Tetrahedron Letters 56 (2015) 3353–3357

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

Accessing nitrosocarbonyl compounds with temporal and spatial control via the photoredox oxidation of *N*-substituted hydroxylamines

Charles P. Frazier, Leoni I. Palmer, Andrey V. Samoshin, Javier Read de Alaniz *

Department of Chemistry and Biochemistry, University of California, Santa Barbara, Santa Barbara, CA 93106-9510, USA

ARTICLE INFO

Article history:
Received 2 December 2014
Revised 29 December 2014
Accepted 2 January 2015
Available online 13 January 2015

Keywords:
Hydroxylamine
Nitrosocarbonyl
Photoredox
Temporal and spatial control
Block co-polymer

ABSTRACT

Photoredox catalysis is employed to generate highly reactive acylnitroso species from hydroxamic acid derivatives. The conditions are shown to be comparable to a previously developed transition metal aerobic oxidation and are amenable to a range of transformations including Diels–Alder and ene reactions. This unique application of such an approach gives access to temporal and spatial control in nitroso chemistry.

Nitrosocarbonyl compounds are exceptionally reactive intermediates that have found widespread use in a number of classic C–N or C–O bond-forming reactions, such as the ene,[1] Diels–Alder,[2] and aldol reactions.[3] In recent years, a number of research groups have explored new methodologies to generate nitrosocarbonyl intermediates, such as oxidation under aerobic conditions,[1–3] utilizing transition metals with stoichiometric peroxide,[4] manganese dioxide oxidations,[5] and oxidations employing TEMPO and BPO,[6] among others.[7] While many of these new oxidation methodologies have facilitated the expansion of nitrosocarbonyl chemistry, none have explored the potential of generating nitrosocarbonyl intermediates with temporal and spatial control. This unique property, often neglected in the context of small molecule organic synthesis, is an important facet to consider when expanding nitrosocarbonyl chemistry into biological and materials science applications.

Photoredox catalysis is an emerging tool for the synthesis of complex molecules that has been shown to be effective in contexts requiring temporal and spatial control. While the genesis of photoredox catalysis can be traced back to Kellog in the 1970’s, the field has undergone a renaissance in recent years, based on the pioneering work of a number of research groups.[8] In particular, the recent work by the groups of Yoon,[9] and Stephenson,[10] and Macmillan[11] highlights the advantageous usage of photoredox catalysis in the oxidative generation of reactive intermediates. In 2012, Hawker and co-workers translated photoredox catalysis into material science, providing control of a living radical polymerization using visible light[12] and subsequently demonstrated excellent spatial arrangement of functional groups at surfaces.[13] The key to this methodology was visible-light mediated Ir-catalyzed atom-transfer radical addition (ATRA) chemistry developed by Stephenson and co-workers.[14] Because nitrosocarbonyl compounds participate in a variety of organic reactions, the in situ formation of this highly reactive functional group using photoredox conditions would furnish a general procedure for patterning surfaces bearing a range of properties. Moreover, because nitrosocarbonyl compounds serve as HNO donors,[15] it could also provide a means to generate HNO in situ using visible-light to control its release. To evaluate this potential, we began by investigating the in situ generation of nitrosocarbonyl compounds using photoredox conditions. A recent report by Tan inspired us to disclose our results in this area (Fig. 1).[16]

Due to the transient nature of nitroso compounds and their associated inherent instability,[17] we selected the nitroso HDA reaction to test the feasibility of a photoredox catalyst system. Nitroso compounds directly attached to an electron withdrawing group undergo rapid [4+2] cycloaddition reactions with conjugated dienes, a reaction platform that has been explored extensively by our research group[2a] and others.[18] Cbz-protected hydroxylamine **1** and 1,3-dicyclohexadiene **2** were elected as candidates for

---

* Corresponding author. Fax: +1 8058934120.
E-mail address: javier@chem.ucsb.edu (J. Read de Alaniz).

http://dx.doi.org/10.1016/j.tetlet.2015.01.024
0040-4039/Published by Elsevier Ltd.

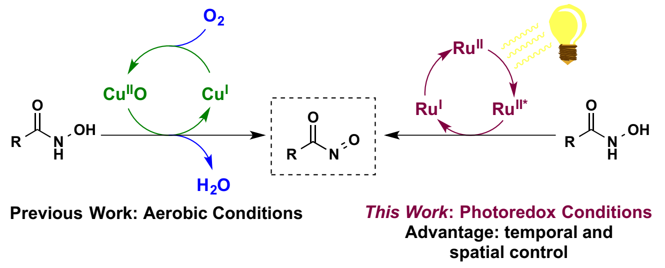


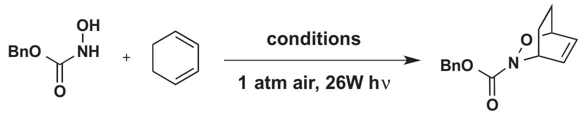
Figure 1. Exploring photoredox conditions for the generation of nitrosocarbonyls.

standardizing reaction conditions (Table 1) and investigations began with commercially available and widely employed $Ru(bpy)_3Cl_2{\cdot}6H_2O$. At 1 mol % loading and in DCE at room temperature, we were pleased to see a 35% yield of the desired oxazine product (entry 1). Analysis of the reaction mixture revealed a large amount of an undesired hetero Diels–Alder (HDA) product resulting from reaction of the diene with diatomic oxygen in a [4+2] cycloaddition and subsequent ring-opening reaction,[19] suggesting the potential interference of singlet oxygen on our desired reaction pathway.[20] Pleasingly, the addition of pyridine (2.0 equiv) completely inhibited this unproductive pathway (entry 2) and allowed us to achieve an improved yield of 80%. Screening other Ru photocatalysts, (entries 3–6) showed no improvement in yield or reaction duration over $Ru(bpy)_3Cl_2{\cdot}6H_2O$. In considering which photoredox catalysts to employ, $Ru(bpy)_3^{2+*}$ is both a good oxidant and reductant.[8] Switching to a photocatalyst like $Ir(ppy)_3$, which is more reducing in its excited state, had a negative impact on the yield (entries 7 and 8). Using a Eu-based catalyst (entry 9) satisfactorily augmented the yield but has the added disadvantage of requiring UV light for activation. Based on this, we elected to further optimize the reaction with $Ru(bpy)_3Cl_2{\cdot}6H_2O$.

