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$InCl_3$ as an Efficient Catalyst for Synthesis of Oxazolines under Thermal, Ultrasonic and Microwave Irradiations

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Efficient synthesis of 2-oxazolines by the reaction of nitriles with *β*-aminoalcohols using $InCl_3$ as catalyst under reflux conditions is reported. This catalyst can be successfully applied to the chemoselective conversion of dicyanobenzenes to their corresponding mono- and *bis*-oxazolines. The application of ultrasonic and microwave irradiation improved the yields and reduced the reaction times. Another advantage of this catalytic system is its ability to carry out large-scale reactions under ultrasonic and MW irradiations. Alkylnitriles such as acetonitrile was also converted to its corresponding 2-methyloxazoline in the presence of catalytic amounts of $InCl_3$.

Keywords: Indium(III) chloride, Nitrile, Oxazoline, Ultrasonic irradiation, Microwave irradiation

INTRODUCTION

2-Oxazolines are an important class of heterocycles and are versatile intermediates in synthetic organic chemistry [1-5]. They have been found in a variety of biologically active natural products including siderophores and postsynthetically modified nonribosomal polypeptides [6-8]. These compounds are also used as protecting groups for carboxylic acids and hydroxylamines [9]. Chiral oxazolines have been extensively used in asymmetric synthesis both as auxiliaries and ligands [10-12]. A number of methods have been developed for the preparation of 2-oxazolines from carboxylic acids [13], carboxylic esters [14], nitriles [15-17], aldehydes [18], hydroxyamides [19] and olefins [20]. However, many of these procedures have several drawbacks including strong acidic conditions, long reaction times, low yields of products, use of complex reagents and toxic solvents. Therefore, there is still a need to search for a better catalyst with regards to toxicity, selectivity, availability and easy work-up conditions for the synthesis of 2-oxazolines.

The ultrasonic irradiation (US) leads to cavitation phenomenon, which is accompanied by few extreme effects, such as local increase of temperature, local high pressure, and the formation of intense liquid microflows [21]. These effects may enhance liquid-solid mass transfer and cause considerable physicochemical changes in the medium [22].

Microwave (MW) energy is a non-classical energy source, with ultrasound, high pressure, mechanical activation, or plasma discharge. Since first reports of the use of MW heating to accelerate organic chemical transformations [23], several articles have been published on the subject of microwave-assisted synthesis and related topics-microwave chemistry has certainly became an important field of modern organic chemistry [24-29]. Microwave activation increases the efficiency of many chemical processes and can simultaneously reduce formation of the byproducts obtained from conventionally heated reactions. On the other hand, the combination of transition metal homogeneous catalysis and

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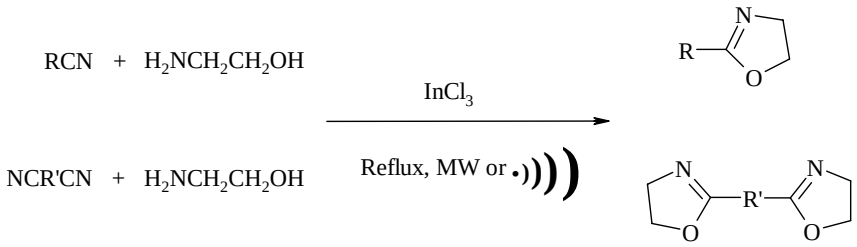


Scheme 1

microwave irradiation is likely to have an impact on modern chemistry.

In continuation of our ongoing studies for the synthesis of imidazolines and oxazolines [17,30], here we report an efficient method for the synthesis of oxazolines by the reaction of nitriles with 2-aminoethanol catalyzed by $InCl_3$ under reflux conditions, under ultrasonic and MW irradiations (Scheme 1).

EXPERIMENTAL

All materials were commercial reagent grade. The reactions under ultrasonic irradiation were carried out at room temperature in a 40 ml glass reactor. A UP 400S ultrasonic processor equipped with a 3 mm wide and 140 mm long probe, which was immersed directly into the reaction mixture, was used for sonication. The operating frequency was 24 kHz and the output power was 0-400 W trough manual adjustment. A Milestone Micro-SYNTH labstation instrument was used for microwave irradiation.

