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Efficient microwave-assisted synthesis of oximes from acetohydroxamic acid and carbonyl compounds using $BF_3{\cdot}OEt_2$ as the catalyst

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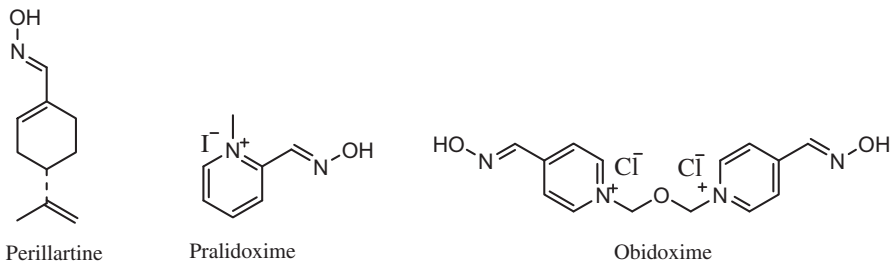
ABSTRACT

An efficient synthesis of oximes by reaction of carbonyls with acetohydroxamic acid using $BF_3{\cdot}OEt_2$ as a catalyst is described.

Oximes are of great interest as intermediates in organic synthesis for the preparation of nitriles,[1] nitro compounds,[2] amines,[3] amides,[4] isooxazolines,[5] isoquinolines,[6] and oximes are also very important ligands in the formation of mono- and polynuclear metal complexes.[7] Oxime functionality is an important structural feature in several biologically active compounds such as perillartine, an oxime of perillaldehyde, which is about 2000 times as sweet as sucrose[8] and, pralidoxime and obidoxime, which are important antidotes for organophosphate poisoning[9] (Fig. 1). In addition, oximes are also found as antimicrobial agents,[10] insecticides,[11] antioxidants,[12] vasodilators,[13] and inhibitors of P450.[14] The classical methods for the preparation of oximes include reaction of a carbonyl compound with hydroxylamine hydrochloride in the presence of a stoichiometric amount of a base,[15] reaction of nitrite such as ethyl nitrite with an active methylene compound[16] and reduction of a nitro compound.[17]

Acetohydroxamic acid ($CH_3CONHOH$), also known as Lithostat®, is a stable organic compound, which is derived from the reaction of hydroxyl amine and ethyl acetate. Acetohydroxamic acid is a drug used for the treatment of urinary tract infections[18] and it is also widely employed as a chelating agent in UREX process, for separation of uranium from spent nuclear fuel.[19] However, in organic chemistry, synthetic applications of acetohydroxamic acid have scarcely been explored and herein, we report the first application



Perillartine Pralidoxime Obidoxime

Figure 1. Some biologically active oximes.

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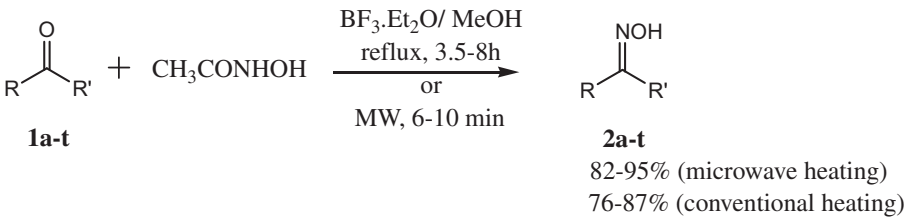
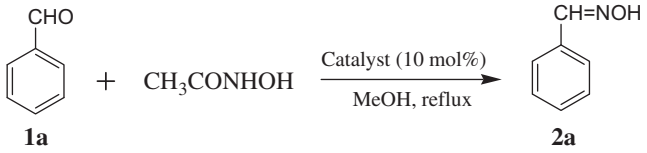


Scheme 1. In our preliminary study, a variety of Lewis and Bronsted acids such as $BF_3{\cdot}OEt_2$, $Bi(OTf)_3$, $Yb(OTf)_3$, $Sc(OTf)_3$, $Zn(OTf)_2$, $InBr_3$, $InCl_3$, $ZnCl_2$, *p*-toluene sulfonic acid (PTSA), H_2SO_4, and HCl were studied as catalysts for promoting the reaction of acetohydroxamic acid with benzaldehyde**1a** under reflux in methanol to obtain benzaldoxime **2a** and the results are shown in Table 1.

