

# Metal-Free: A Novel and Efficient Aerobic Oxidation of Primary Amines to Oximes Using *N,N',N''*-Trihydroxyisocyanuric Acid and Acetaldoxime as Catalysts in Water

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Received: 18.03.2014; Accepted after revision: 25.04.2014

**Abstract:** A general, efficient, and metal-free method for aerobic oxidation of aromatic primary amines to the corresponding oximes catalyzed by *N,N',N''*-trihydroxyisocyanuric acid and acetaldoxime with water as solvent is described. This practical method can use air as economic and green oxidant, water as green solvent, and tolerates a wide range of substrates, which can afford the target oximes in moderate to good yields.

**Key words:** amines, catalysis, hydrogen transfer, oxygen, oxidation

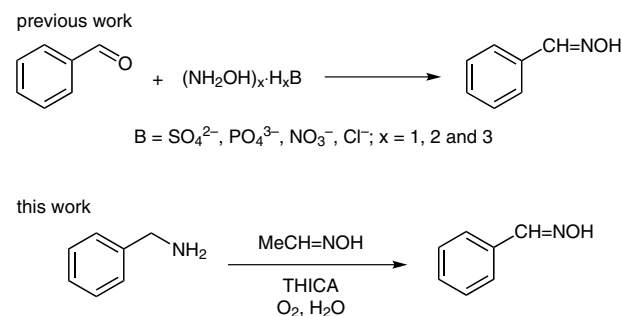
Oximes have been widely utilized in medicine, industry, and analytical chemistry, and they are very useful intermediates for the synthesis of commodity products, fine chemicals, medicines, and biologically active compounds.<sup>1–5</sup> Moreover, oximes are valuable synthetic tools, which can be either reduced to amines or oxidized to nitrile oxides,<sup>6,7</sup> and they can also be dehydrated to nitriles or undergo an acid-catalyzed Beckmann rearrangement to obtain amides.<sup>8</sup> The general method for the synthesis of oximes is the nucleophilic addition of hydroxylamine to aldehydes or ketones. Despite this methodology is also applied industrially on a large scale for the production of various oximes, the use of hydroxylamine appears to be quite dangerous from a safety point of view, especially in large amounts in processes. In order to reduce safety hazards, hydroxylamine salt[(NH<sub>2</sub>OH)<sub>x</sub>·H<sub>x</sub>B, B = SO<sub>4</sub><sup>2-</sup>, PO<sub>4</sub><sup>3-</sup>, NO<sub>3</sub><sup>-</sup>, Cl<sup>-</sup>; x = 1, 2, and 3] is often used instead of hydroxylamine.<sup>9,10</sup> However, this method has some drawbacks to restrict its further application: (1) stoichiometric or excess amounts of hydroxylamine salt cost relative to the respective substrates; (2) large amounts of byproducts are introduced into oximation reactions; (3) the poor yields of the oximes as the resulting oximes can undergo either dehydration to nitriles or acid-catalyzed Beckmann rearrangement to amides. Therefore, the need for a waste-free and in situ synthesis of oximes is an increasing challenge for chemists. Moreover, some studies have been performed to obtain oximes via the reduction of primary nitroalkanes involving the use of Se/NaBH<sub>4</sub>, Bu<sub>3</sub>SnH, SnCl<sub>2</sub>/PhSH, or Au/TiO<sub>2</sub>/H<sub>2</sub>.<sup>11,12</sup> However, these methods generally suffer from many limitations such as the excess

use of organic solvents, harsh reaction conditions, and employment of toxic metal salts. Therefore, a general, green, mild, efficient, and practical method for oxime synthesis is still highly desirable.

Recently, catalytic oxidation of primary amines is attracting attention due to its fundamental importance for both bioorganic and synthetic aspects.<sup>13,14</sup> Various methods have been reported. However, useful methods are limited, because of the poor selectivity of the oxidation of amines.

