New Approach to Oximes through Reduction of Nitro Compounds Enabled by Visible Light Photoredox Catalysis

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A range of nitro compounds are smoothly reduced to their corresponding oximes under the synergistic effects of visible light irradiation, the Ru(bpy)₃Cl₂ photocatalyst, Hünig's base, Mg(ClO₄)₂ activation, and MeCN solvent. This remarkably mild and environmentally benign protocol, when orchestrated with classical Beckmann rearrangement, enables such high-value industrial feedstock as caprolactam to be readily accessed from simple precursor nitrocyclohexane.

Photoredox catalysis enabled by green visible light irradiation and efficient transition-metallic as well as organic photosensitizers has in recent years emerged as a powerful synthetic technology, bringing about a wide range of organic transformations that are either impossible or impractical with conventional protocols.¹

As a highly versatile class of substances, oximes are known to serve as useful precursors to various compounds that have found numerous applications in material science, pharmaceuticals, and agrochemicals,² and great efforts have been made to develop efficient protocols enabling their facile preparations. As shown in Scheme 1, traditionally, direct condensations of an aldehyde or a ketone with hydroxylamine are the most frequently employed method. An alternative is the reduction of primary nitroalkanes, as well as α,β -unsaturated nitrocompounds, to oximes involving the use of Se/NaBH₄, Bu₃SnH, SnCl₂/PhSH, or Au/TiO₂/H₂.^{3,4} However, these established methods generally suffer from one or more limitations such as harsh reaction conditions, poor selectivity, and employment of toxic metal salts. Therefore, a strong need remains for mild, convenient methods for oxime synthesis. In this context, based on recent remarkable progress on

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Scheme 1. Various Synthetic Approaches to Oximes Formation and Their Common Transformations



uncovering both new catalysis concepts and robust synthetic reactions^{5–9} by means of visible light-enabled photocatalysis, exploring its possible implications in designing and identifying useful scenarios for alternative oxime synthesis is appealing.

Motivated by this possibility, we set out to explore a set of optimal reaction conditions conducive for oxime formation by the readily available visible light photosensitizer Ru(bpy)₃Cl₂.¹ Eventual success emerged from a range of screenings (Table 1) which proved that the formation of oximes in synthetically meaningful efficiency depends critically on the synergy of several factors, most notably the amine reductive quencher, Lewis acidic additive, and

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Table 1. Identification of the Optimal Reaction Conditions

NO2 Ru(bpy) ₃ Cl ₂ •6H ₂ O (0.05 equiv) amine, additive, solvent, rt, Ar						
Me	0~~/	1 visit	ole light (45	W bulb) MeO	\checkmark :	2
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entry	mol % Ru	amine (equiv)	solvent	additive (equiv)	time (n)	yield (%) ⁶
1	5	/Pr ₂ NEt (3.00)	MeCN	1	36	46
2	5	iPr ₂ NEt (3.00)	DMF	1	48	trace
3	/	1	MeCN	1	36	NR
4 ^a	5	iPr ₂ NEt (3.00)	MeCN	1	36	NR
5	5	iPr ₂ NEt (3.00)	MeCN	H ₂ O (3.00)	36	15
6	5	/Pr ₂ NEt (3.00)	MeCN	Cs ₂ CO ₃ (1.00)	36	20
7	5	/Pr2NEt (3.00)	MeCN	LiBF ₄ (1.00)	20	75
8	5	iPr ₂ NEt (3.00)	MeCN	Sc(OTf)3 (1.00)	20	81
9	5	/Pr ₂ NEt (3.00)	MeCN	Sc(OTf)3 (0.20)	22	65
10	5	iPr ₂ NEt (3.00)	MeCN	La(OTf) ₃ (0.20)	22	67
11	5	/Pr ₂ NEt (3.00)	MeCN	Eu(OTf) ₃ (0.20)	22	63
12	5	/Pr ₂ NEt (5.00)	MeCN	LiClO ₄ (0.50)	14	63
13	5	/Pr2NEt (5.00)	MeCN	Mg(ClO ₄) ₂ (0.50)	12	82
14	5	/Pr ₂ NEt (5.00)	MeCN	Mg(ClO ₄) ₂ (1.00)	12	78
15	5	Et ₃ N (5.00)	MeCN	Mg(ClO ₄) ₂ (0.50)	36	NR
16	5	TMEDA (5.00)	MeCN	Mg(ClO ₄) ₂ (0.50)	36	[c]
17	5	/Pr ₂ NEt (5.00)	NMP	Mg(ClO ₄) ₂ (0.50)	12	decomp
18	5	iPr ₂ NEt (5.00)	MeOH	Mg(ClO ₄) ₂ (0.50)	24	trace
19	Eosin	<i>i</i> Pr ₂ NEt (5.00)	MeCN	Mg(ClO ₄) ₂ (0.50)	24	trace

