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Acetohydroxamic acid: a new reagent for efficient synthesis of nitriles directly from aldehydes using $Bi(OTf)_3$ as the catalyst

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ABSTRACT

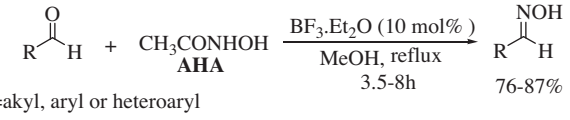
An efficient method for the preparation of nitriles directly from aldehydes by reaction with AHA using $Bi(OTf)_3$ as the catalyst is described. $Bi(OTf)_3$ is shown to be an efficient catalyst also for the conversion of aldoximes into nitriles.

Nitriles are important starting materials for the preparation of amines, amides, carboxylic acids, aldehydes, esters, and ketones[1] and they are also industrially important for the production of polymers, agrochemicals, pharmaceuticals, and dyes.[2] The classical methods for the preparation of nitriles include Kolbe nitrile synthesis,[3] ammoxidation of aldehydes,[4] hydrocyanation of alkenes,[5] Sandmeyer reaction of diazonium salts,[6] and Rosenmund–von Braun reaction of aryl halides.[7] During the past decade, studies on preparation of nitriles from aldehydes[8] and aldoximes[9] have received more focus and several methods are reported in literature. Most of the existing methods suffer from one or more of the disadvantages such as limited substrate scope, high reaction temperatures, low yields, and use of excess and toxic reagents. Therefore, development of a mild, efficient, and versatile method is still strongly desirable.

Acetohydroxamic acid (AHA) is a simple and stable organic compound, which is widely in use as a drug (Lithostat®) for treatment of urinary tract infections[10] and it also finds application as a chelating agent for extraction of metals, particularly for recovery of uranium from spent nuclear fuel by UREX process.[11] AHA is easily prepared by reacting ethyl acetate and hydroxylamine and it is also commercially available. Since the studies on reactions and applications of AHA in organic synthesis are scarcely recorded, we developed interest to study AHA for its applications and recently we showed that AHA is a useful reagent for conversion of aldehydes into aldoximes in high yields under $BF_3{\cdot}Et_2O$ catalysis in methanol as shown in Scheme 1.[12]

In the above reaction we did not observe the formation of nitriles even in trace quantities. However, the literature shows that some of the Lewis acids such as $Ga(OTf)_3$,[9a] $InCl_3$,[9b] $TiCl_3(OTf)$,[9c] $Cu(OAc)_2$,[9d] $PtCl_4(EtCN)_2$,[9e] and $Pd(OAc)_2$[9f] promote conversion of aldoximes into nitriles. Hence, we envisaged the scope for formation of nitriles by reacting an aldehyde and AHA and modifying the reaction conditions. Accordingly, we explored the reaction conditions with several acid catalysts and solvents to obtain nitriles and herein we report for the first time, an efficient method for the preparation of nitriles in high yields (88–97%) by reaction of an aldehyde with AHA under reflux in acetonitrile using $Bi(OTf)_3$ as the catalyst as shown in Scheme 2.

In our initial experiments, we studied the reaction of 4-isopropylbenzaldehyde **1a** and AHA using a variety of acid catalysts such as $Bi(OTf)_3$, $Zn(OTf)_2$, $Y(OTf)_3$, $Eu(OTf)_3$, $Sc(OTf)_3$, $La(OTf)_3$,



R=akyl, aryl or heteroaryl

Scheme 1. Synthesis of aldoximes by reaction of AHA with aldehydes under $BF_3{\cdot}Et_2O$ catalysis.

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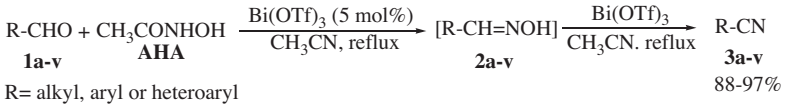
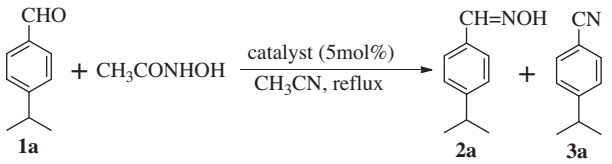


Scheme 2. Synthesis of nitriles by reaction of AHA with aldehydes under $Bi(OTf)_3$ catalysis.