Molecular oxygen used as an environmentally benign terminal oxidant is extremely important for the catalytic oxidation of amines. In 2012 and 2013, Hermans, Suzuki, and their respective co-workers reported the aerobic oxidation of primary and secondary amines using WO<sub>3</sub>/Al<sub>2</sub>O<sub>3</sub>/DPPH (1,1-diphenyl-2-picrylhydrazyl) as catalysts giving oximes in good yields.<sup>15,16</sup>

In recent years, the thermally stable carbon radical producing catalyst *N,N',N''*-trihydroxyisocyanuric acid (THICA) is attracting attention due to its highly catalytic efficiencies for the aerobic oxidation of substituted toluenes. In the last decades, Ishii and co-workers had developed an efficient method for the preparation of THICA and it is used as catalyst in aerobic oxidation of substituted toluenes.<sup>17</sup> But these methods generally require metal salts as the co-catalyst. In our previous study,<sup>18</sup> we have conducted a novel and efficient aerobic oxidation of toluene derivatives catalyzed by THICA under metal-free conditions using dimethylglyoxime as the nonmetallic co-catalyst. On the basis of our previous work, we extend this catalytic system in other aerobic oxidative reactions.



**Scheme 1** Aerobic oxidation of primary amines to the corresponding oximes catalyzed by THICA/acetaldoxime

*SYNLETT* 2014, 25, 1873–1878

Advanced online publication: 09.07.2014

DOI: 10.1055/s-0033-1338646; Art ID: st-2014-w0237-1

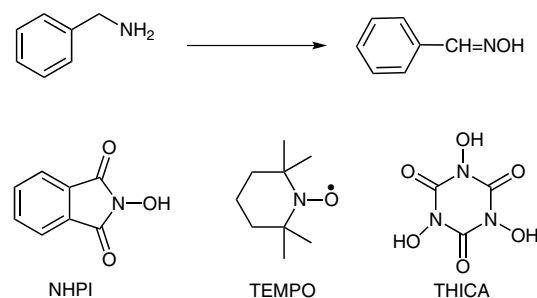
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Herein we introduce a general, efficient, and metal-free method for the aerobic oxidation of primary amines to the corresponding oximes catalyzed by THICA/acetaldoxime with H<sub>2</sub>O as solvent (Scheme 1). This practical method can use O<sub>2</sub> as the economic and green oxidant and tolerates a wide range of substrates, which can afford the target oximes in moderate to good yields.

Based on our continuing efforts to achieve THICA-catalyzed oxidation of primary amines to oximes, benzylamine was selected as a model substrate to optimize the reaction conditions including catalyst, additive, solvent, reaction temperature, and gas. As shown in Table 1, we

first studied the oxidation of primary amines with O<sub>2</sub> catalyzed by THICA (2.5 mol%) combined with acetaldoxime (10 mol%) in H<sub>2</sub>O. To our delight, the desired benzaldoxime was obtained in 75% yield (Table 1, entry 1). Initial catalyst screening revealed that THICA was the best choice for this reaction, and other catalysts such as NHPI and TEMPO were also effective, albeit affording the products with slightly diminished yields (Table 1, entries 1–3). Various acetaldoxime analogues were compared, and we found that acetoxime, dimethylglyoxime, or cyclohexanone led to lower yields (Table 1, entries 1, 4–6). Screening of different solvents revealed that the sol-

