Selective Debromination and α-Hydroxylation of α-Bromo Ketones Using Hantzsch Esters as Photoreductants

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Abstract: Two transformations initiated by photoinduced one-electron transfer to α -bromo ketones have been demonstrated. Hantzsch esters donate one electron to α -bromo ketones under photoirradiation, promoting reductive debromination. Subsequent reactions of the resulting radical species of the ketones with molecular oxygen and Hantzsch esters lead to α -hydroxylation or debromination, respectively. The relative dominance of the two pathways depends profoundly on the reaction conditions, including solvent, O₂ levels, and the concentration of the Hantzsch esters. The synthetic protocols feature advantages because they require the environmentally benign sources, molecular oxygen and visible light.

Keywords: debromination; Hantzsch esters; hydroxylation; photoreductants

Recent advances in synthetic chemistry benefit from one-electron processes mediated by photoredox catalysts. The use of photoredox catalysts enables reactions to proceed under mild conditions, as photon absorption provides large redox power to execute reactions that are thermodynamically challenging. Indeed, a variety of photoredox reactions have been devised to promote diverse organic transformations with synthetic and industrial utility, thus replacing the traditional approaches, such as those relying on organotin hydrides. In particular, major advances have been made by employing transition metal complexes of iridium or ruthenium as visible-light photocatalysts.^[1,2] The visible light-driven photoredox catalysis involves photoinduced one-electron transfer of the metal complexes, which produces reactive radical intermediates along with radical cationic or radical anionic species of the catalysts. Completion of the catalytic cycle necessitates restoration of the radical ion species of the catalysts to the ground state by dumping or scavenging one electron from sacrificial electron acceptors and donors, respectively. 1,4-Dihydropyridine-3,5-dicarboxylate esters [Hantzsch esters (HEs)]^[3] have been widely employed as the sacrificial electron donor for this purpose.^[4]

In our continuing efforts on the development of photoredox catalysis, we serendipitously found that HEs could act as photoreductants.^[5] We report herein a simple metal-free protocol for transformations of α bromo ketones through the efficient generation of radical intermediates under photoexcitation of HEs. HE (1) and its analogues have been used as both electron and hydrogen-atom donors to promote selective debromination and α -hydroxylation reactions in the absence of any additional reagents (Figure 1). The reaction pathways depended strongly on the conditions, such as solvents, presence of O_2 , and the concentration of HEs. The synthetic protocol exhibited high functional group compatibility under mild reaction conditions. Studies based on the Stern-Volmer analysis and photoluminescence lifetime measurements using time-correlated single-photon-counting techniques were performed to elucidate the role of HEs. The mechanistic studies revealed that HEs were versatile photoreductants.



Figure 1. Photoinduced transformations of α -bromo ketones using Hantzsch esters.

The investigation for the reaction with HE started using 2-bromo-1-(4-methoxyphenyl)ethanone (2a) as the model substrate (Table 1). The photoirradiation of a DMSO solution of 2a and HE using a compact fluorescent lamp (14 W) at room temperature for 4 h^[6] led to the complete conversion of 2a into a mixture of debrominated product $(3a)^{[7,8]}$ and α -hydroxy ketone (4a) (entry 1). The results prompted us to optimize the reaction conditions for selectivity toward either the debrominated product or the α -hydroxylated product. Thorough deoxygenation by repeated freezepump-thaw cycles yielded 3a only, indicating that O_2 was the oxygenation source. Experiments with varying solvents showed that 2,2,2-trifluoroethanol (TFE) was the best solvent for the debromination reaction (entries 3–6). Interestingly, the yield of **3a** in TFE did not decrease even when the irradiated solution was purged with oxygen gas (entry 7, 96% yield). Further optimization with changes in the stoichiometry of HE showed that use of 1.2-1.3 equiv. of HE afforded the highest yields (entries 6 and 8-11). Additives, such as an Ir photocatalyst and tertiary amine, did not improve the reaction yields (entries 12-14). Control experiments revealed that both HE and photon source were prerequisites for the debromination of α -bromo ketones (entries 17 and 18).

Although α -hydroxy carbonyl compounds are valuable synthetic intermediates for the preparation of a variety of biologically active compounds including 2-amino-1-arylethanols, only a few methods are available in the literature.^[9,10] Therefore, our photoinduced α -hydroxylation of α -bromo ketones carries synthetic utility. It was found that, in addition to the presence of O_2 , the concentration of HE was the key factor that determined the selectivity and efficiency of the α -hydroxylation of α -bromo ketone (2a). For instance, low concentrations of HE preferred α -hydroxylation, whereas 0.1 M concentration yielded nearly equal amounts of the debrominated product along with the α -hydroxylated product (Table 1, entries 1 and 19– 23). The optimal conditions for α -hydroxylation involved the use of 3 equiv. of HE in 0.005 M oxygenated DMSO solution (entry 27).

