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Thiocyanate Radical Mediated Dehydration of Aldoximes with Visible Light and Air

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We developed a new means of activating aldoximes by in situ generated thiocyanate radical from ammonium thiocyanate and molecular oxygen at the room temperature. With catalytic amount of organic dye aizenuranine as the photocatalyst, the dehydration of aldoximes processes smoothly under visible light irradiation, providing a simple to handle, excellent functional group tolerance, and metal-free protocol for a wide range of nitriles.

Nitriles are highly valuable synthetic precursors in preparative organic chemistry in the synthesis of carboxylic acids, esters, alcohols, amines and amides.¹ Furthermore, a nitrile moiety is contained in a great number of functional materials, pharmaceuticals, agricultural chemicals, dyes and bioactive compounds.² In search of new synthetic methods of nitriles is widely concerned by chemists. The transformation of aldoximes to the corresponding nitriles is one of the most widely used methods in organic synthesis and this method cyanides.³ avoids using highly toxic Typically. it was very common that used an electrophile to activate the hydroxyl group on the aldoximes followed by elimination, during which stoichiometric activating reagents are used such as polymeric reagent,^{4a} burgess reagent,^{4b,4c} BOP reagent,^{4d} [bmim] BF_4^{4e} and XtalFluor- $E^{4\bar{f}}$. Despite the success achieved in this area, the dehydration of aldoximes employing in-situ generated precursors as activating reagents is relatively undeveloped. To date, there are only limited successful strategies that could realize this direct route (Scheme 1a, 1b).⁵ Compared to previous reported methods,^{3e, 4-7} several noteworthy features of in situ formed activated precursor are apparent, such as cheap and easily available material, the easy work-up procedure, mild reaction conditions and excellent functional group compatibility.

Thiocyanate has long been known as an inexpensive and

easily accessible pseudohalide that is often used in organic synthesis.⁸ The thiocyanate anions can be transformed to thiocyanate radicals via one-electron oxidation under aerobic photoredox conditions.^{9,10} While addition of thiocyanate radicals to unsaturated bonds has been frequently used to achieve various thiocyanations,⁹ utilization of thiocyanate radicals as hydrogen abstraction agents is relatively unexplored.¹⁰ Thanks to the weaker bond dissociation energy of O–H in aldoximes (O–H BDE pprox 79.4 kcal/mol), we envisaged that electronegative thiocyanate radicals could activate aldoximes via the formation of iminoxyl radical¹¹ by hydrogen abstraction, thereby opening a path to nitriles synthesis (Scheme 1c). As this process proceeds in neutral conditions at room temperature and all materials are inexpensive and easily accessible, it may provide a facile protocol for dehydration of aldoximes with outstanding functional group tolerance.



The initial studies focused on the dehydration of (1R)-(-)myrtenal oxime (**1a**) with NH₄SCN under air with 6 W blue LEDs irradiation. After extensive screening (see the Supporting Information), we were glad to find that the reaction of **1a** with NH₄SCN in dry CH₃CN solution containing aizenuranine (2 mol %) as a photocatalyst provided the respective nitrile **2a** in 85% yield. Control experiments indicated that both aizenuranine and visible light were essential for the success of this reaction.

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With the above optimized conditions in hand, we explored using a series of aliphatic aldoximes (Table 1) and aromatic aldoximes (Table 2). As illustrated in Table 1, (1R)-(-)-myrtenal oxime (1a) and cinnamaldehyde oxime (1b) were smoothly transformed to corresponding nitriles under the standard conditions with 85% and 66% yields respectively. Whereafter, we screened a series of representative straight chain primary aldoximes (1c-1s), they were compatible with this system and gave the desired products 2c-2s with yields ranging from 55% to 87%. For methyl ether (1e), methylene ether (1f), 4methylbenzene ether (1j), benzyl ether (1k) and 4-(tert-butyl) benzene ether (1l, 1m) substituted aliphatic aldoximes, the corresponding products could be obtained in good to excellent yields. It is worth noting that acid-susceptible groups like (tert-butyldimethylsilyl)oxyl (OTBS) substituted hexanaloxime (1i) could be converted into the corresponding nitrile under standard conditions with 73% yield. Furthermore, octanal oxime (1g) and undecanal oxime (1h) could transform into nitriles with 87% and 78% yields respectively. When the substituents on the nitrogen atom of N-(2-(hydroxyimino) ethyl)-4-toluenesulfonamide were benzyl, allyl, pentenyl, pro-