^{1}H NMR spectra were recorded on a Bruker-Arance AQS 300 MHz. All melting points were obtained by Stuart Scientific apparatus. All reactions were monitored by TLC and all yields refer to isolated products.

General Procedure for the Synthesis of Oxazolines Catalyzed by $InCl_3$ under Reflux Conditions or under Ultrasonic Irradiation

In a 50 ml flask equipped with a condenser, a magnetic stirrer and an oil-bath, a mixture of nitrile (4 mmol), 2-aminoalcohol (16 mmol) and $InCl_3$ (0.2 mmol) was prepared. The reaction mixture was refluxed or was exposed to ultrasonic irradiation for the appropriate time as indicated in Table 1. The progress of the reaction was monitored by TLC. After the reaction was completed, the mixture was diluted with $CHCl_3$ (10 ml). The mixture was filtered and the solid material was washed with $CHCl_3$ (10 ml). The solvent was evaporated and the crude product was purified by column chromatography on neutral alumina to afford the pure 2-substituted oxazoline (Table 1). IR and ^{1}H NMR spectral data confirmed the identities of the products.

General Procedure for the Preparation of Oxazolines and Bis-oxazolines under MW Irradiation

The microwave system used for this experiment included the following items: Micro-SYNTH labstation, complete with glass door, dual magnetron system with pyramid-shaped diffuser, 1000 Watt delivered power, exhaust system, magnetic stirrer, “quality pressure” sensor for flammable organic solvents, ATCFO fiber optic system for automatic temperature control.

All reactions were carried out at 80 °C, with 400 W applied power in a 50 ml round-bottom flask provided with two openings, and equipped with a glass condenser.

A mixture of nitrile (5 mmol), aminoalcohol (20 mmol) and $InCl_3$ (0.25 mmol) was irradiated with MW for an appropriate period of time, as mentioned in Table 1. After completion of the reaction (monitored by TLC, eluent: EtOAc/MeOH, 4:1), $CHCl_3$ (10 ml) was added and filtered. The catalyst was washed with CH_3Cl (10 ml). Evaporation of the solvent under reduced pressure and purification of the crude product on a neutral alumina column (eluent: EtOAc/MeOH, 4:1) gave the product. The identities of products were confirmed by m.p., IR and ^{1}H NMR spectral data.

RESULTS AND DISCUSSION

Synthesis of 2-Oxazolines and *Bis*-oxazolines Catalyzed by $InCl_3$ under Reflux Conditions

Initially, we investigated the ability of this catalyst for the synthesis of 2-oxazoline. In this manner, the reaction of

Table 1. Synthesis of 2-Oxazoline and *Bis*-oxazoline Catalyzed by $InCl_3$ under Reflux and under Ultrasonic Irradiation

