Tin or Gallium-Catalyzed Cyanide-Transition Metal-Free Synthesis of Nitriles from Aldehydes or Oximes

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ABSTRACT

Tin or gallium chloride catalyzed transformation of oximes or aldehydes to nitriles is described. Various nitriles were obtained in up to 99% of yields. The gram-scale reaction or the optically active dinitrile was also available. This synthetically useful method has avoided toxic organic or inorganic cyanides as well as transition or noble metal catalysts.

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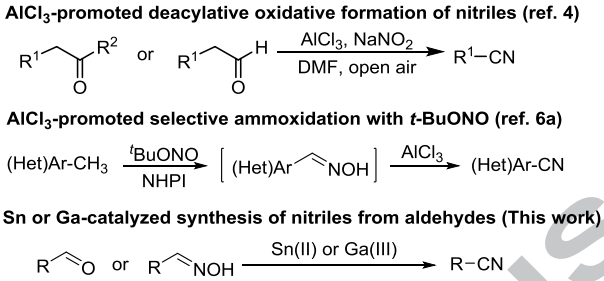
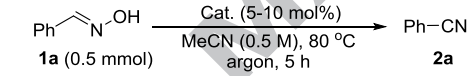
Nitriles are important and useful intermediates for the synthesis of amides, amines, carboxylic acids, oxazolines and ketones.[1] Among conventional approaches,[2,3] The transformation of aldoximes to nitriles has been established in 1881.[3] The conversion of cheap and easily available oximes to nitriles is a straight forward synthetic strategy and a variety of catalysts have been developed.[3] Besides oximes, ketones,[4] aldehydes[4,5] and methylarenes[6] are all suitable starting materials for nitriles. The coupling reactions have also been applied in the synthesis of nitriles from various [CN]-sources.[7] In our previous work of the synthesis of nitriles from methylarenes or carbonyl compounds, $AlCl_3$ has proven to be an efficient catalyst or reagent for promoting these reactions.[4,6a] In this work, gallium and tin chlorides were found even more efficient than $AlCl_3$ as Lewis acids in the conversion of oximes to nitriles.

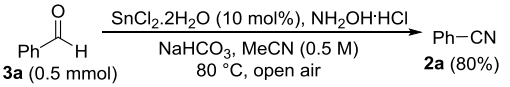


Scheme 1. Group 13 metal-catalyzed synthesis of nitriles.

Initially, various Lewis acids were investigated (Scheme 2). Several catalysts such as $GaCl_3$, $SnCl_2$, $Zn(OTf)_2$, and $Ga(OTf)_3$ were all found to be efficient, whereas $GaCl_3$ and $SnCl_2$ were proven to be the best. In the transformation of oximes to nitriles, $GaCl_3$ and $SnCl_2$ were both selected as the catalysts, whereas only $SnCl_2$ was selected for the synthesis nitriles from aldehydes. Compared with $GaCl_3$, $SnCl_2$ was not sensitive to moisture, therefore reactions could be carried out in the open air in the presence of $SnCl_2$.