Next we looked at the dependence of the reaction on the chosen additive; screening various bases (NEt_3, *i*Pr_2NEt, etc.) led us to determine that 2,6-lutidine was the additive of choice for our reaction set up. Variations in the additive loading (entries 10–12) indicated 2.0 equiv of 2,6-lutidine was optimal, and a brief solvent screen (entries 13 and 14) indicated DCE to indeed be our preferred solvent. Finally, the reaction does not proceed in the dark under the same conditions and duration (entry 15), nor is any conversion observed in the absence of catalyst (entry 16). Based on these results we elected to explore the reaction with 1 mol % $Ru(bpy)_3Cl_2{\cdot}6H_2O$ and 2 equiv 2,6-lutidine in DCE (entry 10).

With optimized reaction conditions in hand, we elected to briefly explore the scope of the Diels–Alder reaction to ensure generality of reaction conditions (Table 2). To our satisfaction, both the 5- and 6-membered ring dienes readily underwent the Diels–Alder reaction with no competing production of the endoperoxide or hydroxyenone (**7** and **3**). Additionally, 1,4-diphenylbutadiene also underwent clean conversion to the desired oxazine product (**8**). The reaction was not limited to Cbz-protected hydroxylamines, as Boc-protected hydroxylamines were readily converted to the corresponding oxazine products (**9** and **10**).

Table 1
Optimizing photoredox conditions for the generation of nitrosocarbonyls

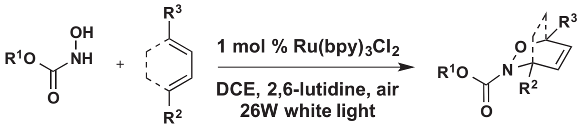


1 **2** **3**

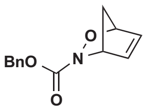
Entry	Catalyst (1 mol %)	Solvent	Additive (equiv)	Yield[a] (%)
1	$Ru(bpy)_3Cl_2{\cdot}6H_2O$	DCE	–	35
2	$Ru(bpy)_3Cl_2{\cdot}6H_2O$	DCE	Pyridine (2.0)	80
3	$Ru(bpz)_3Cl_2$	–	–	49
4	$Ru(bpz)_3Cl_2$	DCE	Pyridine (2.0)	73
5	$Ru(bpm)_3BArF_2$	DCE	pyridine (2.0)	30
6	$Ru(phen)_3Cl_2$	DCE	Pyridine (2.0)	24
7	Ir-*fac*$(ppy)_3$	DCE	Pyridine (2.0)	34
8	$Ir(BTP)_3$	DCE	Pyridine (2.0)	63
9	$Eu(dbm)_3(phen)$[b]	DCE	Pyridine (2.0)	95
10	$\mathbf{Ru(bpy)_3Cl_2{\cdot}6H_2O}$	**DCE**	**2,6-Lutidine (2.0)**	**87**
11	$Ru(bpy)_3Cl_2{\cdot}6H_2O$	DCE	2,6-Lutidine (0.5)	74
12	$Ru(bpy)_3Cl_2{\cdot}6H_2O$	DCE	2,6-Lutidine (0.05)	60
13	$Ru(bpy)_3Cl_2{\cdot}6H_2O$	$MeNO_2$	2,6-Lutidine (2.0)	63
14	$Ru(bpy)_3Cl_2{\cdot}6H_2O$	MeCN	2,6-Lutidine (2.0)	55
15	$Ru(bpy)_3Cl_2{\cdot}6H_2O$	DCE	2,6-Lutidine (2.0)	<5%[c]
16	–	DCE	2,6-Lutidine (2.0)	<5%[c]

[a] Isolated yields.
[b] 280 nm light was used.
[c] Starting material was recovered.

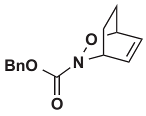
Table 2
Scope of the nitrosocarbonyl HDA under photoredox conditions



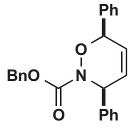
4 **5** **6**



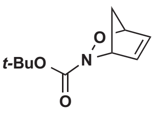
7
93%



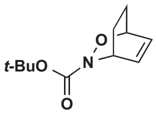
3
87%



8
54%

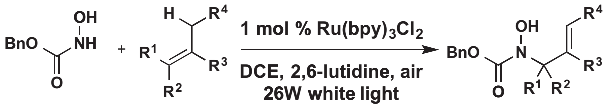


9
89%

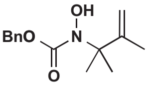


10
77%

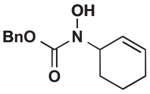
Table 3
Scope of nitrosocarbonyl ene reaction under photoredox conditions



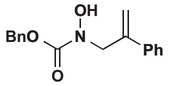
1 **11** **12**



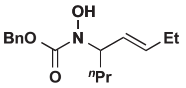
13
99%



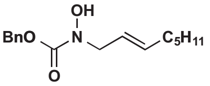
14
68%



15
85%



16
78%



17
34%