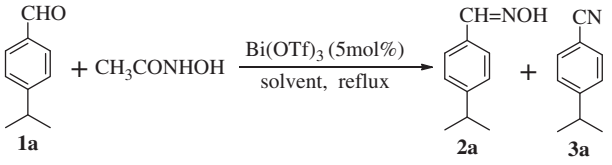
Table 1
Reaction of AHA and 4-isopropylbenzaldehyde in the presence of an acid catalyst



S. No.	Catalyst	Reaction time (h)	% Yield[a]		S. No.	Catalyst	Reaction time (h)	% Yield[a]	
			2a	**3a**				**2a**	**3a**
1	$Bi(OTf)_3$	14	0	97	7	$Eu(OTf)_3$	24	60	0
2	$Zn(OTf)_2$	15	15	80	8	$InCl_3$	24	95	0
3	$Y(OTf)_3$	15	33	65	9	$BF_3{\cdot}Et_2O$	24	80	0
4	$Sc(OTf)_3$	24	55	40	10	$Cu(OAc)_2$	24	60	0
5	$La(OTf)_3$	24	52	40	11	H_2SO_4	15	31	65
6	$Sm(OTf)_3$	24	46	50	12	PTSA	24	66	30

[a] Isolated yields.

Table 2
Study of the solvent effect on the reaction of an aldehyde with AHA under $Bi(OTf)_3$ catalysis



S. No.	Solvent	Reaction time (h)	% Yield[a] **2a**	% Yield[a] **3a**
1	CH_3CN	14	0	97
2	*N,N*-Dimethylformamide	24	12	80
3	Toluene	24	81	15
4	Dichloromethane	24	84	10
5	MeOH	24	97	0
6	1,4-Dioxane	24	95	0
7	Tetrahydrofuran	24	96	0

[a] Isolated yields.

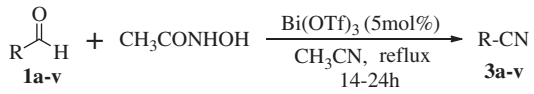
$Sm(OTf)_3$, $Cu(OAc)_2$, $BF_3{\cdot}Et_2O$, $InCl_3$, H_2SO_4, and *p*-toluenesulfonic acid (PTSA) under reflux in acetonitrile and the results are shown in Table 1. In this study, we observed the formation of nitrile **3a** (30–97% yields) with catalysts such as $Bi(OTf)_3$, $Zn(OTf)_2$, $Y(OTf)_3$, $Sc(OTf)_3$, $La(OTf)_3$, $Sm(OTf)_3$, H_2SO_4, and PTSA. Under similar conditions, catalysts such as $BF_3{\cdot}Et_2O$, $InCl_3$, $Eu(OTf)_3$, and $Cu(OAc)_2$ produced exclusively aldoxime **2a** in 60–95% yields. In this study, nitrile **3a** was obtained in maximum yield (97%) with $Bi(OTf)_3$.

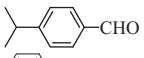
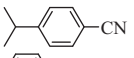
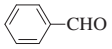
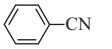
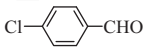
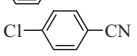
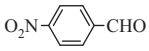
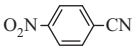
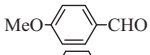
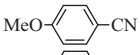
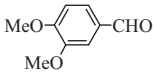
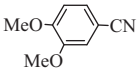
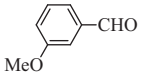
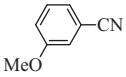
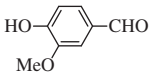
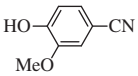
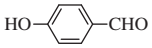
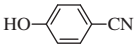
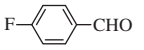
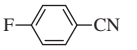
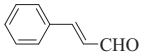
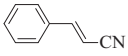
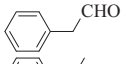
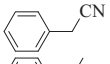
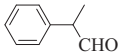
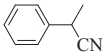
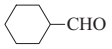
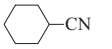
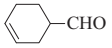
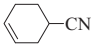
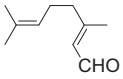
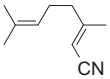
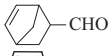
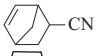
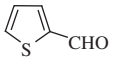
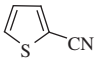
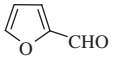
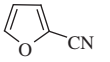
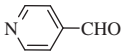
In the present reaction, we observed profound influence of the solvent on the catalysis of $Bi(OTf)_3$. For example, the reaction of AHA and 4-isopropylbenzaldehyde **1a** under $Bi(OTf)_3$ catalysis produced nitrile **3a** in solvents such as acetonitrile, *N,N*-dimethylformamide, toluene, and dichloromethane and it produced exclusively aldoxime **2a** in solvents such as methanol, 1,4-dioxane, and tetrahydrofuran as shown in Table 2. $Bi(OTf)_3$ is a oxophilic and hard Lewis acid. Hence, it experiences strong chelating effect in solvents such as methanol, 1,4-dioxane, and tetrahydrofuran. As a consequence, Lewis acidity of $Bi(OTf)_3$ is possibly not sufficiently strong in these solvents to promote dehydration of an aldoxime.