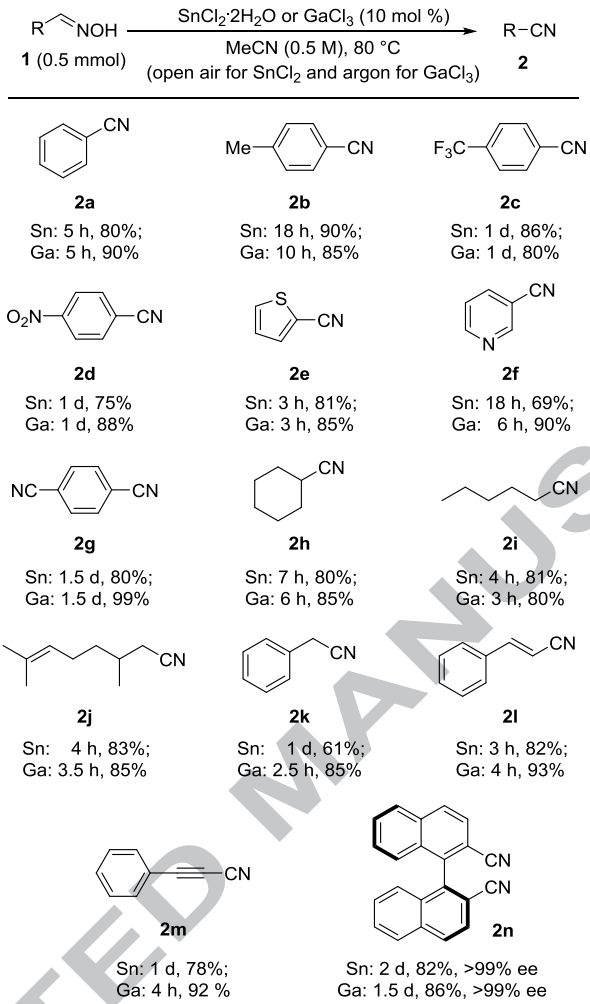
Cat. (mol%)	**2a** (%)	Cat. (mol%)	**2a** (%)
$BF_3{\cdot}OEt_2$ (10)	16	$ZnCl_2$ (10)	31
$AlCl_3$ (10)	19	$SnCl_2{\cdot}2H_2O$ (10) (air)	**91**
$GaCl_3$ (10)	**99**	$CoCl_2$ (10)	<5
$GaCl_3$ (5)	57	$CaCl_2$ (10)	<5
$InCl_3$ (10)	53	$Ni(ClO_4)_2{\cdot}6H_2O$ (10)	18
$Ga(OTf)_3$ (10)	73	$Sc(OTf)_3$ (10)	31
$Zn(OTf)_2$ (10)	86	HCl in Et_2O (10)	13



($BF_3{\cdot}OEt_2$ or $AlCl_3$ or $GaCl_3$ instead of [Sn]: < 5%)

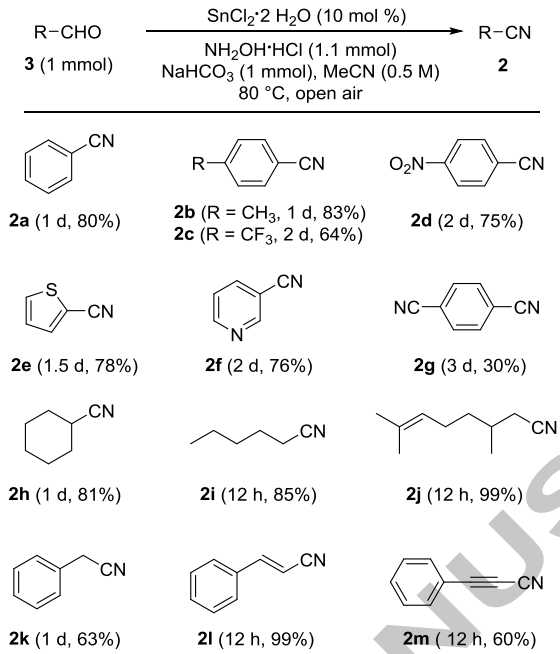
Scheme 2. Reaction conditions.

Various oximes bearing different substituents were subjected to the reaction conditions catalyzed by tin(II) chloride (method 1A) or gallium(III) (method 1B) (Scheme 3).[8] Either aliphatic or aromatic oximes were smoothly converted to desired nitriles in generally high yields. Even if the substrates bearing strong electron-withdrawing groups such as nitryl or trifluoromethyl gave corresponding nitriles in 75-86% of yields (**2c** and **2d**). Heteroaryl nitriles such as **2e** and **2f** were obtained in high yields with gallium catalyst. Nicotinonitrile **2f** is the precursor of Niacin or nicotine derivatives. Dinitrile **2g** was obtained in up to 99% of yield. With respect to aliphatic nitriles, all nitriles (**2h**, **2i**, **2j** and **2k**) examined were isolated in more than 80% of yields with gallium catalyst. Cinnamonitrile **2l** and 3-phenylpropiolonitrile **2m** were readily synthesized from corresponding oximes in good to high yields. Chiral dinitriles **2n** was obtained in 86% of yield with more than 99% ee for corresponding enantioenriched dioxime. In the transformation of oximes to nitriles, $SnCl_2$ generally demonstrated lower efficiency compared with $GaCl_3$.



