

Photoinduced Oxidative Formylation of *N*,*N*-Dimethylanilines with Molecular Oxygen without External Photocatalyst

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Supporting Information



ABSTRACT: A photoinduced oxidative formylation of *N*,*N*-dimethylanilines with molecular oxygen in the absence of an external photocatalyst was developed and provided the corresponding formamides in good yields under mild reaction conditions. Investigations indicated that both the starting material and product act as photosensitizers and that ${}^{1}O_{2}$ coexists with $O_{2}^{\bullet-}$ during the reaction through energy transfer and single electron transfer process.

S ince MacMillan developed the direct asymmetric alkylation of aldehydes by merging photoredox with organocatalysis under visible-light irradiation in 2008,¹ visible light, as an abundant and green energy source has been shown to induce a number of organic transformations through single-electron transfer, energy transfer, and hydrogen atom transfer process and has received considerable attention.² A variety of C-C and C-heteroatom bond formations in the presence of a suitable photosensitizer, including Ru, Ir, Au, Cu, and Ni complexes, organic dyes, or semiconductor nanoparticles under visible-light irradiation have been disclosed.³ To preserve the precious metals (Ru, Au, and Ir complexes) and expensive organic dyes (acridinium and pyrylium salts) that have been used as photocatalysts, hypervalent iodine reagent catalyzed organic reactions under visible-light irradiation without the use of a photosensitizer have been reported.⁴ Further, Melchiorre developed a visible-light-induced organic reaction that relied on the formation of photon-absorbing electron donoracceptor complexes without an external photosensitizer.⁵ Most recently, Li and Hong described the direct trifluoromethylation of arenes and phosphonation of quinolinones under photocatalyst-free and light-irradiation conditions.⁶

N-Methyl-*N*-arylformamides are widely used as organic intermediates and formylation reagents in Vilsmeier reactions.⁷ Traditionally, they have been prepared by the reaction of *N*methylaniline with formic acid.⁸ There are a number of modifications that have been developed in recent years. For example, the Au-catalyzed *N*-formylation of amines with paraformaldehyde,⁹ the boron-catalyzed *N*-methylation of *N*methylaniline using formic acid,¹⁰ and the formylation of amines using CO₂ and hydrosilanes¹¹ were reported. Additionally, the Pd-catalyzed oxidation of *N*,*N*-dimethylanilines¹² and the Fe^{III}-catalyzed transformation of *N*,*N*-dimethylanilines with H₂O₂ have been described.¹³

Most recently, the visible-light-induced oxidation of a benzylic $C(sp^3)$ -H to a ketone by oxygen with acridinium

salt as the photosensitizer¹⁴ and the visible-light-induced and Ircatalyzed photoredox reactions of *N*,*N*-dimethylanilines with oxygen were established.¹⁵ It is also worth noting that an autooxidation of $C(sp^3)$ –H of glycine derivatives to oxalic acid derivatives with molecular oxygen was reported.¹⁶ On the basis of this understanding and our work,^{4b} we report a photoinduced oxidative formylation of *N*,*N*-dimethylanilines with molecular oxygen without an external photocatalyst. The reactions generated the corresponding formamides in good yields under mild conditions.

First, the reaction conditions were optimized by using N,Ndimethylaniline (1a) as the model substrate, as shown in Table 1. When the model reaction was carried out under the irradiation of LEDs (420-425 nm) with molecular oxygen in toluene at room temperature for 12 h, the oxidation product Nmethyl-N-phenylformamide (2a) was isolated in 56% yield (Table 1, entry 1). It was found that the desired product 2a was obtained in 65% and 59% yields with the irradiation of LEDs at 380-385 and 410-415 nm, respectively (Table 1, entries 2 and 3). When the wavelength of the light source was in the range of 450-455 nm or a white light was used, no reaction occurred, and the starting material 1a was recovered (Table 1, entries 4 and 5). Thus, LEDs (380-385 nm) were the best light source for the reaction. The ultraviolet-visible absorption spectra of the substrates indicated that they have a stronger absorption intensity at 380-385 nm than that at visible ranges (Figure S6, S8, and S10 in SI). The effect of the solvent on the reaction was examined, and DME is the best choice. When the model reaction was performed in DME, an 87% yield of 2a was generated (Table 1, entry 6). Other solvents, such as THF, dioxane, PhCl, MeCN, acetone, 1,2-dichloroethane, and CHCl₃, exhibited less reactivity, providing 2a in 24-79% yields