Table 1. Optimization of the debromination reaction of α -bromo ketone (**2a**) by Hantzsch ester.^[a]



Enter	Solvon	t Additive		Yield [%] ^[b]	
Entry	Solven	a Additive	variations	3a	4a
1	DMSO	no deoxygenatio	n -	56	42
2 ^[c]	DMSO	Ar (after deoxygena	tion) -	90	-
3	DMF	-	-	62	-
4	MeCN	-	-	trace	-
5	THF	-	-	trace	-
6	TFE	-	-	97	-
7	TFE	O ₂ bubbling	-	96	-
8	TFE	-	HE (1.5 equiv.)	97	-
9	TFE	-	HE (1.3 equiv.)	97	-
10	TFE	-	HE (1.2 equiv.)	94	-
11	TFE	-	HE (1.1equiv.)	88	-
12	TFE	<i>fac</i> -Ir(ppy) ₃ (1 mol	%) -	94	-
13	TFE	DIPEA (2 equiv.)	-	14	-
14 ^[d]	TFE	<i>fac</i> -Ir(ppy) ₃ /DIPEA		50	-
15	TFE	-	HE (1.3 equiv.), 0.5 M	85	-
16	TFE	-	HE (1.3 equiv.), 0.1 M	89	-
17	TFE	-	no HE	-	-
18	TFE	-	no lamp	-	-
19 ^[e]	DMSO	open to air	0.005 M	-	45
20	DMSO	open to air	0.01 M	20	75
21	DMSO	open to air	0.05 M	33	63
22	DMSO	open to air	0.1 M	40	57
23	DMSO	open to air	0.005 M, 18 h	-	85
24	DMSO	open to air	0.005 M, 18 h, HE (1 equiv.)	-	80
25	DMSO	open to air (0.005 M, 18 h, HE (2.5 equiv.) -	89
26	DMSO	open to air	0.005 M, 18 h, HE (3 equiv.)	-	92
27	DMSO	O ₂ bubbling	0.005 M, 18 h, HE (3 equiv.)	-	95
28	DMSO	O ₂ bubbling	no lamp	-	-

^[a] Reaction scale: α -bromo ketone **2a** (0.1 mmol).

^[b] Yields were determined by gas chromatography with dodecane as the internal standard.

- ^[c] The reaction mixture was deoxygenated by freeze-pump-thaw cycling.
- ^[d] 1 mol% of *fac*-Ir(ppy)₃ and 2 equiv. of DIPEA were used.
- ^[e] After 4 h, approximately 50% of α -bromo ketone **2a** was consumed.

The photophysical properties of the analogues of HE (5-8; Figure 2) have also been investigated.^[11] UV-vis absorption spectra showed that HE (1) and its methyl (5), isopropyl (6), and *tert*-butyl (7) derivatives



Figure 2. UV-visible absorption spectra of the HE and its derivatives (50 μ M in DMSO).

had similar absorbance properties, whereas the 4methyl derivative of HE (8) showed a distinct blue shift. Except for 8, all the HE analogues featured strong absorption $(4-9 \times 10^3 M^{-1} cm^{-1})$ in the near-UV regions extending to 400–430 nm.

The capability of the HE analogues for debromination of **2a** has been compared after 2 h photoirradiation in TFE. To exclude the possibility for the self-absorption of **2a**, a cut-on filter that passed wavelengths greater than 400 nm was employed. As shown in Table 2, the extent of debromination correlated line-

Table 2. Debromination of α -bromo ketone (2a) using HE and its derivatives.^[a]

	O ↓Br	photoreduc (1.3 equi	ictant O iv.) H
MeO	2a	TFE (0.25 CFL lamp (14 r.t., 2 h	5 M) MeO 3a
Entry	Phot	oreductant	Conversion Yield [%] ^[b]
1		1 (HE)	80
2		5	75
3		6	62
4		7	51
5		8	-

^[a] Reaction scale: α -bromo ketone (**2a**; 0.1 mmol).

^[b] The yields after 2 h irradiation were determined by gas chromatography with dodecane as the internal standard.

