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Synthesis of Alkyl Halides from Aldehydes via Deformylative Halogenation

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Abstract

An unprecedented deformylative halogenation of aldehydes to alkyl halides is presented. Under oxidative conditions, 1,4-dihydropyridine (DHP), derived from an aldehyde, generated a C(sp³)–radical that coupled with a halogen radical that was generated from inexpensive and atom-economical halogen sources (NaBr, NaI, or HCl), to yield an alkyl halide. Because of the mild conditions, a wide range of functional groups were tolerated, and excellent site selectivity was achieved.

Graphical Abstract

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ASSOCIATED CONTENT

Supporting Information

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Experimental detail and copies of NMR spectra (PDF)

The authors declare no competing financial interest.

Halogenated organic compounds are ubiquitous in organic chemistry.¹ They not only play significant roles as synthetic intermediates and building blocks in organic transformations such as cross-coupling reactions and nucleophilic substitutions,² but they are also versatile precursors for most organometallic species, including Grignard, organozinc, and organocuprate reagents.³ Halogenated organic compounds have also been used as essential designer molecules in the pharmaceutical,⁴ agrochemical,⁵ and material science applications.⁶ Their syntheses have been carried out through substitutions,⁷ Markovnikov additions,⁸ and less common radical-based protocols⁹ such as the Hunsdiecker reaction¹⁰ and its variations.¹¹

Recently, the use of visible light as an efficient, clean, and inexpensive energy source for radical-based organic synthesis has received much attention.¹² However, halogenations using photocatalysis are very rare.¹³ In particular, the chlorination or bromination of arenes was usually restricted to electron-rich substrates,¹⁴ while the construction of alkyl chloride or bromide faced more challenges such as controlling site selectivity, choice of appropriate substrates, and halogen sources.¹⁵ Nicewicz and co-workers reported a photocatalyzed *anti*-Markovnikov hydrochlorination of styrenes.¹⁶ They utilized the stable benzylic radical to initiate the photoredox reaction and achieve the site-selective installation of chlorine, but only styryl substrates were showcased (Scheme 1a). The Glorius' group reported a Hunsdiecker decarboxylative halogenation strategy using diethyl bromomalonate, NCS, and NIS as halogen sources under photoirradiation (Scheme 1b).¹⁷ Alexanian and co-workers designed an amide-based halogenating reagent for aliphatic C–H halogenation (Scheme 1c).¹⁸

This protocol exhibited predominant δ -selectivity, but the formation of other regioisomers was also observed, in yields ranging from 18% to 46%. Roizen and co-workers reported a γ -selective intramolecular chlorination which required preinstallation of a chlorine-directing group, sulfamate ester (Scheme 1d).¹⁹

Aldehydes are among the most common functionalities in synthesis, and they are starting materials for a variety of organic transformations, among which deformylative transformation has significant synthetic value because it can integrate one-carbon degradation and further functionalization in a single step. However, such strategies are rare.²⁰ The reported methods relied on the generation of an acyl radical through hydrogen-atom transfer (HAT), followed by CO extrusion to form an alkyl radical for further functionalization. But the dissociation of an acyl radical to generate an alkyl radical is a high energy process, and acylated products are more commonly observed.²¹ An alternative is an oxidative process followed by elimination of CO₂ to furnish a one-carbon-shorter alkyl radical;²² however, the use of strong and stoichiometric oxidants is not desirable in synthesis. Recently, 1,4-dihydropyridines (DHP) easily prepared from aldehydes under neutral redox conditions have been used in deformylative transformations.²³ Its robustness allows for a wide range of structural derivatizations (see Supporting Information (SI)). Under photoirradiation, DHPs undergo homolysis to generate C(sp³)-centered alkyl radicals, which can be employed for further radical coupling reactions. However, these coupling reactions were primarily used in the construction of C–C bonds. Herein we report the first photoredox-catalyzed deformylative halogenation strategy to achieve the transformation of

aldehydes to alkyl halides using readily available, inexpensive, and atom-economical NaBr and HCl as halogen sources. In addition, we have successfully developed a photocatalyst-free deformylative iodination using NaI as a halogen source (Scheme 1).

First, we established the conditions for the deformylative bromination using DHP **1a** as the substrate (Table 1). After extensive screening, the optimized conditions furnished the desired brominated product **2a** in 98% yield without the formation of the regioisomer derived from the more stable benzylic radical (Table 1, entry 1). H₂O was important to dissolve salts and achieve better yields (Table 1, entries 2–3). Other commonly used photocatalysts (**B–D**) exhibited lower efficacy (Table 1, entries 4–6). The use of organo-oxidants DTBP and TBN or the lack of an oxidant led to poor yields or no reaction (Table 1, entries 7–9). The yield was dramatically decreased when only half the amount of NaBr was used (Table 1, entry 10). Both blue LED irradiation and photocatalyst **A** were crucial to produce **2a** in higher yields (Table 1, entries 11–13). A low yield was obtained when this reaction was conducted under air (Table 1, entry 14).