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Table 1. Optimization of the Reaction Conditions^a

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	Me molecular NMe room tem	r oxygen	Ne N↓ H
	1a light irrad	liation ?	2a
entry	light source	solvent	yield ^b (%)
1	420-425 nm (1.5 W)	toluene	56
2	380-385 nm (1.5 W)	toluene	65
3	410-415 nm (1.5 W)	toluene	59
4	450-455 nm (1.5 W)	toluene	NR
5	white light (18 W)	toluene	NR
6	380-385 nm (1.5 W)	DME	87
7	380-385 nm (1.5 W)	THF	79
8	380-385 nm (1.5 W)	dioxane	66
9	380-385 nm (1.5 W)	PhCl	61
10	380-385 nm (1.5 W)	MeCN	46
11	380-385 nm (1.5 W)	acetone	54
12	380-385 nm (1.5 W)	1,2-dichloroethane	51
13	380-385 nm (1.5 W)	CHCl ₃	24
14	380-385 nm (1.5 W)	DMA	NR
15	380-385 nm (1.5 W)	EtOH	NR
16	380-385 nm (1.5 W)	DMF	NR
17	380-385 nm (1.5 W)	DMSO	NR
18	380-385 nm (1.5 W)	H ₂ O	NR
19	in dark (no light)	DME	NR
20	380-385 nm (1.5 W)	DME	NR ^c

^{*a*}Reaction conditions: *N*,*N*-dimethylaniline (**1a**, 0.30 mmol), solvent (2.0 mL) at room temperature under light irradiation in air for 12 h. ^{*b*}Isolated yield, NR = no reaction. ^{*c*}Under N₂ atmosphere.

(Table 1, entries 7–13). It should be noted that no desired product **2a** was formed when the reaction was carried out in DMA, EtOH, DMF, DMSO, or H_2O (Table 1, entries 14–18). In the absence of light or molecular oxygen, no reaction was observed either (Table 1, entries 19 and 20).

With the optimized conditions in hand, the generality of the oxidative formylation of N-alkyl-N-methylanilines was explored. The results are listed in Scheme 1. First, a variety of N,Ndimethylanilines was examined under the standard conditions, indicating a broad tolerance of substituted groups on the aromatic rings. N,N-Dimethylanilines with an electron-donating group, such as Me, t-Bu, or MeCONH at the para-position of the aromatic rings, reacted with O_2 to generate the corresponding products 2b-d in 61-88% yields. Meanwhile, N,N-dimethylanilines bearing an ester group, such as benzoyloxy, *n*-butanoyloxy, and cyclopropanecarbonyloxy, generated the desired products 2e-g in 91-96% yields. The reactions of N,N-dimethylanilines with a m-methyl, or m,mdimethyl on the benzene rings afforded 2h and 2i in 57% and 75% yields, respectively. Furthermore, N,N-dimethylanilines that possessed an electron-withdrawing group, including F, Br, F₃CO, CN, MeCO, PhCO, HCO, EtO₂C, or (Me)₂CHCH₂CH₂O₂C on the para-position of the benzene rings, underwent the oxidative formylation with O₂ to afford the anticipated products 2j-r in 75-97% yields. Substitution at the meta-aromatic position of N,N-dimethylanilines with Cl or Br exhibited good reactivity and afforded the corresponding products 2s and 2t in 95% and 92% yields, respectively. It should be noted that an oxidative formylation of N,Ndimethylnaphthalen-2-amine proceeded well, leading to 2u in 82% yield. However, N-ethyl-N-methylaniline, N-methyl-N-(npropyl)aniline, and N-benzyl-N-methylaniline failed to generate





