A Novel and Chemoselective Synthesis of 2-Aryloxazolines and Bis-oxazolines Catalyzed by Bi(III) Salts

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Abstract: Different arylnitriles react with β-aminoalcohols in the presence of catalytic amounts of Bi(III) salts such as $Bi(TFA)_3$, $Bi(OTf)_3$ and $BiOClO_4{\cdot}xH_2O$ producing the corresponding 2-aryloxazolines in high yields. Selective synthesis of mono- and bis-oxazolines from dicyanobenzenes and selective conversion of arylnitriles to their 2-oxazolines in the presence of alkylnitriles can be considered as noteworthy advantages of this method.

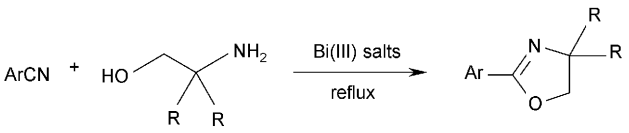
Key words: oxazolines, aminoalcohols, nitriles, bismuth(III) salts

2-Oxazolines are of great interest since they are present in a wide variety of biologically active natural products[1] and can be used as versatile synthetic intermediates.[2] These heterocycles are also used as protecting groups for carboxylic acids.[3] Optically active oxazolines have been extensively used as valuable auxiliaries in asymmetric synthesis.[4]

Several methods for the synthesis of 2-oxazolines from carboxylic acids,[5] esters,[6] nitriles,[7] hydroxyamides,[8] aldehydes[9] and olefins[10] have been reported previously. However, some of these methods suffer from disadvantages such as strongly acidic conditions, long reaction times, low yields of products, the use of complex reagents and the use of harmful halogenated hydrocarbons such as CCl_4 or hexachloroethane. Therefore, it is imperative that new 'environmentally friendly' reagents and more selective and efficient methods for the synthesis of 2-oxazolines be developed.

Recently, bismuth compounds have become attractive candidates for use as reagents in organic synthesis because they are relatively non-toxic, easy to handle, low in cost and relatively insensitive to air and moisture.[11] In continuation of our studies using Bi(III) salts for various organic transformations,[12,13] we report herein a new, efficient and highly selective method for the synthesis of 2-aryloxazolines from arylnitriles and β-amino alcohols in the presence of catalytic amounts of $Bi(TFA)_3$, $Bi(OTf)_3$ and $BiOClO_4{\cdot}xH_2O$ (Scheme 1).

Preliminary experiments were carried out on benzonitrile (**1a**) in order to find the best reaction conditions. The reactions were performed in the presence of different molar ratios of β-aminoalcohol and Bi(III) salts at room temperature and under reflux conditions. The best results were obtained with molar ratio of nitrile:β-aminoalcohol:catalyst, 1:4:0.25 for $Bi(TFA)_3$ and 1:4:0.05 for both $Bi(OTf)_3$ and $BiOClO_4{\cdot}xH_2O$ under reflux conditions (Table 1).[14]

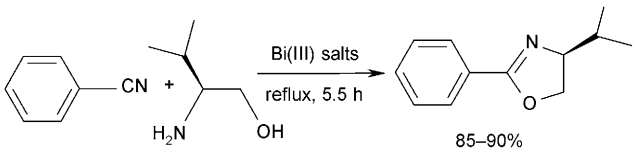


R = H, Me
Bi(III) salts = $Bi(TFA)_3$, $Bi(OTf)_3$, $BiOClO_4{\cdot}xH_2O$

Scheme 1

Following the above reaction conditions, different arylnitriles reacted with β-aminoalcohols in the presence of the above-mentioned Bi(III) salts to afford the corresponding 2-aryloxazolines in high yields (Table 1, entries a–k). It is important to note that selective synthesis of mono- and bis-oxazolines from dicyanobenzenes can be achieved by this method. As shown in Table 1, 1,3-dicyano- and 1,4-dicyanobenzenes (**1l** and **1m**) were converted to their corresponding mono-oxazolines (**2l** and **2m**) in 87–92% yields after 0.6–1 hour. By increasing the reaction times, however, the corresponding bis-oxazolines (**2n** and **2o**) were obtained in 80–88% yields after 10–12 hours.