Since we observed an efficient formation of nitrile **3a** from the reaction of **1a** and AHA using $Bi(OTf)_3$ as the catalyst under reflux in acetonitrile, we studied a variety of akyl, aryl, and heteroaryl aldehydes **1a–v** under similar conditions to obtain corresponding nitriles **3a–v** in 88–97% yields as shown in Table 3.[13]

The plausible mechanism for the present transformation of aldehyde into nitrile using AHA under $Bi(OTf)_3$ catalysis is shown in Scheme 3. In this mechanism, we believe that $Bi(OTf)_3$ catalyzes reaction of an aldehyde **1** and AHA producing aldoxime **2** in the initial step and next it converts aldoxime **2** into nitrile **3** by reacting with it. In this process, we envisage that the catalyst splits into transient $Bi(OTf)_2OH$ and TfOH and regenerates $Bi(OTf)_3$ under the reaction conditions as shown in Scheme 3.

Table 3
Synthesis of nitriles by reaction of an aldehyde with AHA under $Bi(OTf)_3$ catalysis

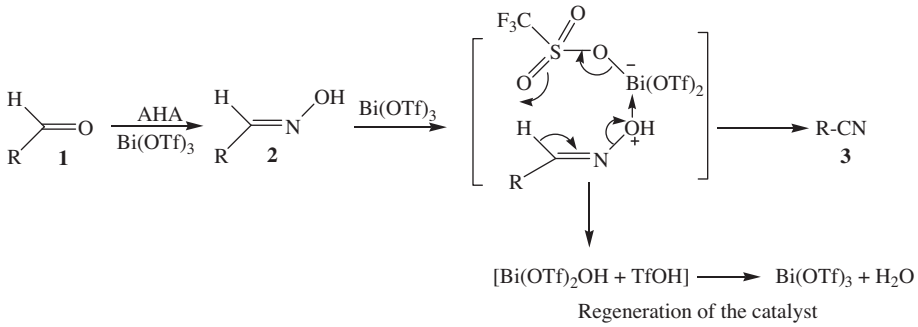


Entry	Aldehyde **1**	Nitrile **3**	Reaction time (h)	% Yield[a] **3**	mp (°C) **3**	mp (°C) **3** (L)
a			14	97	Liquid	
b			15	93	Liquid	
c			17	96	91–93	92–93[14a]
d			16	95	146–148	148[14b]
e			17	95	58–60	57–58[14a]
f			16	93	69–71	67–68[14c]
g			16	94	Liquid	
h			15	94	87–89	87–88[14d]
i			16	90	111–112	110[14a]
j			18	90	35–36	35–36[14a]
k			18	93	Liquid	
l			16	95	Liquid	
m			16	90	Liquid	
n			24	88	Liquid	
o			16	97	Liquid	
p			14	90	Liquid	
q			15	92	Liquid	
r			15	94	Liquid	
s			16	91	Liquid	
t			15	89	77–78	75–77[14a]
u			14	89	175–177	176–177[14f]
v			15	92	181–182	183–184[14e]

[a] Isolated yields. All products gave satisfactory ^1H & ^{13}C NMR, IR, and mass spectral data.