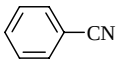
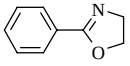
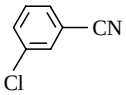
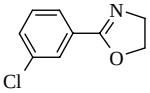
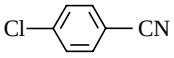
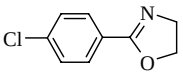
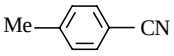
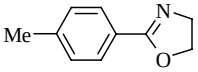
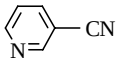
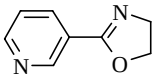
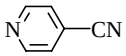
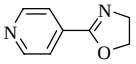
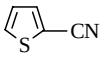
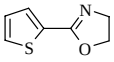
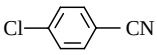
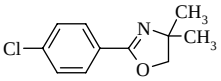
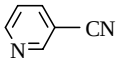
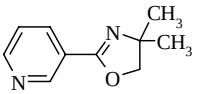
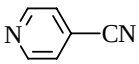
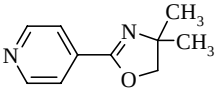
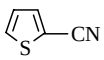
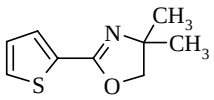
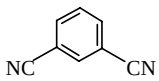
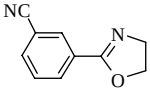
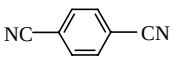
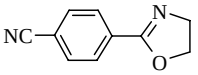
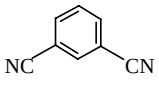
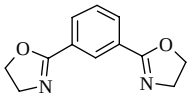
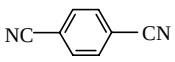
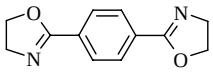
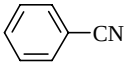
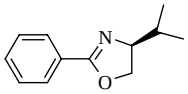
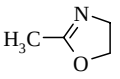
Row	Nitrile	Oxazoline	Reflux conditions		Ultrasonic irradiation		MW Irradiation		M.p. (°C)[a]
			Time (min)	Yield (%)	Time (min)	Yield (%)	Time (min)	Yield (%)	
a			90	95	30	95	4	90	Oil [36]
b			60	95	10	95	2	90	41-43 [37]
c			180	80	30	95	3	91	77-79 [38]
d			120	90	20	95	3.5	90	69-71 [36]
e			60	95	10	95	1.5	95	66-68 [36]
f			30	93	5	97	1	97	109-111 [39]
g			60	95	15	95	2	95	58-60 [40]
h			180	80	45	82	3	92	78-80 [42]
i			180	90	45	91	2	94	Oil [15]
j			180	95	45	95	2	96	48-50 [15]
k			180	80	45	81	2.5	94	30-32 [43]
L			10	94	10	48 (mono) 48 (bis)	-	-	98-100 [17]
m			15	95	5	48 (mono) 48 (bis)	-	-	109-111 [41]

Table 1. Continued

n			120	97	20	96	4	95	136-138 [44]
o			240	96	10	95	3	96	137-139 [38]
p[b]			180	84	45	90	2	93	Oil [43][b]
q	CH_3CN		180	95	40	95	3	94	Liquid (b.p.) 108-109 [45]

[a]Isolated yields; All products were identified by comparison with authentic samples (IR, ^{1}H NMR, m.p.). [b]$[\alpha]_D^{25}$ -72 (**c** 6.5, $CHCl_3$).

benzonitrile with 2-aminoethanol was carried out under reflux conditions and 2-phenyloxazoline was obtained in 95% isolated yield. As shown in Table 1, treatment of a series of nitriles with 2-aminoethanol and 2-amino-2-methylpropanol in the presence of catalytic amount of $InCl_3$, provided the corresponding 2-oxazolines in high yields (entries **a**-**k**).

The preparation of mono-oxazolines from dinitrile compounds is of great interest, because the remaining nitrile group can be converted to other functional groups [31]. Therefore, the reactions of dicyanobenzenes with 2-aminoethanol in the presence of this catalyst were also investigated. The reaction of dinitriles in shorter times led to exclusively mono-oxazolines (entries **l** and **m**) in excellent yields, while, in longer reaction times, *bis*-oxazolines (entries **n** and **o**) were produced in high yields (Table 1). *Bis*-oxazolines have gained special consideration as efficient ligands in asymmetric reactions [32]. Blank experiments showed that in the absence of the catalyst, only small amount of product was detected in the reaction of benzonitrile and 2-aminoethanol.

The actual mechanism of the reaction is not clear; however, a proposed mechanism is presented in Scheme 2.

In order to show the high catalytic activity of $InCl_3$, the effect of other Lewis acids such as $AlCl_3$, $FeCl_3.6H_2O$, $NiCl_2.6H_2O$, $CoCl_2.6H_2O$, $MnCl_2.4H_2O$, $CuCl_2.2H_2O$, $ZnCl_2$, $ZrOCl_2.8H_2O$ and WCl_6 in the synthesis of 2-phenyloxazoline, under reflux conditions, was also investigated. As shown in Table 2, $InCl_3$ is superior in terms of reaction time, yield of the product and toxicity [LD_{50}].