^{*a*} Reaction conditions: **1** (0.2 mmol), NH₄SCN (0.3 mmol), aizenuranine (2 mol %), CH₃CN (2 mL) under air with 6 W blue LEDs irradiation at rt for 10 h. ^{*b*} Isolated yield. ^{*c*} Eosin Y instead of aizenuranine.

pinyl and buta-1,2-dienyl, the desired products (2n-2s) could be produced smoothly in 59–87% yields. It should be noted that α -substituents aliphatic aldoximes (1t-1w) were successful, yielded the corresponding products in good to excellent yields. Page 2 of 4

After successfully investigating different aliphatic aldoximes, we became interested in determining the potential of a comatic aldoximes. For this purpose, aromatic aldoximes (Table 2) were applied under our optimized conditions in 44–98% yields that a variety of functional groups were tolerated. For benzaldoximes substituted with various electron-donating gro-



 a Reaction conditions: 3 (0.2 mmol), NH₄SCN (0.3 mmol), aizenuranine (2 mol %), CH₃CN (2 mL) under air with 6 W blue LEDs irradiation at rt for 10 h. b Isolated yield.

ups such as Me, OMe, OH, methylene, OBn and i-Pr, the dehydration reactions uniformly proceeded in moderate to excellent yields (4b-4f, 4k-4o, 4q-4u). This method exhibited high tolerance for substrates bearing OH group (3f, 3q-3t), which had little effect on the yield of the reaction. When benzaldoxime was substituted by electron-withdrawing groups such as Cl, Br, NO₂, moderate to good yields were afforded (4g-4j, 4p, 4r-4u). Moreover, the more challenging disubstituted or trisubstituted benzaldoximes (3I-3u) were found to be successful and provided the desired products in 44% to 93% yields. In addition, we probed whether heterocyclic and polycyclic aromatic aldoximes would be amenable to the dehydration. An array of heterocyclic aldoximes containing oxygen, sulfur, and nitrogen atoms (3v-3x) were well tolerated, thus affording moderate to well yields. Similarly, representative polycyclic examples tolerated our reaction conditions, giving the corresponding nitriles 4y and 4z in 91% and 88% yields respectively. Ultimately, it was found

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that benzoyl cyanide (**4aa**) also was obtained in a good yield of 74%. To demonstrate the synthetic value of our methodology, we also operated this reaction with 10 mmol of **3e**, and the catalyst loading was reduced to 0.1 mol%. To our delight, **4e** was obtained in 88% isolated yield (Scheme 2a).



In order to gain more information for the dehydration of aldoximes, we performed a series of control experiments. As expected, no desired product 2a was generated when the reaction was carried out under argon atmosphere demonstrating that air is necessary for the reaction (see Table S5). Furthermore, 2 equiv of the radical inhibitor TEMPO relative to 1a was added to the reaction system, no desired product 2a was observed and starting material was recovered. To our delight, the adduct of 'SCN radical with the radical inhibitor BHT was detected by ESI-HRMS (see Figure S1). When 1,1-diphenylethylene (5) was present in a reaction mixture containing 2 equiv BHT and 5 equiv NH₄SCN, 2,6-di-tert-butyl-4-((1,1-diphenyl-2-thiocyanatoethyl)peroxy)-4-methylcyclohex a-2,5-dien-1-one (6) was isolated in 15% yield, thus providing straightforward evidence of the formation of the 'SCN radical (Scheme 2b).^{9c} In addition, the reaction system of **3e** under the standard conditions was studied by GC-MS; The peaks at 116.0 corresponding to (SCN)2, which should be formed by the coupling of SCN radical at room temperature under the visible light irradiation (see Figure S6). The reduction potential of excited photocatalyst is estimated from Gibbs energy of photoinduced electron transfer.^{12a} The reduction potential of