Due to the applications of optically active oxazoline derivatives in asymmetric synthesis, the reaction of benzonitrile with (*S*)-(+)-2-amino-3-methyl-1-butanol in the presence of these catalysts was examined. Under these conditions, (*S*)-(–)-4-isopropyl-2-phenyloxazoline (**2p**) was obtained with >98% optical purity as determined by comparison of its optical rotation with a literature value (Scheme 2).[15]



Scheme 2

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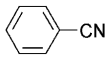
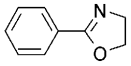
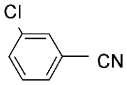
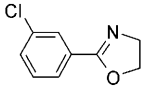
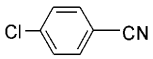
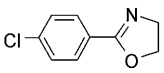
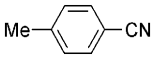
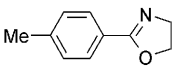
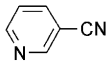
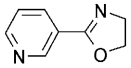
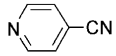
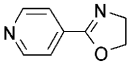
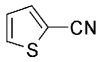
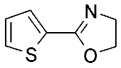
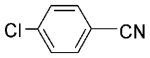
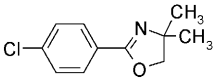
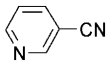
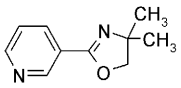
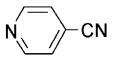
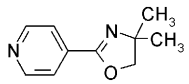
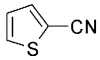
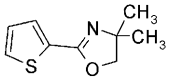
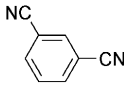
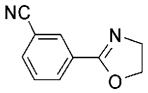
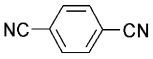
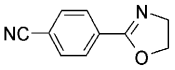
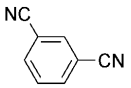
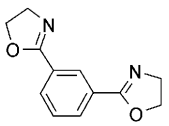
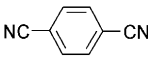
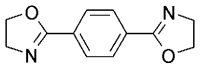
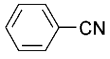
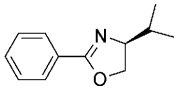
Table 1 Synthesis of 2-Aryloxazolines and Bis-oxazolines from Arylnitriles Catalyzed by Bi(III) Salts

Entry	Nitrile (**1**)	Product (**2**)	Yield (%)[a,b] (Time, h)			Mp (°C)[c]
			$Bi(TFA)_3$	$Bi(OTf)_3$	$BiOClO_4{\cdot}xH_2O$	
a			86 (3.5)	88 (3.5)	80 (4)	Oil[16a]
b			88 (2.5)	90 (2.5)	93 (2.5)	40–42[16b]
c			85 (3.5)	90 (3.5)	90 (3.5)	77–79[16c]
d			80 (5)	88 (6)	78 (6)	69–71[16a]
e			85 (4)	92 (4)	90 (4)	66–68[16a]
f			90 (1.3)	94 (1.25)	93 (1.5)	109–111[16d]
g			82 (4)	92 (4)	90 (4)	58–60[16e]
h			70 (3)	72 (4)	70 (3)	78–80[16f]
i			80 (4.5)	75 (4.5)	70 (4.5)	Oil[7a]
j			85 (3)	90 (3)	88 (3)	48–50[7a]
k			80 (4)	65 (5)	65 (5)	30–32[16g]
l[d]			92 (0.6)	90 (0.7)	90 (0.6)	98–100
m[d]			87 (1)	90 (1)	88 (1)	112–114[16h]
n[d]			88 (10)	85 (10)	85 (10)	137–139[16i]
o[d]			87 (11)	80 (12)	80 (12)	238–240[16a]
p			88 (5.5)	90 (5.5)	85 (5.5)	Oil[15]

[a] Products were identified by comparison of their physical and spectral data with those of authentic samples.
[b] Isolated yields.
[c] References for known compounds.
[d] Dinitrile:β-aminoalcohol:catalyst, 1:8:0.33 for $Bi(TFA)_3$ and 1:8:0.066 for both $Bi(OTf)_3$ and $BiOClO_4{\cdot}xH_2O$.

