European Journal of Chemistry 1 (3) (2010) 232-235

European Journal of Chemistry

Journal homepage: www.eurjchem.com

DABCO as an efficient catalyst for the synthesis of 3-cyano-2(1*H*)-pyridinones and their 2-imino analogues

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COMMUNICATION INFORMATION

Received: 17 May 2010
Received in revised form: 7 June 2010
Accepted: 8 July 2010
Online: 30 September 2010

KEYWORDS

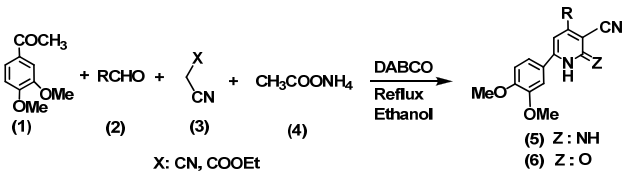
1,4-Diaza-bicyclo[2,2,2]octane
Cyano-2(1H)-pyridinones
Cyano-2(1H)-iminopyridines
3,4-Dimethoxyacetophenone
DABCO
Catalyst

ABSTRACT

3-cyano-2(1*H*)-pyridinones and their 2-imino analogues have been synthesized in good yields via a one-pot multi–component reaction of 3,4-dimethoxyacetophenone, malononitrile or ethylcyanoacetate, ammonium acetate and various aldehydes in the presence of 1,4-diaza-bicyclo[2,2,2]octane (DABCO) in ethanol. DABCO has been widely used as a catalyst for the organic reactions and we selected it as an efficient catalyst to synthesis of 3-cyano-pyridines. All products were characterized by melting point, IR, ^{1}H NMR and GC/MS studies.

1. Introduction

Heteroaromatic rings containing nitrogen atoms often play important roles as the heteroaromatics incorporated into the structure of many pharmaceuticals. Therefore, development of efficient procedures towards functionalized pyridines is a quite attractive target for organic synthesis. 3-Cyano-pyridines are of interest as they are used as intermediates for the synthesis of variety of heterocyclic compounds [2-4]. The formation of 2-oxo- and 2-iminopyridine derivatives were assumed to proceed via the Michael condensation of ethyl cyanoacetate or malononitrile with *α*, *β*-unsaturated ketone, initially formed from the reaction of the aldehyde with acetophenone [5]. Alternatively, the formation of 2-iminopyridines was explained by the initial formation of the arylidene malononitrile from the aldehyde and malononitrile followed by its subsequent reaction with acetophenone [5,6]. Many of the standard procedures require either longer reaction times or in some cases, lead to the mixtures of products and resulted in low yields. In view of the emerging importance of 3-cyano-pyridines, there still is a need to introduce new methods for the synthesis of these compounds using more efficient, convenient and green conditions even safer precursors. In this context, multi component reactions (MCRs) have played an important role in these processes [7]. MCRs in which at least three starting materials react together in one pot to give a product, is in contrast to classical multi-step reactions, where only two starting materials react. Whenever an MCR can be applied in chemistry, this is preferred since it is easier to perform, gives higher yields and is less time consuming [8]. Therefore, we decided to use MCR for the synthesis of 3-cyano-pyridines. We wish to introduce this procedure as a mild, practical and highly efficient reaction for the preparation of these compounds using 1,4-diaza-bicyclo[2,2,2]octane (DABCO) as a catalyst under refluxing conditions (Scheme 1).



Scheme 1

2. Experimental

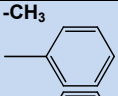
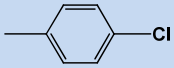
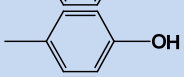
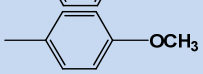
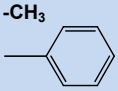
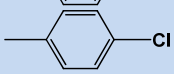
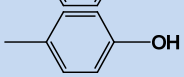
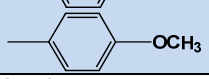
All the chemicals were obtained from Merck Company and used as received. All products are known compounds and were characterized by mp, IR, ^{1}H NMR and GC/MS. Melting points were measured by using the capillary tube method with an electro thermal 9200 apparatus. ^{1}H NMR spectra were recorded on a Bruker AQS AVANCE-300 MHz spectrometer using TMS as an internal standard ($CDCl_3$ solution). 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-packed plates of silica gel, 60 F254 was used to monitor the progress of reactions.