^{*a*} No light was employed. ^{*b*} Yield of isolated product. ^{*c*} Only aza-Henry product (ref 5a).

solvent. With nitro compound 1 as the model substrate and a 45 W household bulb as the light source, we initially serendipitously discovered that the desired oxime 2 was produced in 46% isolated yield (entry 1, Table 1) when the reaction was performed in MeCN at rt and with 5% mol of Ru-catalyst and 3 equiv of amine *i*Pr₂NEt (Hünig's base). Under otherwise identical conditions, a simple switch of the reaction solvent MeCN to DMF was found to dramatically inhibit the reactivity (entry 2). Control experiments conducted without either the Ru-photocatalyst (entry 3) or visible light irradiation (entry 4) confirmed unambiguously that the reproducible formation of 2 demands both. As the commercial Ru(bpy)₃Cl₂ photocatalyst was available in its hexahydrate form, an additional 3 equiv of water were added to the reaction system (entry 5) as a neutral additive, which was found to have negatively influenced the oxime formation. A significant observation was subsequently noted when two reactions with a basic Cs₂CO₃ (entry 6) or Lewis acidic LiBF₄ (entry 7) additive, respectively, were run in parallel; the comparative results revealed the latter to be a far better reaction promoter than the former (75% vs 20% yield of 2). Thus a number of Lewis acidic additives, including $Sc(OTf)_3$, $La(OTf)_3$, $Eu(OTf)_3$, $LiClO_4$, $Mg(ClO_4)_2$,¹⁰ were screened next at various loadings and reaction times (entries 8-13), from which the substoichiometric $Mg(ClO_4)_2$ (0.50 equiv) clearly stood out for its remarkable capacity to deliver the product in high isolated yield (82%, entry 13) and within 12 h at rt. Interestingly, a doubled loading of $Mg(ClO_4)_2$ was found to be detrimental for the product

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Scheme 2. Survey of Reaction Scope



yield (entry 14). Two other amines, Et₃N and tetramethyl ethylenediamine (TMEDA), were employed in place of Hünig's base, and once again dramatic reactivity inhibitions were observed in both cases (entries 15-16). Further manifestations of the critical importance of reaction parameters came from the experiments shown in entries 17-18. where the use of solvent MeOH or N-methylpyrrolidone (NMP) under condition otherwise identical to those of entry 13 led to either a complicated mixture or nearly complete reactivity inhibition. Finally, an organic dye-type photosensitizer Eosin¹¹ (5% mol) was examined while the Ru-catalyst was absent (entry 19); the result suggested that, at least in this specific context, Eosin is practically ineffective in promoting the desired reactivity. Collectively, these screenings established that an efficient visible light photoredox reduction of nitro compound 1 to its oxime 2 at ambient temperature depends on the synergy of 5% mol of Ru(bpy)₃Cl₂ photocatalyst, 5.00 equiv of Hünig's base, 0.50 equiv of Mg(ClO₄)₂ additive, and MeCN as the solvent.

With the above optimal reaction conditions in hand, a range of structurally variable aliphatic or aromatic nitro compounds **3** were subjected to this visible light-promoted photocatalytic reduction protocol to examine its general applicability. As compiled in Scheme 2, in each case the reaction proceeded smoothly to furnish the desired oxime product **4** in various isolated yields (35–86%) and geometrical isomers (E/Z ratios ranging from 1.0 to 4.1). Neither the aryl ring sizes (**4a** and **4b**) nor the electron-withdrawing

Scheme 3. Representative Transformations of Oxime 2



or -donating nature of the substituents on the aryl rings (4c-4i) seemed to pose a significant influence on the reactivities. The size variations of aliphatic substituents (4i-4l) were also well accommodated, and for comparison. the presence of a bulky, π -character ethoxyfuranone in **4m** appeared to retard the reduction to some extent (51%) vield). The formation of aromatic oxime 4n progressed at a faster rate (6 h); although the isolated yield was moderate (36%), the product was obtained as exclusively an E-isomer. Heteroaromatic ring-containing substrates were also successful, and their corresponding oximes 40-4q were produced in 63-82% yields. Purely aliphatic oxime 4r was prepared in 54% yield. Notable reactivity decreases were observed for 4s-4t. While the formations of aldoximes 4a-4r generally required ~12 h for completion, ketoximes 4s-4t required more reaction time (74% of 4s after 26 h and 35% of 4t after 28 h, respectively). From the results exemplified in Scheme 2, what merits particular attention is this new protocol's broad tolerance of such synthetically versatile functionalities as cyano (4e), bromo (4g), phenol (4h), alkynyl (4i), ethoxyfuranone (4m), heterocycles (40-4q), and hydroxyl (4r), thereby yielding considerable freedom for further needed structural manipulations.

