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NITROGEN-CONTAINING ORGANIC BASE-CATALYZED SYNTHESIS OF FUNCTIONALIZED 2-IMINO-2*H*-CHROMENES: A COMPARATIVE EXPERIMENTAL STUDY

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Abstract: Catalytic performance of three nitrogen-containing organic basic catalysts including1,4-diazabicyclo[2.2.2]octane (DABCO), 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU), and morpholine has been investigated in the synthesis of *N*-alkyl-2-imino-2*H*-chromene-3-carboxamides by reaction of salicylaldehydes with *N*-alkyl-2-cyanoacetamides. Among various tested reaction conditions, the results showed that DABCO was the more efficient basic catalyst than DBU and morpholine. The reactions completed within shorter reaction times in a mixture of ethanol and water as solvent with higher yields.

Keywords:2-Imino-2*H*-chromenes, Organic base, DABCO,DBU,Morpholine

Introduction

The use of non-metallic catalysts for the acceleration of organic reactions has been of great interest in recent years. In this broad research field, it is possible to identify a large number of important organic transformations that are catalyzed by metal-free organic catalysts[i-vi].These catalysts have advantages such as commercially availability, lower activation energies, and reduced toxicity, because the reactions are metal-free which will hopefully stimulate the application of them in new organic reactions.In this regard, a number of organic reactions have been performed in the presence of secondary or tertiary amines such as morpholine, Et_2NH, Et_3N, 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU), 1,4-diazabicyclo[2.2.2]octane (DABCO), etc., as nitrogen-containing organic basic catalysts[vii-xii].Among them, DABCO with a cage-like structure has been relatively of more interest[xiii]. This small organic diazabicyclic molecule is inexpensive, non-toxic, non-corrosive highly reactive, and easy to handle and thus widely used as a superb catalyst for many organic reactions such as Baylis-Hillman reaction[xiv,xv], Cloke-Wilson rearrangement[xvi], synthesis of three-membered carbocyclic compounds[xvii],synthesis of various heterocycles containing oxygenor nitrogen[xviii-

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[xxi] and some others. Moreover, DABCO is used as ligand in the cross-coupling reactions such as Suzuki-Miyaura[xxii,xxiii] and Sonogashira-Hagihara[xxiv].

The chromene moiety often appears as an important structural component in both biologically active and natural compounds. It widely found in natural alkaloids,flavonoids, tocopherols and anthocyanins[xxv-xxviii]. Moreover, it has been known that certain chromenes possess importantbiological activities such as antiviral[xxix],antileishmanial[xxx], antihypertensive[xxxi],antioxidant [xxxii],anticancer[xxxiii], antifungal[xxxiv],anticonvulsant[xxxv], and anti-HIV[xxxvi]properties. A number of compounds with chromene moiety are also known to activate potassium channels and as potential inhibitors of h-MAO-B[xxxvii], AChE[xxxviii], and TNF-α[xxxix].Among various chromenes, 2-imino derivatives have been a growing interest during the last few years. Although a number of these compounds are used as protein tyrosine kinase (PTK) inhibitors[xl]as well as anticancer[xli], antimicrobial[xlii], and anti-Alzheimer[xliii], agents, there are a few reports on the synthesis of functionalized 2-iminochromenes. The classic method for the synthesis of these compounds is the reaction of salicylaldehydes with active cyanomethylene compounds catalyzed by a few catalysts[xliv-xlix].While each of these methods has its own advantage, many suffer from limitations such as the use of relatively expensive catalysts, prolonged reaction times, unsatisfactory yields, and tedious isolation procedures. Thus the search for efficient, easily accessible, inexpensive, and environmentally friendly organocatalysts are still a challenge.

Prompted by these facts and as part of our research on the development of environmentally friendly methods for the synthesis of organic compounds using reusable catalysts[xlx-xlxix],we report here the results of our investigation on the application of DABCO, DBU, and morpholine (Figure 1) as homogeneous catalysts in the synthesis of*N*-alkyl-2-imino-2*H*-chromene-3-carboxamides **3a-j**by reaction of salicylaldehydes**1a-c**with *N*-alkyl-2-cyanoacetamides**2a-d**in mixture of EtOH and H_2O as solvent (Scheme 1).