Table 1
Acid catalyzed conversion of benzaldehyde to benzaldoxime with acetohydroxamic acid



Entry	Catalyst	Reaction time (h)	**2a** Yield[a] (%)
1	$BF_3{\cdot}OEt_2$	3.5	87
2	$Bi(OTf)_3$	6	83
3	$Yb(OTf)_3$	7	78
4	$Sc(OTf)_3$	7	75
5	$InBr_3$	8	68
6	$InCl_3$	8	65
7	$ZnCl_2$	12	55
8	PTSA	12	62
9	H_2SO_4	6	73
10	HCl	6	58

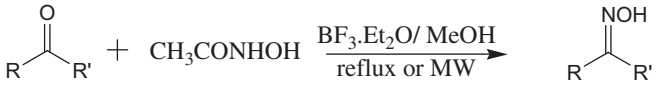
[a] Isolated yields.

of acetohydroxamic acid for the efficient preparation of oximes from carbonyls using $BF_3{\cdot}OEt_2$ as a catalyst under reflux in methanol as shown in Scheme 1.

Among all the catalysts studied (Table 1), $BF_3{\cdot}OEt_2$ gave benzaldoxime **2a** in maximum yields (87%, 3.5 h,) under reflux in methanol. We studied a variety of aldehydes **1a–j** and ketones **1k–t** under similar conditions and obtained corresponding oximes 2a–**t** in 76–87% yields. We have also studied these reactions under microwave heating and obtained oximes **2a–t** in 83–95% yields in relatively short reaction times (6–10 min) when compared to those observed under conventional heating (3.5–8 h) as shown in Table 2.[20]

In this study, both aldehydes and ketones formed only oximes when methanol was used as a solvent. However, in aprotic solvents such as dichloromethane, acetonitrile, and tetrahydrofuran, they reacted differently with acetohydroxamic acid, for example, under reflux in dichloromethane using $BF_3{\cdot}Et_2O$ as a catalyst; we obtained only oxime with an aldehyde and a mixture of oxime acetate and oxime with a ketone as shown in Table 3.

Table 2
Reaction of acetohydroxamic acid with carbonyls in MeOH using $BF_3{\cdot}Et_2O$ as a catalyst