**Table 1** Screen of Reaction Conditions<sup>a</sup>



Entry	Catalyst (mol%)	Additive (mol%)	Solvent	Temp (°C)	Gas	Conv. (%)	Yield (%) <sup>b</sup>
1	THICA (2.5)	acetaldoxime (10)	H <sub>2</sub> O	100	O <sub>2</sub>	82	80
2	NHPI (2.5)	acetaldoxime (10)	H <sub>2</sub> O	100	O <sub>2</sub>	62	61
3	TEMPO (2.5)	acetaldoxime (10)	H <sub>2</sub> O	100	O <sub>2</sub>	54	53
4	THICA (2.5)	acetoxime (10)	H <sub>2</sub> O	100	O <sub>2</sub>	77	75
5	THICA (2.5)	dimethylglyoxime (10)	H <sub>2</sub> O	100	O <sub>2</sub>	74	73
6	THICA (2.5)	cyclohexanone (10)	H <sub>2</sub> O	100	O <sub>2</sub>	70	69
7	THICA (2.5)	acetaldoxime (10)	DMSO	100	O <sub>2</sub>	trace	trace
8	THICA (2.5)	acetaldoxime (10)	DMF	100	O <sub>2</sub>	trace	trace
9	THICA (2.5)	acetaldoxime (10)	EtOH	100	O <sub>2</sub>	trace	trace
10	THICA (2.5)	acetaldoxime (10)	MeCN	100	O <sub>2</sub>	trace	trace
11	THICA (2.5)	acetaldoxime (10)	H <sub>2</sub> O	80	O <sub>2</sub>	78	77
12	THICA (2.5)	acetaldoxime (10)	H <sub>2</sub> O	60	O <sub>2</sub>	55	54
13	THICA (2.5)	acetaldoxime (10)	H <sub>2</sub> O	40	O <sub>2</sub>	33	32
14	THICA (2.5)	acetaldoxime (10)	H <sub>2</sub> O	RT	O <sub>2</sub>	14	13
15	THICA (5)	acetaldoxime (10)	H <sub>2</sub> O	100	O <sub>2</sub>	89	88
16	THICA (10)	acetaldoxime (10)	H <sub>2</sub> O	100	O <sub>2</sub>	89	88
17	THICA (5)	acetaldoxime (5)	H <sub>2</sub> O	100	O <sub>2</sub>	65	63
18	THICA (5)	acetaldoxime (20)	H <sub>2</sub> O	100	O <sub>2</sub>	89	88
19	THICA (5)	acetaldoxime (10)	H <sub>2</sub> O	100	O <sub>2</sub>	78	77
20	THICA (5)	acetaldoxime (10)	H <sub>2</sub> O	100	N <sub>2</sub>	trace	trace

<sup>a</sup> Reaction conditions: Benzylamine (1 mmol), THICA (5 mol%), acetaldoxime (10 mol%), O<sub>2</sub>, H<sub>2</sub>O (5 mL), 100 °C.

<sup>b</sup> Isolated yields.

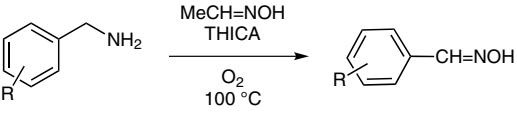
vent plays an important role in this reaction. Notably, H<sub>2</sub>O was the only efficient solvent for the formation of benzaldoxime, while no reaction occurred in other solvents (Table 1, entries 1, 7–10). Moreover, the effect of the reaction temperature was also examined, and it was found that a temperature of 100 °C was optimal for this reaction (Table 1, entries 1, 11–14). Further optimization by screening the loadings of acetaldoxime and THICA, the result showed that the optimum amount of acetaldoxime was 10 mol% and THICA was 5 mol% (Table 1, entries 15–18). Additionally, the reaction was less efficient when proceeding in air (Table 1, entry 19), no product could be detected in the atmosphere of N<sub>2</sub> (Table 1, entry 20).