Figure 1 ESR measurements of (a) a CH_3CN solution of aizenuranine and NH_4SCN under the irradiation of 6 W blue LEDs; (b) a CH_3CN solution of aizenuranine and NH_4SCN in the presence of DMPO under the irradiation of 6 W blue LEDs.

excited aizenuranine is around 1.15 V (vs. saturated calomel electrode (SCE)) (see the Supporting Information),^{12b} which is enough to oxidate ammonium thiocyanate (E_{ox} = +0.71 V vs

SCE) (see Figure S5), suggesting that the electron transfer from aizenuranine to ammonium thiocyanate all the form of the form of the form of the second sec

To lend additional support to our proposed mechanism, 5,5dimethyl-1-pyrroline-Noxide (DMPO) was used as a probe to capture the active species. As shown in Figure 1, no any signal was detected when the mixture containing aizenuranine and NH₄SCN was irradiated by 6 W blue LEDs. However, a characteristic signal of [•]SCN radical captured by DMPO was clearly observed after addition of DMPO.¹³ Data analysis suggests that [•]SCN radical is promptly trapped by DMPO to produce the metastable radical ($\alpha_N = 14.42$ G, $\alpha_H = 16.82$ G, and g = 2.0054), which is consistent with the previous report (see the Supporting Information for details).¹³ It revealed that [•]SCN radical is generated from NH₄SCN by single-electron transfer (SET) under the present reaction conditions. Therefore, [•]SCN radical should be formed by the reductive quenching of the aizenuranine with [–]SCN anion.



Figure 2 Analysis of the reaction pathway. Quantum mechanical calculations were performed using Gaussian 09. All geometries and single point energies were calculated with M06-2x/6-31+G(d,p) and SMD model for acetonitrile.

To preclude the possibility that $(SCN)_2$ as an electrophile to activate the hydroxyl group on the aldoximes, the density functional theory (DFT) calculation was performed (Figure 2, Path II). The calculated energy barrier for the nucleophilic attack of $(SCN)_2$ with aldoxime **3a** via **TS1b** is 61.6 kcal/mol. Whereas, for the iminoxyl radical involved pathway (Figure 2, Path I), the hydrogen abstraction of aldoxime **3a** with ^{*}SCN radical occurs through **TS1**, and the energy barrier of which is 12.0 kcal/mol. Subsequent radical coupling of iminoxyl radical **INT1** with another ^{*}SCN radical through **TS2** (18.6 kcal/mol) delivers eneaminooxyl sulfanecarbonitrile **INT2**, which can barrierlessly produce **4a** and NSCO with the aid of superoxide anion radical (O_2^{\bullet}) . According to these results, the pathway involving ^{*}SCN radical hydrogen abstraction / cross-coupling sequence appears to be more favorable.

On the basis of the aforementioned experimental results and previous reports,^{9, 10} a plausible mechanism is outlined (Scheme 3). Initially, under visible light irradiation, dye

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photocatalyst (aizenuranine) is converted to excited dye*. A single electron transfer between dye* and "SCN anion generates dye radical anion (dye^{*}) and 'SCN radical. Subsequently, molecular oxygen oxidizes dye^{*} back to its ground state to finish the photocatalytic cycle. Meanwhile, O_2 is reduced to form O_2^{*} . Then 'SCN radical directly reacts with aldoximes affording iminoxyl radical I and thiocyanic acid. In addition, O_2^{*} may also serve as the HAT agent and reacts with aldoximes affording iminoxyl radical I and HO_2^{-14} The generated intermediate I could further react with 'SCN radical to produce eneaminooxyl sulfanecarbonitrile II. The abstraction of a proton from intermediate II by O_2^{*} produces corresponding nitriles spontaneously.



Scheme 3 Proposed mechanism.

Conclusions

In conclusion, we have disclosed an effective catalytic process for the dehydration of aldoximes by *in-situ* generated [•]SCN radical under visible-light irradiation. The reaction is highlighted by its cheap and easily available material, the easy work-up procedure, excellent functional group tolerance and generation of various aliphatic and aromatic nitriles in moderate to excellent yields under mild reaction conditions.

Conflicts of interest

There are no conflicts to declare.

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