With the optimized conditions established, we proceeded to evaluate the scope of the deformylative bromination process. As shown in Scheme 2, a myriad of DHPs were suitable substrates, giving the corresponding brominated products in good to excellent yields. Notably, no regioisomeric products were observed even when active benzylic positions were available (**2a–2c**). A diverse range of functional groups were well tolerated, such as hydroxyl, ether, ester, ketone, aldehyde, thioether, nitro, and nitrile groups (**2d–2m**). Heterocyclic compounds such as furan (**2n**), thiophene (**2o**), thiazole (**2p**), benzotriazole (**2q**), indole (**2r**), and *N*-Boc-piperidine (**2s**) were suitable substrates. Benzylic DHPs also succeeded in delivering the brominated products in good yields (**2t–2x**).

Once the versatility of the deformylative bromination was demonstrated, we focused our attention on deformylative chlorination. Our newly developed HCl/DMPU^{24,8b} was superior to other inorganic chloride salts (Table 2, entries 1–7), while Ir(ppy)₃ (**B**) was a more efficient photocatalyst (Table 2, entries 7–9). Both light and photocatalyst were crucial in the production of **3a** (Table 2, entries 10–11). With these modified conditions in hand, we examined the scope of the deformylative chlorination protocol. As illustrated in Scheme 3, our method produced the corresponding chlorinated products in good to excellent yields. Various functional groups (**3a–3p**) as well as heterocyclic arenes (**3q–3t**) were tolerated.

The scalability of our deformylative halogenation was evaluated using 3 mmol of DHP substrate **1a**. The halogenated products were generated in yields of 79% and 67%, respectively (Figure 1a). To highlight the excellent site selectivity of this protocol, two similar but distinguishable DHPs (**1x** and **1y**) were prepared and subjected under the standard conditions to both parallel and crossover experiments (Figure 1b). In the former, only *in situ* DHP-substituted products were observed, while, in the latter, two brominated products (**2y** and **2z**) were formed with the same mole ratio as the starting DHPs, indicating that the reactivities of **1x** and **1y** were the same and that no isomerization occurred during this reaction.

To gain insight into the reaction mechanism, the bromination of **1a** was monitored with the light on/off over time. A smooth transformation under irradiation by blue LEDs and no further production of **2a** in the dark suggested that the reaction proceeded through a photoredox catalytic pathway rather than a radical chain pathway (Figure 1c). A radical quenching experiment was also conducted by adding the radical scavenger 2,2,6,6-tetramethylpiperidine-1-oxyl (TEMPO) to the reaction of **1a**. We observed that the bromination was completely inhibited (Figure 1d). Based on the above observations, we proposed a plausible mechanism for this bromination process, shown in Scheme 4a. Upon visible light irradiation the excited photocatalyst $^*\text{Ru}(\text{bpy})_3^{2+}$ is oxidized by $\text{K}_2\text{S}_2\text{O}_8$ ($E_{\text{red}}(\text{S}_2\text{O}_8^{2-}/\text{SO}_4^{2-}) = +2.01 \text{ V vs SCE}$)²⁵ through single electron transfer (SET), resulting in the formation of SO_4^{2-} , $\text{SO}_4^{\bullet-}$, and a strong oxidative $\text{Ru}(\text{bpy})_3^{3+}$ ($E_{\text{red}}^{\text{III/II}} = +1.29 \text{ V vs SCE}$) species.^{12o} Then the single-electron oxidation of DHP **1** ($E_{\text{red}} = +1.03 \text{ V vs SCE}$)^{26,23g} yields radical **II** and reductively quench the photocatalyst. The resulting radical **II** then fragments to an alkyl radical **IV** along with pyridine derivative **III**, driven by aromatization. The high reduction potential of the generated $\text{SO}_4^{\bullet-}$ ($E(\text{SO}_4^{\bullet-}/\text{SO}_4) = +2.6 \text{ V vs SCE}$) enables the further oxidation of Br^- ($E_{\text{red}}(\text{Br}^{\bullet}/\text{Br}^-) = +0.8 \text{ V vs SCE}$)²⁷ to its radical form, thus rendering the radical coupling with alkyl radical **IV** to furnish the brominated product **2**. In the chlorination process, however, the single electron transfer (SET) from the ground state of DHP **1** ($E_{\text{red}} = +1.03 \text{ V vs SCE}$)^{26,23g} to either the photoexcited Ir(III) ($E_{\text{red}}^{\text{III/II}} = +0.31 \text{ V vs SCE}$)^{12o} or the oxidized Ir(IV) ($E_{\text{red}}^{\text{IV/III}} = +0.77 \text{ V vs SCE}$)^{12o} is not favored. Therefore, the possibility of generating radical **V** via photo-excited DHP **1*** was suggested, which has been experimentally proved.^{23f} This different radical initiation is also evident by the formation of the chlorinated product in moderate yield when only the blue LED was employed (Table 2, entry 10). The radical **V** would reductively quench the oxidized photocatalyst Ir(IV) to form the pyridine derivative **III**. The resulting alkyl radical **IV** would follow a similar radical coupling route as the bromination, giving rise to chlorinated product **3** (Scheme 4b).