2.1. Typical procedure for preparation of 4-aryl(alkyl)-6-(3,4-dimethoxyphenyl)-3-cyano-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 DABCO (5mol %) in ethanol

ISSN 2153-2249 (Print) / ISSN 2153-2257 (Online)
DOI:10.5155/eurjchem.1.3.232-235.112

Table 1. Synthesis of 3-cyanopyridines derivatives catalyzed by DABCO.

Entry	R	X	Z	Product	Time (h)	Yield (%)[a]		
						25°C	45°C	78°C
1	-CH_3	CN	NH	5a	2	45	65	87
2		CN	NH	5b	2	45	70	91
3		CN	NH	5c	2	40	68	90
4		CN	NH	5d	2	45	72	88
5		CN	NH	5e	2	50	71	89
6	-CH_3	COOEt	O	6a	2	45	65	88
7		COOEt	O	6b	2	45	72	94
8		COOEt	O	6c	2	40	70	90
9		COOEt	O	6d	2	45	72	88
10		COOEt	O	6e	2	50	75	89

[a]Yield of isolated products.

(5 mL) was refluxed for 2h. the mixture was cooled to room temperature and the precipitated products were separated by filtration then washed successively with water, dried and crystallized.

2.1.2. 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:

5a: M.p.: 213 °C (Lit. 212-214 [21]). IR (KBr) (ν_{max}, cm^{-1}): 3513, 3420, 2218. ^1H NMR ($CDCl_3$, 300 MHz) δ_H (ppm): 3.65 (s, 3H, 3-OCH_3), 3.77 (s, 3H, 4-OCH_3), 7.22–7.63 (m, 9H, aromatic), 10.48 (brs, 1H, NH), 10.57 (brs, 1H, NH). MS: *m/z* = 331 (M^+).

5b: M.p.: 207 °C (Lit. 203-207 [21]). IR (KBr) (ν_{max}, cm^{-1}): 3467, 3340, 2225. ^1H NMR ($CDCl_3$, 300 MHz) δ_H (ppm): 3.75 (s, 3H, 3-OCH_3), 3.89 (s, 3H, 4-OCH_3), 7.18–7.68 (m, 8H, aromatic), 10.51 (brs, 1H, NH), 10.62 (brs, 1H, NH). MS: *m/z* = 365 (M^+).

5c: M.p.: 202 °C (Lit. 205-207 [21]). IR (KBr) (ν_{max}, cm^{-1}): 3428, 3345, 2246. ^1H NMR ($CDCl_3$, 300 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 (1H, OH), 10.65 (brs, 1H, NH). MS: *m/z* = 347 (M^+).

5d: M.p.: 167 °C (Lit. 165-167 [21]). IR (KBr) (ν_{max}, cm^{-1}): 3429, 3365, 2216. ^1H NMR ($CDCl_3$, 300 MHz) δ_H (ppm): 3.61 (s, 3H, 3-OCH_3), 3.94 (s, 3H, 4-OCH_3), 3.96 (s, 3H), 7.32–7.88 (m, 8H, aromatic), 10.51 (brs, 1H, NH), 10.62 (brs, 1H, NH). MS: *m/z* = 361 (M^+).

5e: M.p.: 194 °C (Lit. 190-192 [21]). IR (KBr) (ν_{max}, cm^{-1}): 3461, 3310, 2220. ^1H NMR ($CDCl_3$, 300 MHz) δ_H (ppm): 2.96 (s, 3H), 3.82 (s, 3H, 3-OCH_3), 3.93 (s, 3H, 4-OCH_3), 7.35–7.63 (m, 4H, aromatic), 10.51 (brs, 1H, NH), 10.62 (brs, 1H, NH). MS: *m/z* = 269 (M^+).

6a: M.p.: 285 °C (Lit. 287-289 [21]). IR (KBr) (ν_{max}, cm^{-1}): 3330, 2228, 1641. ^1H NMR ($CDCl_3$, 300 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). MS: *m/z* = 332 (M^+).

6b: M.p.: 295 °C (Lit. 292-294 [21]). IR (KBr) (ν_{max}, cm^{-1}): 3425, 2220, 1638. ^1H NMR ($CDCl_3$, 300 MHz) δ_H (ppm): 3.78 (s, 3H, 3-OCH_3), 3.94 (s, 3H, 4-OCH_3), 7.11–7.63 (m, 8H, aromatic), 11.92 (brs, 1H, NH). MS: *m/z* = 366 (M^+).