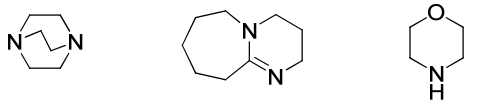
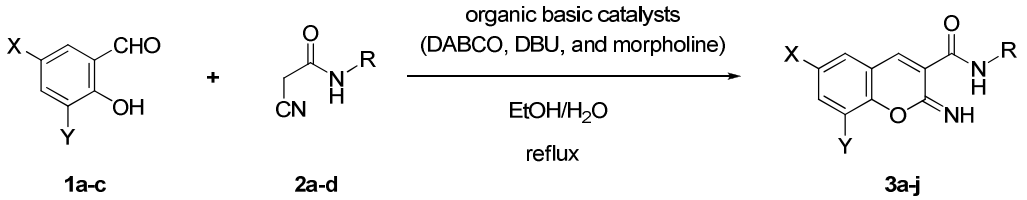


Figure 1.Structures of used organic basic catalysts



Scheme 1.Synthesis of functionalized 2-iminochromenes using organic basic catalysts

Experimental

N-Alkyl-2-cyanoacetamides **2a-d**were prepared according to the literature procedures [xxxviii,xlviii]. All chemicals were purchased from Merck and Aldrich and used without purification. Melting points were measured on a Stuart SMP3 melting point apparatus. The IR spectra were recorded as KBr pellets on a Tensor 27 Bruker spectrophotometer. The ^{1}H spectra were measured on a Bruker 300 FT spectrometer using TMS as the internal standard.

General procedure for the synthesis of *N*-alkyl-2-imino-2*H*-chromene-3-carboxamides 3a-j catalyzed by organic basic catalysts.

A mixture of salicylaldehydes**1a-c** (1 mmol), *N*-alkyl-2-cyanoacetamides**2a-d**(1 mmol) and an organic basic catalyst(DABCO, DBU, or morpholine, 12mol%)in EtOH-H_2O (3.0:3.0 mL) was heated under reflux for 8-25 min. After completion of the reaction, monitored by TLC, the mixture was cooled to room temperature. The precipitated solid was collected by filtration, and recrystallized from ethanol to give compounds **3a-j** in high yields.

Results and discussion

First, in order to investigate the optimizing reaction conditions for the synthesis of N-cyclohexyl-2-imino-2*H*-chromene-3-carboxamide **3b**, we carried out the reaction between salicylaldehyde **1a** (1 mmol), and *N*-cyclohexyl-2-cyanoacetamide **2b** (1 mmol), as a model,in different sets of reaction conditions. A summary of the optimization experiments is provided in Table 1.Low yields of the desired product **3b** were obtained under catalyst-free conditions in refluxing EtOH, H_2O, or mixture of them and also under solvent-free conditions at high temperature(entries 1-4).Several organic bases were evaluated in the reaction as catalyst,including DABCO, DBU and morpholine. The reactions were carried out in different solvents, including EtOH, H_2O, EtOH-H_2O, and also under solvent-free conditions. EtOH-H_2O proved to be a much better solvent in terms of yield as well as reaction time than all the others. For finding the best catalyst amount, we started the experiments using 8 mol% of each catalyst. Moderate yields of the product were obtained in this condition. Increasing the amount of the catalyst increased the yield of the product **3b**. The optimal amount was 12 mol% (Entry 15). Increasing the amount of the catalyst beyond this value had no significant effect on the yields and reaction times.

Table 1

Optimization of reaction conditions for the synthesis of compound **3b** catalyzed by organic basic catalysts[a]

Entry	Catalyst	Catalyst amount (mol%)	Solvent	T (°C)	Time (min)	Isolated Yield (%)
1	DABCO/DBU/morpholine	-----	EtOH	reflux	60	27
2	DABCO/DBU/morpholine	-----	H_2O	reflux	60	23
3	DABCO/DBU/morpholine	-----	EtOH-H_2O	reflux	50	29
4	DABCO/DBU/morpholine	-----	-----	120	120	28
5	DABCO/DBU/morpholine	8	-----	100	60/70/90	52/46/47
6	DABCO/DBU/morpholine	8	-----	120	60/70/80	50/47/44
7	DABCO/DBU/morpholine	8	EtOH	reflux	40/50/60	59/56/57
8	DABCO/DBU/morpholine	8	H_2O	reflux	45/60/70	54/50/47
9	DABCO/DBU/morpholine	8	EtOH-H_2O	reflux	30/35/45	65/58/54
10	DABCO/DBU/morpholine	10	EtOH	reflux	25/30/40	68/68/63
11	DABCO/DBU/morpholine	10	H_2O	reflux	35/40/45	60/56/52
12	DABCO/DBU/morpholine	10	EtOH-H_2O	reflux	20/25/30	78/75/69
13	DABCO/DBU/morpholine	12	EtOH	reflux	12/15/18	85/82/80
14	DABCO/DBU/morpholine	12	H_2O	reflux	15/15/20	78/75/71
15	DABCO/DBU/morpholine	12	EtOH-H_2O	reflux	10/12/15	92/89/85
16	DABCO/DBU/morpholine	12	EtOH-H_2O	50	15/17/20	77/72/73
17	DABCO/DBU/morpholine	12	EtOH-H_2O	r.t.	30/40/45	61/58/56
18	DABCO/DBU/morpholine	14	EtOH-H_2O	reflux	12/15/15	91/90/87

[a]Reaction conditions: salicylaldehyde**1a** (1 mmol) and *N*-cyclohexyl-2-cyanoacetamide**2b** (1 mmol).