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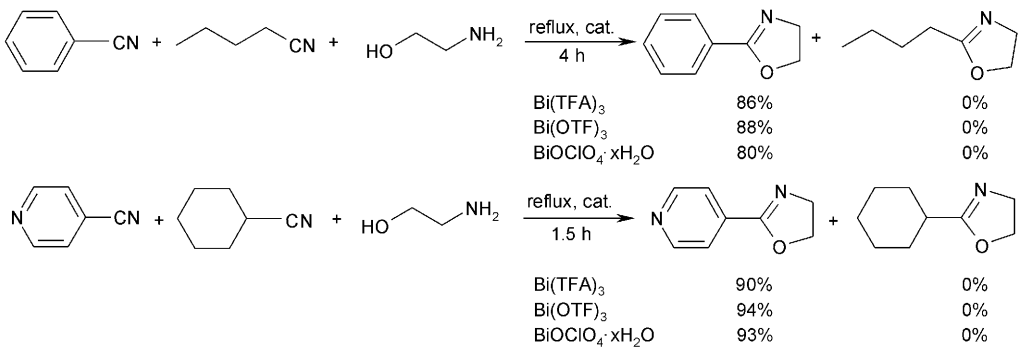

Scheme 3

It is also noteworthy that alkylnitriles did not produce the corresponding 2-oxazolines under the same reaction conditions. With this objective, a set of competitive reactions was conducted between arylnitriles and alkylnitriles, the results of which are shown in Scheme 3. The results indicate that the present protocol is potentially applicable for the chemoselective conversion of arylnitriles to their corresponding 2-oxazolines in the presence of alkylnitriles.

In conclusion, we have demonstrated a new and efficient method for the synthesis of 2-aryloxazolines using catalytic amounts of $Bi(TFA)_3$, $Bi(OTf)_3$ and $BiOClO_4{\cdot}xH_2O$ as novel catalysts. Furthermore, easy handling, low cost and non-toxicity of the catalysts make this method eco-friendly and environmentally acceptable. Moreover, high product yields, short reaction times, easy work-up and also high degree of chemoselectivity are other noteworthy advantages of this new method, which will make it a useful and important addition to the present methodologies.

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(14) **General Procedure.**
To a mixture of arylnitrile (1 mmol) and β-aminoalcohol (4–8 mmol) was added the catalyst [0.25–0.33 mmol of $Bi(TFA)_3$ and 0.05–0.066 mmol of $Bi(OTf)_3$ or $BiOClO_4{\cdot}xH_2O$]. The reaction mixture was stirred under reflux conditions for the appropriate time according to Table 1. The progress of the reaction was monitored by TLC (*n*-hexane–EtOAc, 2:1). The reaction mixture was cooled to r.t. and the crude product was purified by column chromatography on neutral alumina to afford the pure product (Table 1).
Compound **2l**: mp 98–100 °C. IR (KBr): 3040, 2900, 1647, 1490, 1230, 1056, 930, 670 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 4.09 (t, *J* = 9.6 Hz, 2 H), 4.46 (t, *J* = 9.6 Hz, 2 H), 7.53 (t, *J* = 7.8 Hz, 1 H), 7.74 (d, *J* = 7.7 Hz, 1 H), 8.18 (d, *J* = 7.8 Hz, 1 H), 8.22 (s, 1 H). Anal. Calcd for $C_{10}H_8N_2O$: C, 69.76; H, 4.68; N, 16.27. Found: C, 69.80; H, 4.70; N, 16.15.

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