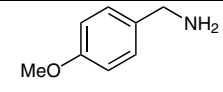
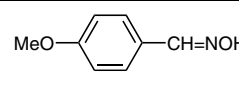
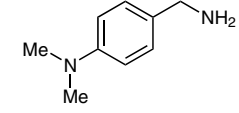
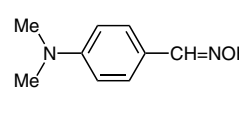
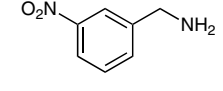
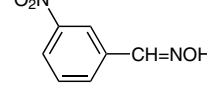
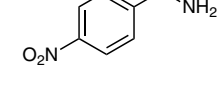
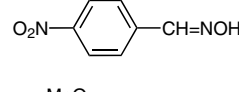
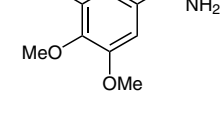
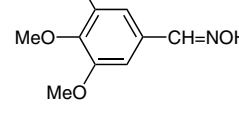
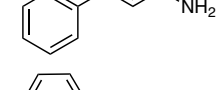
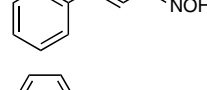
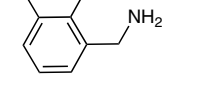
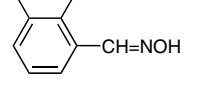
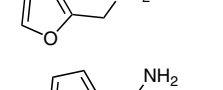
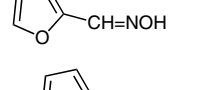
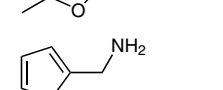
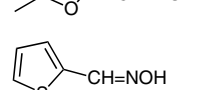
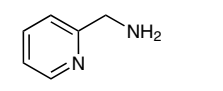
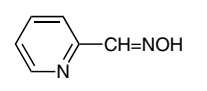
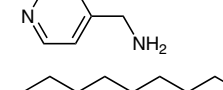
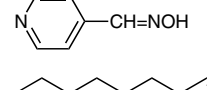
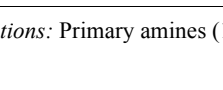
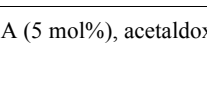
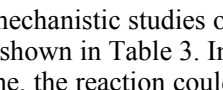
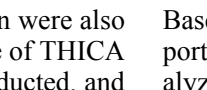
With the optimized conditions in hand, we turned our attention to the scope of the reaction. As summarized in Table 2, a variety of primary amines were examined to the corresponding oximes. The reaction could be successfully applied to a range of different substituted benzylamine and gave the corresponding products in moderate to excellent yields. Benzylamine with either electron-donating or electron-withdrawing groups on the benzene ring smoothly generated the corresponding products in moderate to good yields. Clearly, electronic effects play an important

role, as electron-withdrawing substituents (Table 2, entries 11 and 12) on the benzene ring favored the transformation. Meanwhile, electron-donating substituents (Table 2, entries 7–10, 13) objected the transformation. Additionally, the reaction conditions were also compatible with fluoro, chloro, and bromo substituents (Table 2, entries 2–6). When the benzylamines is bearing electron-donating substituents, the yield was slightly lower with the chloro groups in the *ortho* position than in the *para* position (Table 2, entries 4 and 5). That may be due, in part, to steric hindrance. Fortunately, 1-naphthalenemethylamine and 3-phenyl-2-propylene amine could also be successfully converted into the corresponding oximes in good yields in this reaction system. Moreover, we also conducted heterocyclic primary amines under the employed reaction conditions. To our surprise, heterocyclic amines show high reactivity to give the corresponding oximes in good yields. To demonstrate the scope and efficiency of the present method, this catalytic system was then extended for the synthesis of aliphatic oximes. However, we found that the octylamine did not react and gave very low conversion and trace amount of yield.

**Table 2** Aerobic Oxidation of Primary Amines to Oximes Catalyzed by THICA/Acetaldoxime<sup>a</sup>

Entry	Benzylamine	Product	Time (h)	Conv. (%)	Yield (%) <sup>b</sup>
1			36	89	88
2			36	80	79
3			36	87	86
4			36	86	85
5			36	82	81
6			36	84	83
7			35	87	85
8			34	90	88

**Table 2** Aerobic Oxidation of Primary Amines to Oximes Catalyzed by THICA/Acetaldoxime<sup>a</sup> (continued)


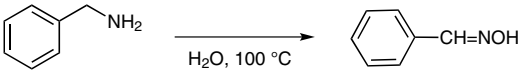
Entry	Benzylamine	Product	Time (h)	Conv. (%)	Yield (%) <sup>b</sup>
9			34	85	84
10			34	83	82
11			40	89	87
12			40	91	90
13			34	81	80
14			40	77	76
15			38	88	87
16			40	80	79
17			40	82	81
18			40	76	75
19			42	79	78
20			42	83	82
21			24	trace	trace

<sup>a</sup> Reaction conditions: Primary amines (1 mmol), THICA (5 mol%), acetaldoxime (10 mol%), O<sub>2</sub>, H<sub>2</sub>O (5 mL), 100 °C.