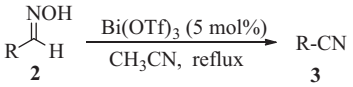
Since we proposed that aldehyde gets converted into nitrile via aldoxime in the above mechanism, we verified the scope for conversion of aldoximes into nitrile using $Bi(OTf)_3$ as the catalyst. In this study, we prepared a variety of aldoximes using our method (Scheme 1) and refluxed in acetonitrile in the presence of $Bi(OTf)_3$ to obtain corresponding nitriles 83–97% as shown in Table 4.[15]

In conclusion, this work describes an efficient one-step method for the preparation of nitriles directly from aldehydes using acetohydroxamic acid as a novel reagent, which was reacted with a variety of aliphatic, aromatic, and heteroaromatic aldehydes under $Bi(OTf)_3$ catalysis to obtain corresponding nitriles in high yields. In this study, we screened several acid catalysts and solvents, and optimized the reaction conditions to obtain nitriles in high yields.



Scheme 3. Plausible mechanism for formation of a nitrile from the reaction of an aldehyde with AHA under $Bi(OTf)_3$ catalysis.

Table 4
Formation of a nitrile from an aldoxime under $Bi(OTf)_3$ catalysis



S. No.	Oxime **2**	Reaction time (h)	Nitrile **3**	% Yield[a] **3**	S. No.	Oxime **2**	Reaction time (h)	Nitrile **3**	% Yield[a] **3**
1	**2a**	6	**3a**	97	6	**2n**	10	**3n**	83
2	**2b**	8	**3b**	93	7	**2o**	8	**3o**	96
3	**2c**	6	**3c**	93	8	**2s**	8	**3s**	86
4	**2d**	6	**3d**	95	9	**2t**	10	**3t**	86
5	**2k**	8	**3k**	87	10	**2v**	8	**3v**	91

[a] Isolated yields.

This work also describes the first application of $Bi(OTf)_3$ as the catalyst for efficient conversion of aldoximes into nitriles.

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13. *A typical method for preparation of nitrile from aldehyde using AHA*: 4-Isopropylbenzaldehyde **1a** (0.50 g, 3.37 mmol), acetohydroxamic acid (0.30 g, 4.05 mmol), acetonitrile (5 ml), and $Bi(OTf)_3$ (0.11 g, 0.17 mmol) were taken into a 25 ml round-bottomed flask fitted with a condenser and calcium chloride guard tube. The mixture was refluxed for 14 h and after completion of the reaction (GC, 10% SE-30 on Chromosorb, 10′ × 1/8″ column), the reaction mixture was cooled to room temperature and the solvent was removed under reduced pressure. The crude product obtained was purified by normal column chromatography(silica gel 100–200 mesh, ethyl acetate/hexane = 1:20) to obtain 4-isopropylbenzonitrile **3a** (0.47 g, 97%) in the form of a colorless liquid and it was characterized by the following spectral data: ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.60–7.56 (d, J = 8.5 Hz, 2H), 7.33–7.30 (d, J = 8.7 Hz, 2H), 3.00–2.91 (q, J = 6.9 Hz, 1H), 1.27–1.25 (d, J = 6.8 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 154.2, 132.1, 127.2, 119.1, 109.4, 29.6, 23.4; IR (neat): υ 3039, 2930, 2227, 1607, 1527, 1461, 1365 cm^{-1}; MS (ESI) 168 (M+Na). HRMS obsd: 168.0792 (Calcd: 168.0789).
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15. *A typical method for preparation of a nitrile from an aldoxime using $Bi(OTf)_3$ as the catalyst*: 4-Isopropylbenzaldoxime **2a** (0.5 g, 3 mmol), $Bi(OTf)_3$ (60 mg, 0.09 mmol) and acetonitrile (5 ml) were taken into a 25 ml round bottomed flask fitted with a condenser and $CaCl_2$ guard tube. The mixture was refluxed and when reaction was complete (GC), the reaction mixture was cooled to room temperature, concentrated under reduced pressure and the crude product was purified by normal column chromatography (silica gel 100–200 mesh, EtOAc/hexane = 1:20) to obtain 4-isopropylbenzonitrile **3a** (0.43 g, 97%), which gave the spectral data identical to that given above.