any of the desired products 2v-x and only resulted in the recovery of starting materials owing to the steric effect of a more bulky group attached to nitrogen atom compared with methyl group. When *N*,*N*-dimethyl-3-nitroaniline (1y) was employed as substrate, a *N*-demethylated product *N*-methyl-3-nitroaniline (2y) was obtained in 73% yield.¹⁷ As *N*,*N*-dimethylbenzylamine (a *N*,*N*-dimethylalkylamine) was used, no desired product was detected.

Next, several *N*-methyldiarylamines **3** as substrates were surveyed, shown in Scheme 2. The oxidative formylation of *N*-methyldiphenylamine, *N*-methyldi(*p*-tolyl)amine, and *N*-methylbis(*p*-bromophenyl)amine with molecular oxygen generated the corresponding products $4\mathbf{a}-\mathbf{c}$ in 57–71% yields.

It was indicated that N-benzyl-N-methylaniline was an ineffective substrate for the reaction (2x), but the oxidative conversion of 2-(methyl(phenyl)amino)-1-phenylethanone





(5a) generated product 6a in 75% yield (Scheme 3). As the analogues of 5a, 2-((4-bromophenyl) (methyl)amino)-1-(p-



tolyl)ethanone (**5b**), 2-((4-bromophenyl) (methyl)amino)-1-(4-chlorophenyl)ethanone (**5c**), and 1-(4-bromophenyl)-2-(methyl(phenyl)amino)ethanone (**5d**) were tolerated and products 6b-d were obtained in 79–84% yields. Normally, an alkyl radical near a carbonyl group would be formed first because it is more stable. Then a free-radical rearrangement would generate an aminomethyl radical for the next oxidative formylation, providing the desired products.

The oxidative carbonylation of the other substrates was further investigated, as indicated in Scheme 4. When the



reactions of 1,3,3-trimethyl-2-methyleneindoline (7) and 1,1diphenylethylene (9) were performed under the optimized reaction conditions, the corresponding terminal vinyl groups were oxidized into ketones 8 and 10 in 88% and 96% yields, respectively (parts a and b, respectively, of Scheme 4).¹⁸ To expand the oxidation of methylenes to carbonyls, the reaction of (2-(allylamino)phenyl)(phenyl)methanone (11) with O₂ afforded *N*-(2-benzoylphenyl)formamide (12) in 82% yield

(Scheme 4c), and 1-(2-(prop-2-yn-1-ylamino)phenyl)ethanone (13) could be converted into 14 in 90% yield (Scheme 4d) along with the cleavage of the carbon–carbon bonds. Under LEDs (380-385 nm) irradiation, the reactions of 1-(2-(benzylamino)phenyl)ethanone (15), diphenylmethane (17) and diphenylmethanol (18) with oxygen afforded 16 in 80% yield, and 10 in 89% and 90% yields, respectively (Scheme 4e– g).¹⁹ The reaction could be performed on a gram scale, treatment 10 mmol of 1a under the optimized conditions afforded the corresponding 2a in 76% isolated yield.

When a radical scavenger 2,2,6,6-tetramethyl-1-piperidinyloxy (TEMPO) was added to the model reaction of 1a with air, the oxidative carbonylation was completely inhibited along with the formation of its adduct with TEMPO, which was detected by HRMS (Figure S1), implying the formation of an aminomethyl radical. On the other hand, ¹⁸O₂-labeling experiments were conducted, and the results are presented in the SI. When the reaction of 1a was performed in the presence of ¹⁸O₂ instead of ¹⁶O₂, a product 2a-¹⁸O was obtained in 81% yield and confirmed by HRMS, and no unlabeled 2a was observed (Figure S2). In addition, when 1a was carried out under an air atmosphere (¹⁶O₂) and with H₂¹⁸O (2.0 equiv), the product 2a was isolated in 78% yield, and no 2a-¹⁸O was detected (Figure S3). These results indicated that oxygen in 2a comes from molecular oxygen.