<sup>b</sup> Isolated yields.

Preliminary mechanistic studies of the reaction were also conducted as shown in Table 3. In the absence of THICA or acetaldoxime, the reaction could not be conducted, and trace amount of product yield was obtained. Besides, when the reaction was conducted under N<sub>2</sub> atmosphere, it also gave trace amount of yield. Thus, THICA, acetaldoxime, and O<sub>2</sub> were essential for the reaction.

Based on these experiment results and the literature reports about the amines oxidation<sup>15–17</sup> and the THICA-catalyzed aerobic oxidation,<sup>18,19</sup> A possible catalytic mechanism of THICA/acetaldoxime in the aerobic oxidative of benzylamine is proposed in Scheme 2. The first step of the reaction was to involve the corresponding *N*-oxyl radical of acetaldoxime, which was formed by the re-

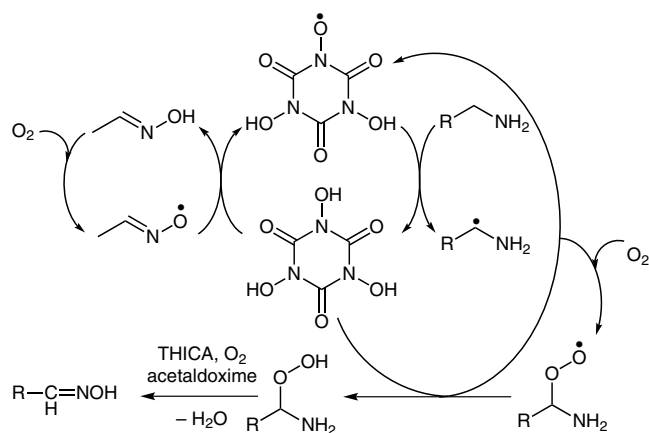
**Table 3** Control Conditions of the Oxidation of Primary Amines<sup>a</sup>


Entry	THICA (mol%)	Acetaldoxime (mol%)	Gas	Yield (%) <sup>b</sup>
1	–	–	O <sub>2</sub>	trace
2	–	10	O <sub>2</sub>	trace
3	5	–	O <sub>2</sub>	trace
4	5	10	N <sub>2</sub>	trace
5	5	10	O <sub>2</sub>	88

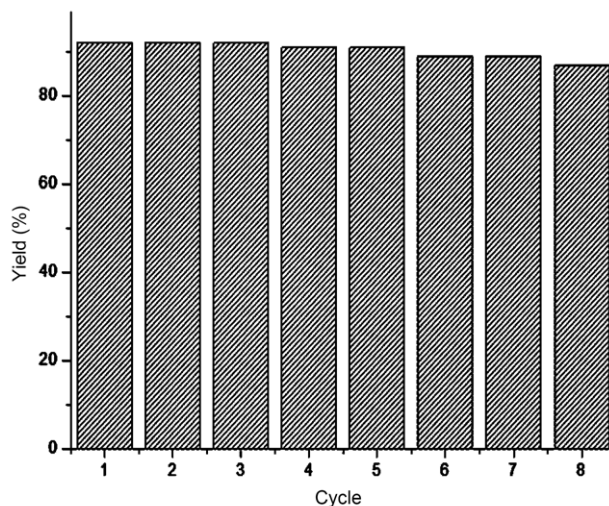
<sup>a</sup> Reaction conditions: Benzylamine (1 mmol), THICA, acetaldoxime, O<sub>2</sub>, H<sub>2</sub>O (5 mL), 100 °C.

<sup>b</sup> Isolated yields.

action of acetaldoxime and dioxygen. And then, this *N*-oxyl radical abstracted hydrogen from THICA to recover the acetaldoxime. Simultaneously, THICA was converted into its radical, which abstracted a hydrogen atom from the primary amines to form an  $\alpha$ -aminobenzyl radical. Then the  $\alpha$ -aminobenzyl radical was readily captured by O<sub>2</sub> to give a  $\alpha$ -aminobenzylperoxy radical, which underwent abstraction of hydrogen from THICA to give an  $\alpha$ -aminobenzyl hydroperoxide and the regenerated THICA radical to complete the catalytic cycle. The  $\alpha$ -aminobenzyl hydroperoxide undergoes a dehydration process to finally produce the oxime product.

