1,4-Diaza-bicyclo[2,2,2]octane as a Novel and Efficient Catalyst for the Synthesis of 3,4,6-Trisubstituted 2-Pyridone Derivatives

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3,4,6-Trisubstituted 2-pyridone derivatives have been synthesized in good to excellent yields through a condensation reaction of various 1,3-diketones with amides in the presence of 1,4-Diaza-bicyclo[2,2,2]octane (DABCO) at reflux temperature.

Keywords 3,4,6-trisubstituted 2-pyridone derivative, 1,4-diaza-bicyclo[2,2,2]octane, 1,3-diketone

Introduction

In recent years there has been an increasing interest in the chemistry of 2-pyridones derivatives because of their biological significance. 2-Pyridones represent a unique class of pharmacophore, which has been observed in various therapeutic agents¹ and antibiotics.² They are also versatile precursors for the construction of complex natural products,³ pyridines.⁴ 3-Cyano-2pyridones are important intermediates in the pharmaceutical, dye and photo industries.⁵ There are numerous methods available for their synthesis,⁶ but most of these procedures have significant drawbacks such as long reaction time, low yields, harsh reaction conditions, difficult work-up and use of environmentally toxic reagents or media. Consequently, there is a need to develop new methods for synthesis of these compounds. 1,4-Diazabicyclo[2,2,2]octane (DABCO) has been widely used as a catalyst for the Baylis-Hillman reactions,⁷ a catalyst for acceleration of benzoylation reactions⁸ and as a structure directing agent for the synthesis of zeolite.⁹ It can also catalyze the self and cross-condensation of α -acetylenic ketones,¹⁰ the coupling of α -keto-esters with acrylonitrile¹¹ and the dimerization of α , β -unsaturated ketones and nitriles.¹²

In our attempts to develop new catalyst systems,¹³ we selected DABCO as a catalyst to synthesize 3,4,6-trisubstituted 2-pyridones derivatives (Eq. 1).



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Results and discussion

In a typical procedure, cyanoacetamide (1 mmol) and acetylacetone (1 mmol) in the presence of a cata-lytic amount of DABCO in ethanol at reflux temperature afforded the desired 2-pyridones 3a in 90% yield (Entry 1, Table 1). The reaction was then applied to a variety of 1,3-diketones and amides in good yields (Table 1). We performed the effect of various solvents on the synthesis of 3a. This reaction was carried out in various solvents and the best results in terms of yield and time were obtained in ethanol (Table 2). The effect of temperature was studied by carrying out the reactions at different temperatures (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. In each reaction, the yield is a function of the reaction time and the best time for all reactions was within 1-1.5 h. The reaction proceeded very cleanly under reflux condition and without any side products. In the absence of the catalyst, the reaction did not complete even after 24 h. The progress of the reaction was monitored by TLC and GC and the results indicate that the yields were affected by changing the catalyst moles. The reactions proceeded well with 1 mol% of catalyst and use of an increased amount of catalyst did not make much difference. DABCO can act as a base catalyst and a plausible mechanism for this reaction is suggested in Scheme 1.

In order to show the merit of the present work, we compared the results of the synthesis of these compounds in the presence of various catalysts but the best result was obtained with DABCO (Table 3).

In conclusion, we have described a highly efficient procedure for the preparation of 2-pyridones via a con-

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Scheme 1



Table 1 Synthesis of 2-pyridones catalyzed by DABCO										
Entry	1	2	Product	Time/h	Yield ^a /%					
Entry					25 °C	40 °C	Reflux			
1	Acetylacetone	Cyanoacetamide	CN NHO 3a	1	62	74	90			
2	1,3-Diphenylpropane-1,3-dione	Cyanoacetamide	Ph Ph N H 3b	1	60	70	85			
3	Ethyl acetoacetate	Cyanoacetamide	HO N O HO SC	1.30	58	70	85			
4	Ethyl benzoylacetate	Cyanoacetamide	HO N O HO HO HO HO HO HO HO HO HO HO HO HO HO HO H	1.20	60	71	90			
5	Methyl acetoacetate	Cyanoacetamide		1.30	59	72	85			
6	Acetyl acetone	1-Naphthylacetamide	N H 3e	1.30	66	78	95			
7	1,3-Diphenylpropane-1,3-dione	1-Naphthylacetamide	Ph Ph N H 3f	1	62	71	98			
8	1,3-Diphenylpropane-1,3-dione	Thioacetamide	HO NHO	1.5	60	71	95			

^{*a*} Yields were analyzed by GC.

densation reaction of various 1,3-diketones with amides using DABCO as a catalyst. The procedure offers sev-

eral advantages including high yields, operational simplicity, cleaner reaction, minimal environmental impact,

Entry	Solvent	Time/h	Yield ^a /%
1	THF	2	68
2	CH ₃ OH	2.20	75
3	CH ₃ CN	3	85
4	CHCl ₃	1.25	75
5	Solvent-free	4	81
6	C ₂ H ₅ OH	1	90

 Table 2
 Synthesis of 3a in different solvents using DABCO as a
catalyst

^a Yields were analyzed by GC.

Table 3Synthesis of 3a using various catalysts

Entry	Catalyst	Time/h	Yield ^a /%
1	Na ₂ CO ₃	1.45	68
2	K ₂ CO ₃	1.30	83 81 $(\pi t)^{16}$
3	Et ₃ N	2	81 (I.I.) 85
4	DABCO	1	90

^a Yields were analyzed by GC.

and low cost, which make it a useful and attractive process for the synthesis of these compounds.

Experimental

Chemicals were purchased from Fluka, Merck and Aldrich chemical companies. Melting points were measured with a Bamstead Electrothermal 9200 apparatus and are uncorrected. GC/MS data 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. ¹H NMR spectra were recorded on a Bruker AQS AVANCE-300 MHz spectrometer using TMS as an internal standard (CDCl₃ solution). Yields refer to isolated pure products. Products were identified by GC/MS and ¹H NMR and the data were compared to those of the authentic samples purchased from commercial sources.

General procedure for preparation of 3,4,6-trisubstituted 2-pyridones: A mixture of a 1,3-diketone (1 mmol), cyanoacetamide (1 mmol), and DABCO 1 mol% in ethanol (5 mL) was refluxed within 1-1.5 h. The progress of the reaction was monitored by TLC. After completion of the reaction, the reaction mixture

was cooled and the precipitate formed was filtered off and recrystallized from ethanol to give pure product.

3a: m.p. 290 °C (Lit.¹⁴ 288—289 °C); ¹H NMR δ : 2.62 (s, 3H, CH₃), 2.68 (s, 3H, CH₃), 6.80 (1H, 5H, Ph); IR (KBr) v: 2200, 1640 cm⁻¹; GC/MS: 148 (M⁺).

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