To further explore the reaction mechanism, the following experiments proved the important role of oxygen in the reaction. When 5,5-dimethylpyrroline N-oxide (DMPO) and 2,2,6,6-tetramethylpiperidine (TEMP) were employed to capture $O_2^{\bullet-}$ and 1O_2 , respectively, the resulting electron-spin resonance (ESR) spectra were recorded, as shown in Figure S4. There was no signal when DMPO was added into a solution of 1a in air-saturated DME in the absence of light irradiation (Figure S4a). However, a strong characteristic signal of an O_2^{\bullet} adduct with DMPO was observed when the above solution was irradiated with LEDs (380-385 nm), and a series of stronger characteristic signals of O2 •- were collected with prolonged irradiation time (Figure S4b-d). A strong signal of the $^{1}O_{2}$ adduct with TEMP was also observed when the above solution was irradiated with LEDs (380-385 nm), but no signal was recorded without light (Figure S5), implying that ¹O₂ coexists with $O_2^{\bullet-}$ during the reaction.

Moreover, the ultraviolet-visible absorption spectra of substrates 1 and their corresponding products 2 demonstrated that they absorb light at 380–385 nm and act as photosensitizers (Figure S6–10), thus avoiding the need for any external photocatalyst. It should be noted that the obtained formamides as products absorb a longer wavelength light, which activates the molecular oxygen in the air more efficiently and accelerates the reaction, so the entire oxidative formylation is self-sustaining in an autocatalytic manner (Figure S11). As a well-known photocatalyst, [Ru(bpy)₃]Cl₂·6H₂O (1.0 mol %) was added to the reaction of 1a, and a superior yield of 2a was observed, thus indicating its positive effect as an $^{1}O_{2}$ -generating photosensitizer.²⁰ It is thought that the singlet oxygen with a photoexcited 1 and 2 via an energy-transfer process.

On the basis of these observations and the literature, a possible mechanism for the photoreaction of 1 with O_2 is proposed in Scheme 5. To begin, substrate 1 is excited by light (380–385 nm) to generate the excited species 1* and acts as a photosensitizer, which then undergoes an energy-transfer pathway with ground-state triplet oxygen ${}^{3}O_{2}$ to afford a

Scheme 5. Possible Reaction Mechanism



higher active excited-state singlet oxygen ${}^{1}O_{2^{\prime}}$ along with regeneration of ground state 1. The formed singlet O_{2} reacts with substrate 1 via a single-electron transfer (SET) process to generate a free-radical cation A and $O_{2}^{\bullet-}$, and a proton transfer between A and $O_{2}^{\bullet-}$ proceeds to afford a superoxide radical HOO[•] and radical B, which reacts directly to form intermediate C. An intermolecular dehydration of C yields product 2. Of course, the formed product 2 is also acts as a photosensitizer to complete catalytic cycle.

In conclusion, we have developed a photoinduced oxidative formylation of *N*,*N*-dimethylanilines with molecular oxygen in the absence of an additional photocatalyst. The reactions can be extended to a terminal vinyl group, an active benzylic sp³ C–H, and an active secondary alcohol, providing the corresponding carbonylative products. Investigations supported a mechanism in which both the starting materials and products act as photocatalysts upon excitation using LEDs (380–385 nm) to photochemically promote ground-state oxygen (${}^{3}O_{2}$) to excited-state oxygen (${}^{1}O_{2}$) via an energy-transfer process. EPR results demonstrated the formation of $O_{2}^{\bullet-}$ and ${}^{1}O_{2}$, which play an important role in the reaction. This protocol provides a simple and mild route to formamides in good yields without an external photocatalyst. Further application of this protocol and its detailed reaction mechanism is underway.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.or-glett.7b01230.

Full experimental details and characterization data for all products (PDF)

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