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^[a] Reaction scale: α -bromo ketone **2a** (1.0 mmol).

arly with the absorption strength (i.e., molar absorb-

ance in the near-UV region). As expected, the reac-

tion did not proceed in the presence of 8 that did not

ductive debromination was investigated (Table 3). The results show that under the optimized reaction conditions, α -bromoacetophenones with diverse elec-

tron-donating and electron-withdrawing substituents

underwent highly efficient debromination reactions (Table 3). Notably, substrates containing CN and NO₂ groups, which are typically incompatible with photodox reaction conditions, underwent debromination (**3k** and **3l**). Furthermore, the selective debromination of diethyl bromomalonate was demonstrated (**3m**). The substrate scope of our α -hydroxylation method was also investigated (Table 4). The results showed that a broad range of α -bromo ketones were converted into corresponding α -hydroxy ketones (**4a**–**4l**) in excellent yields. Compared to the traditional methods for α -hydroxylation involving harsh reaction conditions, such as the use of NaOH, this reaction proceeded under extremely mild reaction conditions, thus al-

lowing excellent functional group tolerance.

Having demonstrated the synthetic utility of photo-

reductive HE and its analogues, the reaction mecha-

nism was investigated. The UV-visible absorption

Next, the substrate scope of the photoinduced re-

^[b] Isolated yields.

absorb light above 400 nm.

Table 3. Substrate scope of photoreductive debromination reaction. $^{\left[a,b\right] }$





^[b] Isolated yields.

spectrum (DMSO) of a mixture of 50 μ M HE and 1.0 mM **2a** was identical with the individual spectra, indicating the lack of charge-transfer interactions in the ground state (Figure 3).^[12]

HE was fluorescent when excited at 380 nm, thus allowing fluorescence titration studies. A DMSO solution containing 50 µM HE was titrated with increasing concentrations of 2a (0-10 mM). The fluorescence spectra were recorded at each step of the titration. The addition of 2a quenched the fluorescence intensity of HE in a concentration-dependent manner (Figure 4a). A Stern-Volmer analysis was carried out for the integrated fluorescence intensities using the Stern-Volmer equation containing a static term (i.e., associative quenching) and a dynamic term (i.e., diffusional quenching): $I_0/I = (1 + K_a \cdot [2a]) \cdot (1 + k_0 \cdot \tau_0 \cdot [2a]),$ where I_0 , I, K_a , k_o , and τ_0 are the integrated fluorescence intensities in the absence (I_0) and presence (I)of 2a, the association constant, the rate constant for the fluorescence quenching, and the fluorescence lifetime of HE in the absence of **2a**, respectively. A τ_0 value of 320 ps was determined for a deaerated DMSO solution containing 50 µM HE after picosecond pulsed laser photoexcitation at 377 nm (Figure 5).

From the non-linear least-squares fit of the titration results to the above equation, the K_a and k_0 values were determined to be $30 M^{-1}$ and $9.4 \times 10^{10} M^{-1} s^{-1}$, respectively (Figure 4b). The small K_a value indicates



Figure 3. UV-vis absorption spectra of 50 μ M HE (black), 50 μ M 2a (blue), and a mixture of 50 μ M HE and 1 mM 2a (red).

a weak intermolecular association between HE and **2a**, consistent with the UV-visible absorption results (*vide supra*). In sharp contrast, the k_0 value was very large, being comparable to the diffusion constant in DMSO at 298 K (~ 10^{10} M⁻¹s⁻¹). These results indicated that the fluorescence quenching was purely diffusional. Because the excited-state oxidation potential of HE was as negative as -2.28 V vs. SCE (Figure 6), the quenching can be attributed to the photoinduced electron transfer from the excited state HE (HE*) to **2a**. The energy transfer from HE* to **2a** was neglected due to the bandgap energy of **2a** being wider than that of HE (Figure 3). These results supported the notion that HE possessed strong photoreduction capability.

The photochemical quantum yields were determined for the debromination and α -hydroxylation of 2a. DMSO solutions (0.5 mL) containing 0.25 M 2a and 2 equiv. HE were photoirradiated (1 h) using broad-band light from a xenon arc lamp. The photon intensity was determined using a standard ferrioxalate actinometry to be 3.3×10^{-9} Einstein s⁻¹. The solutions were either deaerated or O2-saturated prior to the photoirradiation to promote debromination and α-hydroxylation, respectively. The amounts of the products photoirradiation were quantitated after using ¹H NMR spectrometry. Dividing these values with the photon intensity for 1 h yielded quantum yields of 0.14 and 0.038 for debromination and α -hydroxylation, respectively.