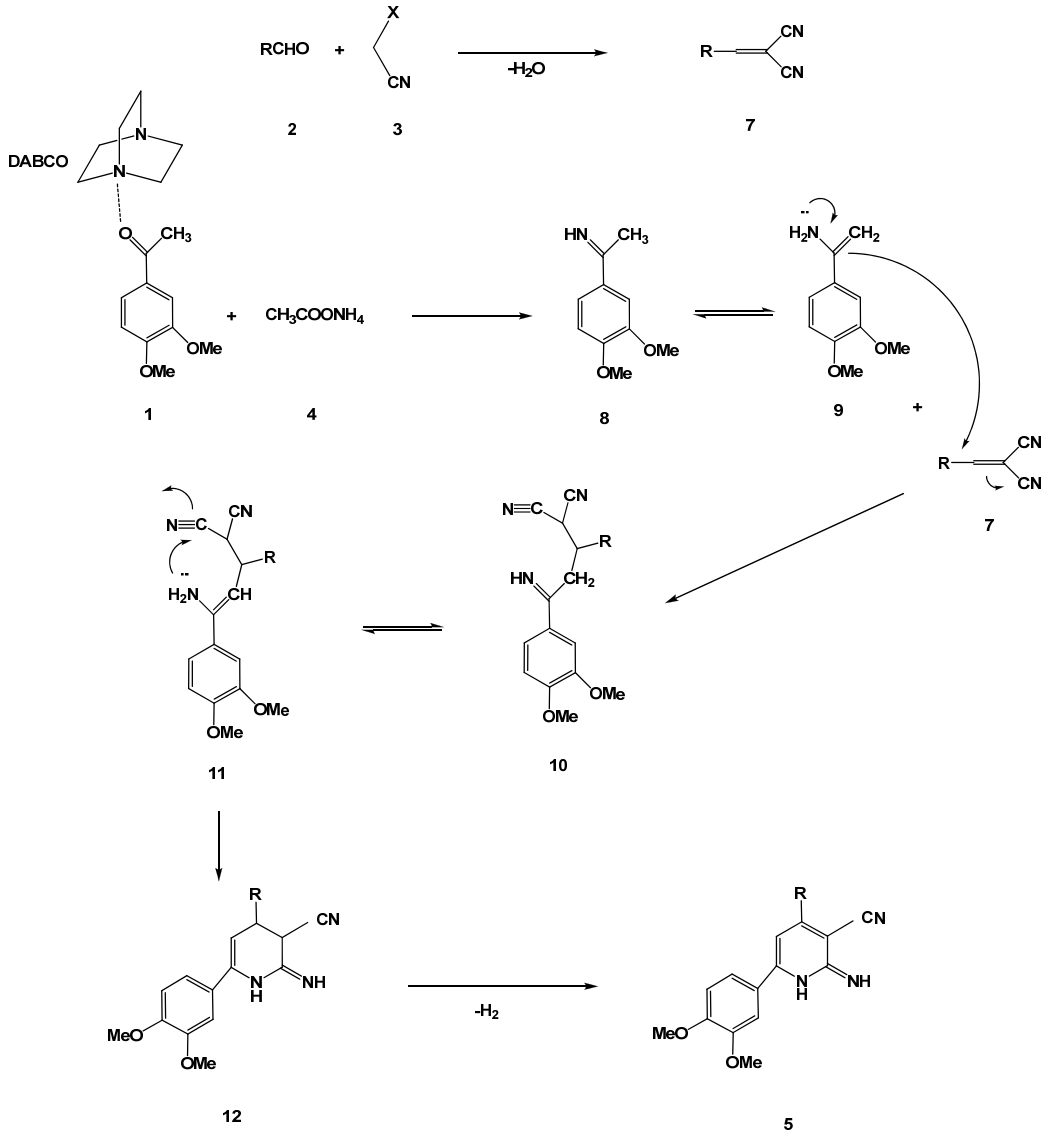
6c: M.p.: 311 °C (Lit. >300 [21]). IR (KBr) (ν_{max}, cm^{-1}): 3328, 2200, 1658. ^1H NMR ($CDCl_3$, 300 MHz) δ_H (ppm): 3.92 (s, 3H, 3-OCH_3), 4.06 (s, 3H, 4-OCH_3), 7.10–7.58 (m, 8H, aromatic), 11.13 (1H, OH), 12.65 (brs, 1H, NH). MS: *m/z* = 348 (M^+).