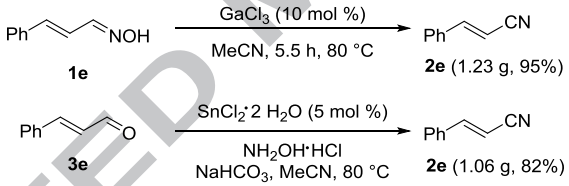
Scheme 3. Synthesis of nitriles from oximes (method 1, for the procedure, see ref. 8).

The direct synthesis of nitriles from aldehydes is more convenient in organic synthesis. In the aforementioned optimization of reaction conditions, $SnCl_2$ was found to be more efficient than $GaCl_3$ in the direct synthesis of nitriles from aldehydes (Scheme 2) due to its tolerance to moisture. Thus $SnCl_2$ was employed to investigate the direct synthesis of nitriles from aldehydes (method 2).[9] Comparable yields were obtained for $SnCl_2$ in the catalysis in conversion of oximes and aldehydes to nitriles. For example, nitrile **2a** was obtained in 80% yield for both cases. Normally longer reaction time was needed for the direct transformation of aldehydes to nitriles.



Scheme 4. Direct synthesis of nitriles from aldehydes (method 2, for the procedure, see ref. 9).

To evaluate the ability of this method in organic synthesis, gram-scale reactions have been carried out. Either oxime **1e** or aldehyde **3e** afforded the desired nitrile **2e** in high yields (Scheme 5).



Scheme 5. Gram-Scale synthesis

In conclusion, a synthetically useful method for synthesis of nitriles from oximes or aldehydes catalyzed by gallium (III) chloride or tin(II) chloride has been developed. Under transition or noble metal-free conditions, either aromatic or aliphatic nitriles were obtained in generally good yields. The gram-scale synthesis indicates it would be useful method in organic synthesis.

Acknowledgments

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8. *General procedure for synthesis of nitriles from oximes (Method 1A and 1B).* The solution of oxime (0.5 mmol) and $SnCl_2{\cdot}2H_2O$ (Method 1A) or $GaCl_3$ (Method 1B) (0.05 mmol) in dry MeCN (1 mL) was stirred at 80 °C monitored by TLC (under open air for $SnCl_2$ and under argon for $GaCl_3$). After completion of the reaction, the mixture was purified by flash chromatography.
9. *General procedure for synthesis of nitriles from aldehydes (Method 2).* The solution of aldehyde (1.0 mmol), $NH_2OH{\cdot}HCl$ (1.1 mmol), $NaHCO_3$ (1.0 mmol) and $SnCl_2{\cdot}2H_2O$ (0.1 mmol) in dry MeCN (2 mL) was stirred at 80 °C under open air and monitored by TLC. After completion of the reaction, the mixture was purified by flash chromatography. This method is not moisture-sensitive.

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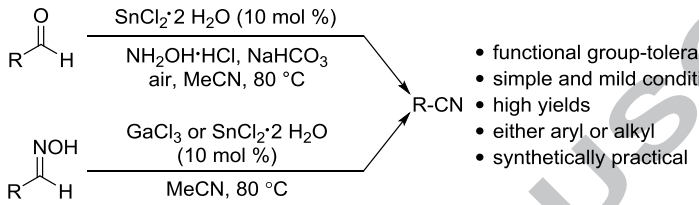

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- ✓ simple and mild conditions
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- ✓ either aryl or alkyl
- ✓ synthetically practical