Based on the results, a mechanism for the photoreactions has been proposed (Figure 7). Ground state association between HE and α -bromo ketone is excluded from the steady-state UV-vis absorption and the Stern–Volmer analysis. Photoexcitation of HE in-

^[a] Reaction scale: α -bromo ketone **2a** (0.5 mmol).



Figure 4. (a) Fluorescence titration of 50 μ M HE (DMSO) with increasing concentration of **2a** (0–10 mM), and (b) the corresponding titration isotherm and its fit to the Stern–Volmer equation. Refer to the main text for the fitting procedure. Titrations were performed in triplicate, and the error ranges are indicated in (b).



Figure 5. Fluorescence decay trace of 50 μ M HE (deaerared DMSO) after picosecond photoexcitation at 377 nm (temporal resolution = 8 ps).

duces one-electron transfer (eT) to α -bromo ketone within an encounter complex, forming the radical anion of the α -bromo ketone along with [HE]⁺. Then, the loss of bromide from the radical anion, followed by dissociation of the encounter complex generates free radical (2A). Two processes are available for 2A, depending on the reaction conditions. In TFE, subsequent hydrogen atom abstraction from [HE]⁺ or HE affords the hydrogenated product 3 and an oxidized form of HE or HE radical. In the presence of O₂, radical-radical recombination between 2A and O₂ occurs to form the α -hydroperoxy ketone (2B). The



Figure 6. Cyclic (CV, black) and differential pulse (DPV, red) voltammograms for HE. *Conditions:* 2.0 mM HE in deaerated DMF containing 0.10M TBAPF₆; a Pt microdisc and a Pt wire were used as the working and counter electrodes, respectively; Ag/AgNO₃ as the pseudo reference electrode; scan rates = 100 mV s^{-1} (CV) and 4.0 mV s⁻¹ (DPV). The ground-state oxidation potential of 0.79 V *vs.* SCE and the bandgap energy of 3.07 eV (Figure 3) were used to calculate the excited-state oxidation potential to be -2.28 V vs. SCE.

weak O–O bond cleavage in **2B** yields α -hydroxy ketone product, **4**. The process that involves O₂ competes with the former pathway (i.e., debromination). The rate of hydrogen atom abstraction may be slow at low HE concentrations, providing enough time for trapping of **2A** by O₂.



Figure 7. Proposed mechanism for the selective photoinduced processes.

In conclusion, α -bromo ketones can be debrominated and α -hydroxylated using HE under photoirradiation in the absence of any additional reagents. Upon photoirradiation, HE donates one electron to α bromo ketone to produce the key radical intermediate. HE also serves as a hydrogen atom source. Reaction conditions, including solvent and the HE concentration, play crucial roles in determining the nature of the subsequent pathways (i.e., hydrogenation or hydroxylation of the radical intermediate). The protocol provides a practical and environmentally benign strategy for debromination and α -hydroxylation of α bromo ketones. Further investigations into the synthetic utility of HEs for various photoinduced organic transformations are in progress.

Experimental Section

Debromination of α-Bromo Ketones with HE (1)

An oven-dried, resealable tube equipped with a magnetic stir bar was charged with α -bromo ketone (1.0 mmol) and HE (1.3 mmol) in TFE (4.0 mL, 0.25 M). The tube was sealed with a silicone septum screw cap. The tube was placed under a compact fluorescent lamp (14 W) at room temperature for 4 h, and the reaction progress was monitored by TLC or gas chromatography. Then, the reaction mixture was diluted with ethyl acetate and washed with water and brine. The organic layer was dried over MgSO₄, concentrated under vacuum, and purified by flash column chromatography, affording the debrominated product.

α -Hydroxylation of α -Bromo Ketones with HE (1)

An oven-dried round-bottom flask equipped with a magnetic stir bar was charged with DMSO (50–100 mL, 0.10–0.005 M) and sparged with oxygen gas for 10 min. Next, HE (1.5 mmol) and α -bromo ketone (0.5 mmol) were added to this solution in an open state (open to air). The flask was then placed under a compact fluorescent lamp (14 W) at room temperature for 18 h, and the reaction progress was monitored by TLC or gas chromatography. Then, the reaction mixture was diluted with dichloromethane and washed with water and brine. Finally, the organic layer was dried over MgSO₄, concentrated under vacuum, and purified by flash column chromatography, affording the α -hydroxylated product.

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