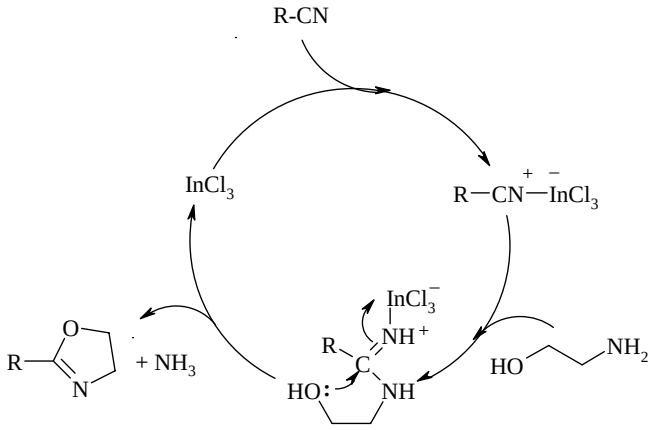
Synthesis of 2-Oxazolines and *Bis*-oxazolines Catalyzed by $InCl_3$ under Ultrasonic Irradiation

The application of ultrasonic irradiation in reactions using heterogeneous catalysts is a promising technique. The advantages of ultrasound procedures, such as good yields, short reaction times and mild reaction conditions, are well documented [33,34]. Ultrasonic irradiation can also be used to influence the selectivity and the yields of reactions. Therefore, we decided to investigate the effect of ultrasonic irradiation on the synthesis of 2-oxazolines and *bis*-oxazolines catalyzed by $InCl_3$. In this procedure, benzonitrile was mixed with 2-aminoethanol in the presence of $InCl_3$ and exposed under ultrasonic irradiation and 2-phenyloxaoline was obtained in excellent yield (95%) after 30 min. The effect of ultrasonic irradiation intensity on this reaction was also investigated and the highest yield of the product **2a** was obtained at 100% intensity. Reactions of a variety of nitriles with 2-aminoethanol and 2-amino-2-methylpropanol, in the presence of $InCl_3$ under ultrasonic irradiation, afforded 2-oxazolines in 80-98% yields (Table 1). The reaction of dicyanobenzene with 2-aminoethanol, under ultrasonic irradiation, afforded a mixture of mono and *bis*-oxazoline. The reaction temperature reached 60 °C during sonication because of cavities collapse, which can accelerate the reaction. In the absence of catalyst,

Table 2. Comparison of Catalytic Activity of other Lewis Acids with $InCl_3$ under Reflux Conditions[a]

Lewis acid	Time (min)	Yield (%)[b]	LD_{50} mg/Kg, oral rat	Other disadvantages
$InCl_3$	90	95	1983	
$AlCl_3$	180	80	3311	Needs sublimation prior to use
$FeCl_3.6H_2O$	180	83	900	Hygroscopic
$NiCl_2.6H_2O$	300	58	105	
$CoCl_2.6H_2O$	240	75	80	
$MnCl_2.4H_2O$	300	62	250	
$CuCl_2.2H_2O$	180	71	584	
WCl_6	300	89	2000	Moisture-sensitive

[a]Reaction conditions: nitrile (4 mmol), 2-aminoalcohol (16 mmol) and Lewis acid (0.2 mmol). [b]Isolated yield based on starting nitrile.



Scheme 2

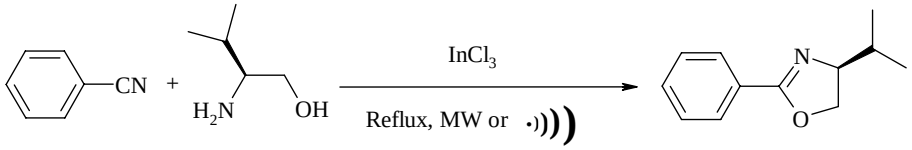
the ultrasonic waves have poor ability to produce the oxazolines.

Synthesis of 2-Oxazolines and *Bis*-oxazolines Catalyzed by $InCl_3$ under MW Irradiation