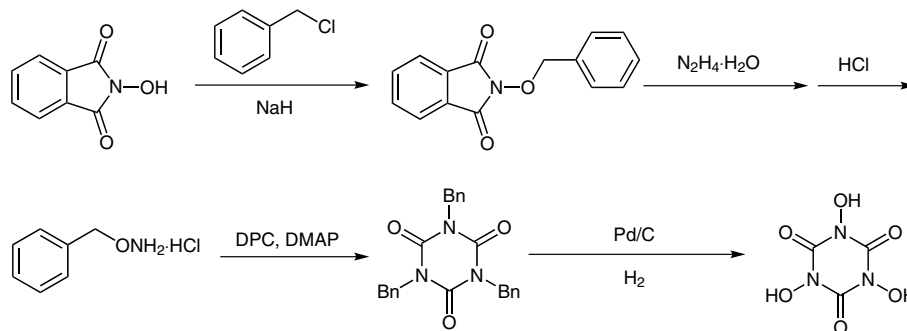
**Scheme 2** A possible reaction mechanism for the aerobic oxidation of the primary amine using the THICA/acetaldoxime system

When the final reaction mixture was cooled to room temperature and extracted with diethyl ether, the upper layer of diethyl ether, containing product and acetaldoxime, was removed by decantation. Then only fresh substrate and acetaldoxime was recharged to the residual THICA and H<sub>2</sub>O. The mixture was heated to react once again. The results from Figure 1 were shown that the procedure was repeated eight times with no appreciable decrease in yields.

**Figure 1** The cycle of THICA in the aerobic oxidation

In conclusion, we have identified THICA/acetaldoxime as an efficient catalyst system with broad substrate scope for aerobic oxidative synthesis of oximes from primary amines. The identity of the solvent is the key factor in achieving selectivity for oximes. This practical reaction can use O<sub>2</sub> as the economic and green oxidant and water as the green solvent. The THICA is readily accessed and efficiently oxidizes various primary amines to give their corresponding oximes in high yield.

All starting materials were purchased from commercial sources and used without further treatment. All known compounds were identified by appropriate technique such as <sup>1</sup>H NMR and compared with previously reported data. <sup>1</sup>H NMR (500 MHz) was recorded on a Bruker 500 spectrometer with tetramethylsilane (TMS) as an internal standard. Analytical thin layer chromatography (TLC) was performed on precoated silica gel 60 F254 plates. Yields refer to the

**Scheme 3** Preparation of THICA

isolated yields of the products after purification by silica-gel column chromatography (300 mesh).

#### Typical Procedure for the Aerobic Oxidative Synthesis of Oximes

THICA was prepared by the literature procedure (Scheme 3).<sup>18</sup> <sup>1</sup>H NMR (500 MHz, DMSO-*d*<sub>6</sub>): δ = 11.177 (s, 3 H) ppm. <sup>13</sup>C NMR (125 MHz, DMSO-*d*<sub>6</sub>): δ = 149.923 ppm. IR: 3400, 3080, 2830, 1710, 1510, 1420, 1390, 1240, 968, 713 cm<sup>-1</sup>.

A mixture of primary amine (1 mmol), THICA (5 mol%), acetaldoxime (10 mol%), and H<sub>2</sub>O (5 mL) was placed in a three-necked flask. O<sub>2</sub> was stirred into the flask at a flow rate of 20 mL/min. The reaction mixture was stirred at 100 °C for several hours, and the reaction progress was monitored by TLC. When the final reaction mixture was cooled to r.t. and extracted with Et<sub>2</sub>O, the organic layer was washed with brine, dried over MgSO<sub>4</sub>, and concentrated under reduced pressure. The residue was pure enough. When necessary, the crude product was purified by chromatography using EtOAc–PE (1:8) as eluent.

**Supporting Information** for this article is available online at <http://www.thieme-connect.com/products/ejournals/journal/10.1055/s-00000083>.

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