With optimized conditions in hand, we began to study the scope of the reaction. Therefore, a range of *N*-alkyl-2-imino-2*H*-chromene-3-carboxamides were prepared by reaction of salicylaldehydeswith various *N*-alkyl-2-cyanoacetamides in the presence of DABCO, DBU

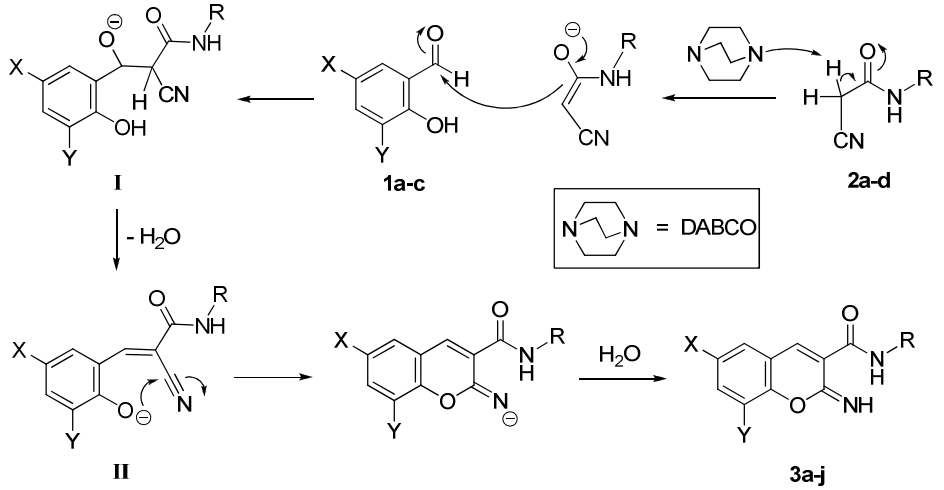
ormorpholine under optimized conditions. As can be seen from Table 2, all reactions proceed very cleanly to give the corresponding *N*-alkyl-2-imino-2*H*-chromene-3-carboxamide **3a-j** in high yields over short reaction times, and no undesirable side-products were observed. Although all three used catalysts showed good catalytic effects, but DABCO proved to be the better catalyst than others in terms of yield and reaction time.

Table 2
Synthesis of functionalized 2-iminochromenes**3a-j** using organic basic catalysts[a]

Product	X	Y	R	Catalyst	Time (min)	Isolated Yield (%)
3a	H	H	$PhCH_2$	DABCO/DBU/morpholine	12/15/15	89/86/85
3b	H	H	Cyclohexyl	DABCO/DBU/morpholine	10/12/15	92/89/85
3c	H	H	Cyclopentyl	DABCO/DBU/morpholine	15/15/17	88/86/83
3d	H	H	CH_3	DABCO/DBU/morpholine	8/10/13	93/91/87
3e	Br	H	$PhCH_2$	DABCO/DBU/morpholine	10/15/15	90/90/88
3f	Br	H	Cyclohexyl	DABCO/DBU/morpholine	12/15/20	91/89/84
3g	Br	H	Cyclopentyl	DABCO/DBU/morpholine	15/17/20	89/86/85
3h	H	OCH_3	$PhCH_2$	DABCO/DBU/morpholine	15/15/17	90/89/86
3i	H	OCH_3	Cyclohexyl	DABCO/DBU/morpholine	15/20/25	89/85/82
3j	H	OCH_3	Cyclopentyl	DABCO/DBU/morpholine	20/25/25	86/82/81

[a]Reaction conditions: salicylaldehydes**1a-c** (1 mmol), *N*-alkyl-2-cyanoacetamides**2a-d**(1 mmol), organic basic catalysts (12 mol%), $EtOH/H_2O$, reflux.

A plausible mechanism for this reaction may proceed as depicted in Scheme 2. On the basis of this mechanism, in the presence of DABCO, *N*-alkyl-2-cyanoacetamides **2a-d**convert to their enolate form, to be able to react easily with salicylaldehydes**1a-c** to form the intermediate **I** which on dehydration affords intermediate **II.** Final cyclization of the later intermediate gave the products **3a-j**. Under these conditions, attempts to isolate the intermediates failed even after careful monitoring of the reactions.



Scheme 2.Plausible mechanism for the formation of *N*-alkyl-2-imino-2*H*-chromene-3-carboxamides catalyzed by organic basic catalysts

Conclusion

Catalytic activity of three nitrogen-containing organic basic catalysts including DABCO, DBU, and morpholine, was compared in the synthesis of *N*-alkyl-2-imino-2*H*-chromene-3-carboxamides by the reaction of salicylaldehydeswith *N*-alkyl-2-cyanoacetamides. The

reaction proceeded in EtOH-H_2O as solvent under reflux temperature giving high yields of the products in short reaction time. Among three tested organocatalysts, DABCO proved to be the most efficient catalyst.

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