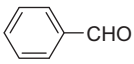
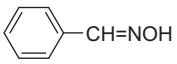
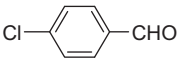
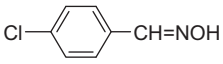
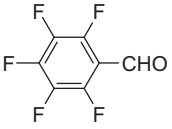
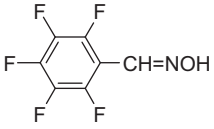
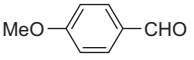
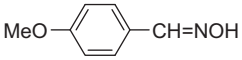
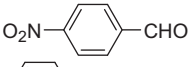
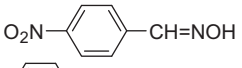
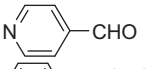
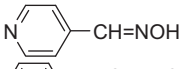
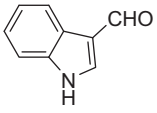
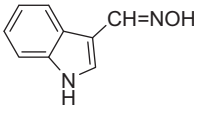
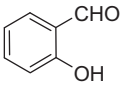
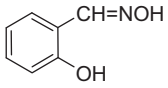
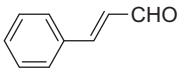
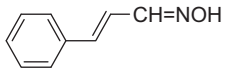
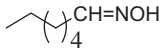
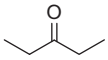
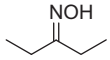
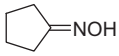
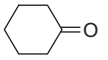
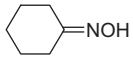
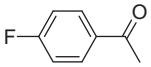
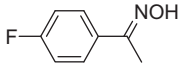
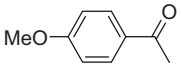
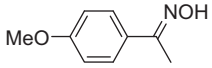
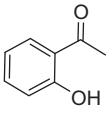
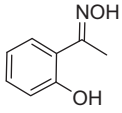
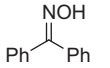
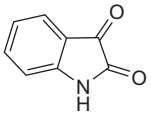
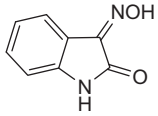
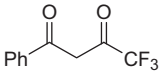
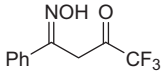
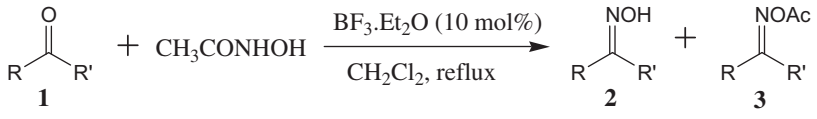
Entry	Carbonyl **1**	Oxime **2**	Conventional heating	Microwave heating
			%Yield[a] (reaction time, h)	%Yield[a] (reaction time, min)
a			87(3.5)	95(6)
b			85(4.0)	89(8)
c			87(5.0)	90(8)
d			85(3.5)	92(7)
e			78(8.0)	83(10)
f			83(4.5)	87(8)
g			78(4.0)	83(6)

Table 2 (*continued*)

Entry	Carbonyl **1**	Oxime **2**	Conventional heating	Microwave heating
			%Yield[a] (reaction time, h)	%Yield[a] (reaction time, min)
h			86(3.5)	92(6)
i			78(5.0)	84(7)
j			76(3.5)	82(6)
k			80(4.0)	87(7)
l			84(4.0)	89(6)
m			80(4.5)	87(7)
n			85(3.5)	93(7)
o			83(4.0)	90(8)
p			80(4.0)	86(8)
q			80(3.5)	90(6)
r			88(5.0)	92(9)
s			83(3.5)	95(7)
t			78(6.0)	83(8)

[a] Isolated yields. All products were characterised by ^{1}H NMR, ^{13}C NMR, mass and IR spectral data.

Table 3
Reaction of acetohydroxamic acid with aldehydes/ketones in dichloromethane under $BF_3{\cdot}Et_2O$ catalysis