Subsequently, we examined the deformylative iodination using NaI as a halogen source.

Unlike in the case of bromination and chlorination, a photoredox catalyst was not required in this protocol because a iodine radical is generated from the NaI/ $\text{K}_2\text{S}_2\text{O}_8$ system.²⁸ After extensive optimization (see SI), we found that 95% of the product could be obtained in the presence of 1.5 equiv each of NaI/ $\text{K}_2\text{S}_2\text{O}_8$. As shown in Scheme 5, various DHPs were suitable substrates, giving the desired iodinated products in good to excellent yields (**4a–4l**) although benzylic DHP **4m** showed less reactivity.

In conclusion, we have developed a highly efficient visible-light-mediated deformylative halogenation protocol using inexpensive and atom-economical halogen sources. This protocol exhibited excellent site selectivity and functional group tolerance, which are highly desired in late-stage functionalization.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1.

(a) Gram-scale synthesis; (b) Light on/off experiment; (c) Selectivity study; (d) Radical quenching experiment.

a) *anti*-Markovnikov hydrochlorination of styrene

b) Decarboxylative halogenation

c) Siteselective aliphatic C-H halogenation

d) Sulfamate ester directed aliphatic C-H chlorination

this work: deformylative halogenation

Scheme 1.

Major Photoinduced Synthetic Methods for Alkyl Halides

Scheme 2.
Scope of Deformylative Bromination^a

Scheme 3.
Scope of Deformylative Chlorination^a

a) proposed bromination mechanism

b) proposed chlorination mechanism

Scheme 4.
Plausible Reaction Mechanism

Table 1.

Optimization of Visible-Light-Mediated Deformylative Bromination of **1a**^a

entry	variations from the standard conditions	yield (%) ^b
1	none	98
2	MeCN/H ₂ O (v/v = 1/1)	89
3	MeCN	9
4	B instead of A	13
5	C instead of A	53
6	D instead of A	9
7	DTBP instead of K ₂ S ₂ O ₈	0
8	TBN instead of K ₂ S ₂ O ₈	11
9	Without K ₂ S ₂ O ₈	0
10	NaBr (1.5 equiv)	16
11	CFL as a light source	47
12	no light	0
13	without A	18
14	under air	17

^aReaction conditions: **1a** (0.1 mmol), NaBr (0.3 mmol), K₂S₂O₈ (0.15 mmol), **A** (1 mol %), MeCN/H₂O (v/v = 9/1) [0.2 M], blue LEDs, rt, 24 h, Ar atmosphere.

^bYields were determined by ¹H NMR using 1,3,5-trimethoxybenzene as internal standard. **A** = Ru(bpy)₃Cl₂·6H₂O, **B** = Ir(ppy)₃, **C** = Eosin Y (Green LEDs), **D** = 9-Mesityl-10-methylacridinium perchlorate, DTBP = Di-*tert*-butyl peroxide, TBN = *tert*-butyl nitrite.

Table 2.Screening of Chlorine Source and Photocatalyst for Deformylative Chlorination of **1a**^a

entry	[Cl]	photocatalyst	yield (%) ^b
1	LiCl	A	37
2	NaCl	A	31
3	KCl	A	16
4	CsCl	A	22
5	NH ₄ Cl	A	54
6	CaCl ₂	A	21
7	HCl/DMPU (43% w/w)	A	62
8	HCl/DMPU (43% w/w)	B	84
9	HCl/DMPU (43% w/w)	C	44
10	HCl/DMPU (43% w/w)	B	47 ^c
11	HCl/DMPU (43% w/w)	B	18 ^d

^aReaction conditions: as in Table 1 (entry 1).^bYields were determined by ¹H NMR using 1,3,5-trimethoxybenzene as an internal standard. DMPU = *N,N'*-Dimethylpropyleneurea.^cWithout **B**.^dNo light.