The oximes thus prepared are capable of participating in several characteristic reactions. For example, as illustrated in Scheme 3, oxime 2 upon oxidation activation by NaClO¹² or NCS¹³ could undergo [3 + 2] dipolar cycloaddition with ethyl acrylate or acetylacetone to deliver functionalized heterocycle 5 or 6, respectively. Furthermore, the C=N bond of 2 could be cleaved *via* ozonolysis¹⁴ to give aldehyde 7, and its oxime moiety could be oxidized by means of I₂/PPh₃¹⁵ to yield the corresponding nitrile 8.

The synthetic utilities of this visible light-enabled photoredox catalysis technology could be further enhanced through intelligent orchestrations with other strategic transformations, thus enabling such operationally simple "one-pot" processes to be conveniently practiced. A few

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Scheme 4. One-Pot Transformations of Some Typical Nitro Compounds



demonstrations were shown in Scheme 4. A one-pot combination of nitro reduction—oxime elimination directly converted 1 to nitrile 8 in 62% isolated yield. A merging of oxime formation—[3 + 2] dipolar cycloaddition events on 3i constructed the tricyclic 8*H*-indeno[2,1-*c*]isoxazole core of 9 in 65% yield. Perhaps of most significance, by teaming up oxime formation with subsequent H₂SO₄-trigger Beckmann rearrangement, the abundantly available nitrocyclohexane 3s could be readily converted to caprolactam (43% yield), the industrial precursor to Nylon 6, an extremely widely used synthetic polymer.

Finally, it is of interest to note that some relevant new reactivities were uncovered during the course of our investigations on the fates of nitrocyclopropane **11** and nitroketone **13** in this photoredox catalysis protocol (Scheme 5). Interestingly, the former was found to fragment efficiently *via* C–C bond cleavage^{5h} to yield ring-opening product **12** (86%), and the latter was reduced to saturated ketone **14** by formal C–N bond cleavage¹⁶ (35%). In both cases, no evidence of oxime formation was obtained. These reactivities, although rather unexpected, could be economically rationalized through the radical intermediates¹⁷ *in situ* generated by hydrogen additions (*vide infra*) to Lewis acid activated carbonyls in **11** and **13**, respectively.

A mechanistic proposal is outlined in Scheme 6, and we believed that these unusual photocatalytic reduction reactivities originate from dynamic interplays of at least three intimately coupled pathways, i.e., a Ru(I)/Ru(II)-photoredox cycle (in green), amine dehydrogenative oxidation

Scheme 5. Visible Light-Promoted C-C/C-N Bond Cleavages



Scheme 6. A Plausible Mechanistic Proposal



(in red), and nitro substrate reduction (in blue). Under visible light stimulation, the initially formed amine radical cation **E** should release a hydrogen radical to produce iminium ion **F** which could subsequently eject a proton to return to a neutral state **G**. Accordingly, the stepwise hydrogen proton capture by the substrate **3**'s resonance form **H** should give rise to a reduced cationic species **I**.¹⁸ The electron deficiency of **I** empowered by its cationic nature could thus grant its oxidation capacity that abstracts an electron from the Ru(I) intermediate, thereby fulfilling a critical step while an externally added oxidant (such as oxygen) was absent. The concomitantly generated species **J** next undergoes Lewis acid promoted dehydration to lead to the final oxime product **4**.

In summary, the established visible light-enabled photocatalytic reductions of nitro compounds to their oximes are generally applicable and compatible with several synthetically significant functionalities. The protocol meanwhile offers a new reaction development platform on which its synergy with other strategic transformations could be conceived and executed in operationally simple "onepot" fashions. The direct conversion of nitrocyclohexane to industrial feedstock caprolactam serves as an interesting lesson and should invite consideration of other exciting possibilities.

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Supporting Information Available. Experimental procedures and spectral data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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