 (s, 3H, 3-OCH_3), 3.89 (s, 3H, 4-OCH_3), 7.01-7.49 (m, 4H, aromatic), 12.05 (brs, 1H, NH). GC/MS: 270 (M^+).

6b. Mp: 285 ºC (lit.287-289 ºC [15]). IR (KBr) (ν_{max}, cm^{-1}): 1641, 2228, 3330.^{1}H NMR (DMSO-D_6, 500 MHz) δ_H (ppm): 3.89 (s, 3H, 3-OCH_3), 4.01 (s, 3H, 4-OCH_3), 7.09-7.52 (m, 9H, aromatic), 12.51 (brs, 1H, NH). GC/MS: 332 (M^+).

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