6d: M.p.: 266 °C (Lit. 262-264 [21]). IR (KBr) (ν_{max}, cm^{-1}): 3354, 2238, 1642. ^1H NMR ($CDCl_3$, 300 MHz) δ_H (ppm): 3.79 (s, 3H, 3-OCH_3), 3.84 (s, 3H, 4-OCH_3), 3.96 (s, 3H), 7.22–7.68 (m, 8H, aromatic), 11.96 (brs, 1H, NH). MS: *m/z* = 362 (M^+).

6e: M.p.: 255 °C (Lit. 255-257 [21]). IR (KBr) (ν_{max}, cm^{-1}): 1670, 2220, 3320.^1H NMR ($CDCl_3$, 300 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). MS: *m/z* = 270 (M^+).

3. Results and Discussion

DABCO has been widely used as a catalyst for the Baylis–Hillman reactions [9]. It has also been reported as a catalyst for acceleration of benzoylation reactions [10]. DABCO has been applied for the synthesis of zeolite as a structure directing agent [11] and can catalyze the self and cross-condensation of α-acethylenic ketones [12]. Furthermore, it was used to catalyze the coupling of α-ketoesters with acrylonitrile [13] and for the dimerization of α, β-unsaturated ketones and nitriles [14]. In connection with our recent interest aimed at the development of efficient protocols for the preparation of biological active heterocycles [15-18], herein, we selected DABCO as a catalyst to synthesis of 3-cyano-pyridines. The reaction of various aldehydes, 3,4-dimethoxyacetophenone, ammonium acetate and ethyl cyanoacetate or malononitrile in the presence of DABCO in ethanol afforded 4-alkyl(aryl)-3-cyano-2(1*H*)-iminopyridines and 2(1*H*)-pyridinones in good yields (Table 1). The reaction times are considerably reduced with improved yields as compared to other procedures. The amount of ammonium acetate was adjusted to get the maximum yield of the products. 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 involved instead of malononitrile, the corresponding 2-1*H*-pyridone was obtained in good yield (Table 1, entries 6-10). The title compounds were characterized on the basis of analytical, spectral data and by comparison with authentic



Scheme 2

samples. For the aldehyde component, not only aromatic but also aliphatic aldehydes proceeded well (Table 1, entries 1, 6).

The reaction was conducted with various solvents for the synthesis of 5b using DABCO as a catalyst. As shown in Table 2, the performance of various solvents are in the following the order: ethanol > acetonitrile > ethyl acetate > THF > dichloromethane. Ethanol provided better yields compared to other solvents. In addition, the time required for completion of the reaction was found to be less in ethanol.

Table 2. Synthesis of 5b with DABCO in the presence of different solvents.

Entry	Solvent	Temperature	Time(h)	Yield(%)[a]
1	Ethanol	reflux	3	91
2	acetonitrile	reflux	3	84
3	ethyl acetate	reflux	4	82
4	THF	reflux	4	78
5	dichloromethane	reflux	6	65

[a]Yield of isolated products.

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 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 condition and free of side products. The reasonable mechanism for this reaction has been suggested in Scheme 2.

The first step may involve condensation reaction of malononitrile or ethyl cyanoacetate with the aromatic aldehyde, followed by attack of **9** to this intermediate which after a cyclization give intermediate **12**. Following oxidative dehydrogenation by O_2 [19], the desired heterocyclic product **5** is obtained. DABCO probably induces polarization of carbonyl group in keton **1**. Then nucleophilic attack of the nitrogen of ammonia obtained from ammonium acetate, on activated carbonyl, results the formation of imino keone **8**. To show the merits and advantages of using DABCO as a catalyst, our method is compared with reported reactions (Table 3). The reaction results without catalyst decrease and the reaction time increases.

Table 3. Comparision of various catalysts for the synthesis of 3-cyanopyridines (**5b, 6b**).

Entry	Product	Catalyst	Time	Yield(%)	Ref.
1	5b	none	6h	33	20
2	5b	$H_{14}[NaP_5W_{30}O_{110}]$	3h	90	21
3	5b	DABCO	2h	91	This article
4	6b	none	6h	33	20
5	6b	$H_{14}[NaP_5W_{30}O_{110}]$	3h	93	21
6	6b	DABCO	2h	94	This article

4. Conclusions

In summary, this method not only affords the products in excellent yields but also avoids the problems associated with catalyst cost, handling, safety and pollution. This catalyst can act as eco-friendly for a variety of organic transformations, non-volatile, recyclable, non-explosive, easy to handle and thermally stable. In view of the emerging importance of the catalyst, we have explored DABCO as a recyclable catalyst for the synthesis of 4-alkyl(aryl)-3-cyano-2(1*H*)-iminopyridines and 2(1*H*)-pyridinones.

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