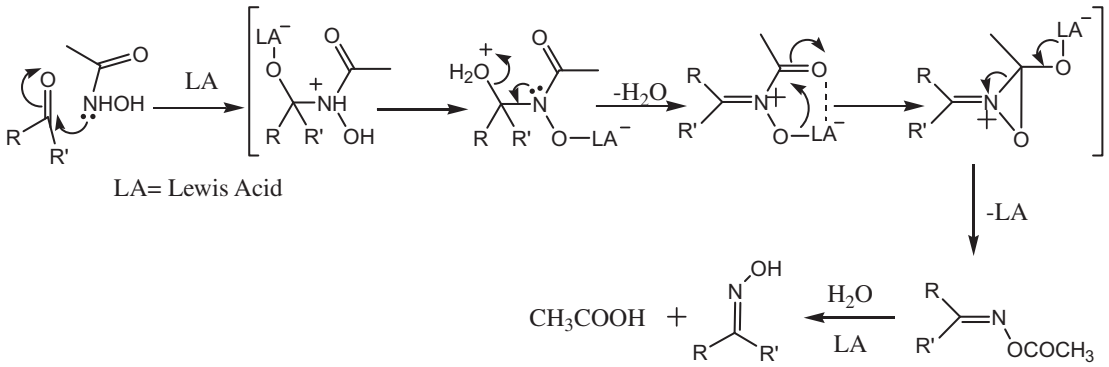


R = alkyl, aryl
R' = alkyl, aryl or H

Entry	Aldehyde	Ketone	Reaction time (h)	Yield[a] (%)	
				Oxime **2**	Oxime acetate **3**
1	**1a**		4/0	90	0
2	**1b**		5.0	87	0
3	**1c**		6.0	72	0
4	**1j**		5.5	82	0
5		**1k**	5.0	55	35
6		**1l**	5.0	46	48
7		**1m**	5.5	52	32
8		**1n**	4.5	50	27
9		**1o**	5.0	46	40

[a] Isolated yields.

In our study, oxime was formed as the only product in methanol and formation of oxime acetate was not detected (tlc) at any stage during the course of the reaction in this solvent. Possibly, oxime acetate undergoes rapid hydrolysis or methanolysis[21] in methanol



Scheme 2. In summary, we have shown an unprecedented microwave-assisted rapid synthesis of oximes in high yields by reaction of carbonyls with acetohydroxamic acid using $BF_3{\cdot}OEt_2$ as a catalyst and methanol as a solvent.

and converts into oxime. The formation of oxime acetate involves the unusual migration of the acyl group from N to O and the plausible reaction pathway for conversion of a carbonyl into an oxime via oxime acetate under Lewis acid (LA) catalysis is shown in Scheme 2. A similar mechanism is also possible with a Bronsted acid.

Acknowledgments

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References and notes

1. (a) Anand, N.; Owston, N. A.; Parker, A. J.; Slatforda, P. A.; Williamsa, J. M. J. *Tetrahedron Lett.* **2007**, *48*, 7761–7763; (b) Mendelsohn, B. A.; Lee, S.; Kim, S.; Teyssier, F.; Aulakh, V. S.; Marco, A.; Ciufolini, M. A. *Org. Lett.* **2009**, *11*, 1539–1542.
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20. *Typical procedure for preparation of oxime under conventional heating:* Benzaldehyde **1a** (1.0 g, 9.4 mmol), acetohydroxamic acid (1.1, 14.1 mmol), methanol (10 ml) and BF_3OEt_2 (135 μl, 0.94 mmol) were taken in a 25 ml round-bottomed flask fitted with a condenser and calcium chloride guard tube. The mixture was refluxed for 3.5 h and after completion of the reaction (TLC), the reaction mixture was cooled to room temperature. Solvent was removed from the mixture under reduced pressure and the crude product was purified by column chromatography (silica gel 100–200 mesh, ethyl acetate-hexane: 1:5) to obtain benzaldoxime **2a** (0.98 g, 87%) in the form of white powder and it was characterized by the following spectral data: ^{1}H NMR (300 MHz, $CDCl_3$): δ = 9.61 (bs, 1H, exchangeable with D_2O), 8.11(s, 1H), 7.54–7.63(m, 2H), 7.33–7.41 (m, 3H,); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 150.05, 131.52, 128.31, 127.08, 126.11; IR (KBr): υ 3380, 2977, 2924, 1762, 1620, 1369, 1494, 1257, 1075, 989, 643 cm^{-1}; EIMS (*m*/*z*, %): 121 (M^+), 104, 77, 51; Exact mass observed for C_7H_7NO: 121.0521(calculated: 121.0528).
Procedure under microwave heating: Benzaldehyde **1a** (1.0 g, 9.4 mmol), acetohydroxamic acid (1.1 g, 14.1 mmol), methanol (1 ml) were taken in a 10 ml pressure tube and to this, BF_3OEt_2 (135 μl, 0.94 mmol) was added and the mixture was subjected to microwave heating (CEM discover, 360 W, 70 °C, 25 psi) for 6 min. The crude product obtained was purified as mentioned above to afford benzaldoxime **2a** (1.1 g, 95%), which gave spectral data same as above.
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