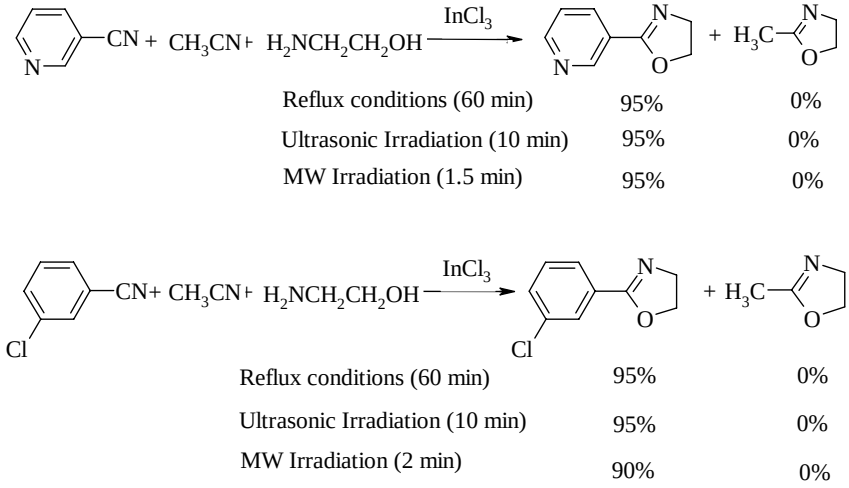
Irradiation of MW to a mixture of benzonitrile and 2-aminoethanol in the presence of $InCl_3$ produced the corresponding 2-phenyloxazoline in 90% yield after 4 min. While, under the same reaction conditions and in the absence of the catalyst, only 15% of 2-phenyloxazoline was detected in the reaction mixture. This observation showed that MW can be used as an efficient tool for accelerating the synthesis of 2-oxazolines and *bis*-oxazolines in the presence of $InCl_3$ as catalyst. The results (Table 1) showed that a variety of nitriles were efficiently converted to their corresponding 2-oxazilines in high yields and very short reaction times under MW irradiation (400 W, 90 ºC). Under the same reaction conditions, dinitriles were exclusively converted to *bis*-oxazolines.

Optically active oxazolines are also widely used in asymmetric synthesis [32]. Therefore, the synthesis of optically active *(S)*-(-)-4-isopropyl-2-phenyl-4,5-dihydrooxazole was also investigated by the reaction of benzonitrile and *L*-valinol using $InCl_3$ as catalyst. As shown in Table 1, under reflux conditions, ultrasonic and MW irradiations, the optically active product was obtained with more than 98% optical purity (entry **p** and Scheme 3). The optical rotation value of this product was confirmed by comparison with the literature value [35].

In order to show the ability of this catalyst in the synthesis of 2-alkyloxazolines, the reaction of acetonitrile with 2-aminoethanol was carried out in the presence of $InCl_3$. The results showed that, under reflux conditions and under ultrasonic or MW irradiation, the corresponding 2-methyloxazoline was obtained in excellent yield (Table 1, entry **q**); while most of the previously reported catalysts are not effective for the synthesis of 2-alkyloxazolines. The chemoselectivity of this catalyst was also investigated in the reaction of equimolar mixture of acetonitrile and arylnitriles with excess amount of 2-aminoethanol, under reflux conditions, ultrasonic or MW irradiation, in the presence of catalytic amounts of $InCl_3$. The results showed that only



Scheme 3



Scheme 4

arylnitriles were converted to the corresponding 2-aryloxazoline in high yields, whereas acetonitrile remained intact in the reaction media (Scheme 4).

In Table 3, the proposed method has been compared with some of the previously reported methods for the synthesis of 2-phenyloxazoline. As can be seen, the present method is superior in terms of yield and reaction time.

Table 3. Comparison of the Obtained Results by $InCl_3$ with some Previously Reported Methods in the Synthesis of 2-Phenyloxazoline

Catalyst	Time (min)	Yield (%)[a]
$InCl_3$	90	95
$ZrOCl_2{\cdot}8H_2O$	300	90 [30]
$ZnCl_2$	720	74 [26]
$Bi(TFA)_3$	210	86 [17]
$Bi(OTf)_3$	210	88 [17]
$BiOClO_4{\cdot}xH_2O$	240	80 [17]
$PhI(OAc)_2$	840	63 [18]
Ersorb-4	300	90 [13]

[a]Isolated yield.

CONCLUSIONS

In conclusion, an efficient and selective catalytic system was reported for the synthesis of 2-oxazolines. High catalytic performance, high product yields, short reaction times, easy availability and low cost of the catalyst, and applicability for the synthesis of 2-alkyloxazolines are noteworthy advantages of this method.

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