Efficient Photolytic Halogenation and Oxidation of Unactivated Alkyl sp3 C-H Bonds with Iodine (III)

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Abstract

A metal-free, green, and sustainable functionalization of unactivated alkyl sp3 C–H bonds is reported using iodine (III) as a feasible dehydrogenation agent under visible light or KBr, and alkyl chlorides, bromides, alcohols, and ketones could be constructed by addi-tion of different coupling reagents. Cheap and safe iodobenzene diacetate was used to form a strong radical to activate the alkyl sp3 C–H bond in a highly efficient manner, which can construct different alkylation products by adding corresponding coupling reagents.

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Keywords

Alkyl sp^3 C-H Bonds | chlorination | bromination | oxidation | Iodine (III)

Comprehensive Summary

A metal-free, green, and sustainable functionalization of unactivated alkyl sp^3 C–H bonds is reported using iodine (III) as a

Background and Originality Content

Functionalization of unactivated sp^3 C–H bonds of cyclic and linear alkanes to high-value-added chemicals is one of the most important classes of chemical transformations and has high synthetic potential in synthetic chemistry.[1]Unfortunately, the high bond dissociation energy, low selectivity of alkyl sp^3 C–H, and over

oxidation of products make them inert to various reactions and lead to low yields or poor selectivity.[2] Despite these challenges, activation of unactivated sp^3 C-H bonds has been received much attention for the construction of halo-alkanes, alcohols, and ketones[3] which are common groups and subunits found ubiquitously in natural products, pharmaceuticals, agrichemicals, and organic materials.[4]In recent years, various methods have been developed for the chlorination, bromination, and oxidation of the inert C-H bonds involving the use of transition metal-containing or free catalysts/reagents.[5]

With environmental problems becoming increasingly prominent, non-metallic and environmentally friendly synthetic approaches, are more and more needed. Aromatic peracids, ozone, dioxiranes, etc., were used for the halogenation or oxidation of alkyl sp^3 C-H bonds.[5f,5j,6] *N* -chloroamines, sodium nitrite (cat.) were employed for the halogenation of alkyl sp^3 C–H bonds.[7]Electron-deficient amide was utilized as the directing group for synthesis of lactones via functionalization of nonactivatedsp^3 C-H Bonds.[8]With growing demands of using inexpensive, commercially available reagents, hypervalent iodine (III) has been widely used to trigger various reactions owing to its unique reactivity, low toxicity, and environment friendliness.[9] For example, Maruoka reported the oxidation of alkyl C-H bonds by *ortho* -nitrophenyl derivative of (diacetoxyiodo)benzene (DIB) in the presence of*tert* -butyl hydroperoxide (TBHP).[10]Laborious preparation of *ortho* -nitrophenyl derivative of DIB and using of explosive peroxide render practicability of this method limited. Yeung's system, which utilizes less moisture-sensitive DIB for the oxidation of C–H bonds, proved to be incompetent for activation alkyl C–H bonds, because of its low activity of iodanyl radical generated from stable DIB.[11] Compared with the other methods (e.g., ligand exchange, thermal decomposition or

Scheme 1 . Functionalization of Alkyl sp^3 C–H Bonds

single-electron transfer approach) photolysis can induce the generation of iodanyl radical from hypervalent iodine (III) reagents under milder conditions.[5f] Therefore, based on our previous work on iodine (III),[12] we assumed that if iodanyl radical with the activity high enough to activate inert C-H bond could be generated from DIB under photolysis, then halogenation, and oxidation of the inert C-H bonds would be realized under mild conditions.

Herein, we report a new photo induced approach to generate iodanyl radical using DIB, which can realize the direct chlorination, bromination, and oxidation of unactivated sp^3 C-H bond by NaCl, KBr, or water, respectively. Inspired by the pioneering work of Maruoka,[10a,13] our strategy for the functionalization of unactivated sp^3 C–H bond with DIB under photolysis is shown in scheme 1. First, an acetoxyl radical**1** and an iodanyl radical **2** would be formed from the photolysis of DIB. Then iodanyl radical **2** reacted with unactivated alkane to afford an alkyl radical **3** through hydrogen abstraction. The alkyl radical **3** couples with different coupling reagents to lead the different alkylation products through path A (radical pathway) or path B (ionic pathway: alkyl cation would be generated by single electron transfer (SET) from alkyl radical, which could be captured with various nucleophilic reagents, such as chloride, bromide, or water to afford haloalkanes, alcohols, ketones, respectively.)

Results and Discussion

Based on the design and our previous work of DIB, cyclohexane was used as a model substrate to optimize the chlorination (Table 1). Delightedly, the desired product chlorocyclohexane could be observed in 32% yield, when DIB was used as the oxidant, and NaCl as the chlorine source in DCM under blue light for 3 h (entry 1). Initially, different amount of DIB was studied (entries 2-5), and 3.5 equivalent of DIB was chosen. Encouraged by the positive experimental results and in consideration of the role of water in the expected pathway, we tested the effect of water on the system. Without water, no product was observed, which may be due to the poor solubility of NaCl. However, when more than 0.5 mL of water was added to the reaction, decreasing yields were obtained, mainly due to the insolubility of DIB in water (entries 8-12). The employment of polar solvents failed to improve the efficiency of the reaction (entries 13-15). Next, the influence of reaction time was also tested, and 5h gave the best result, providing halogenation products in 80% yield, while a further prolonged period led to a slightly declined yield (entries 16-21). The screening of chlo-rides revealed that NaCl performed best (entries 22-23).

Replacement of blue light with purple light resulted in a diminished yield (entry 24). Furthermore, in the dark, the desired product**4a** could not be observed, indicating that irradiation is necessary for the generation of iodanyl radical (entry 25). To our delight, cyclohexyl bromide **4b** and cyclohexanol **4c** can also be constructed albeit in moderate yields just via changing NaCl with KBr or water. The optimal conditions were shown in entries 26 and 27 (for detailed optimizing process, see the Supporting Information).

With these optimal conditions in hands, different cyclic and linear alkanes were investigated, as listed in Table 2. The chlorination, bromination, and oxidation of cycloalkanes such as cyclopentane and cyclooctane were first tested and both provided the corresponding chlorocycloalkanes, bromocycloalkanes, alcohols, and ketones, in moderate to good yields when NaCl, KBr or H_2O was added, respectively (products **5a-5c** and **6a-6c**). The activation of inert secondary and tertiary sp^3 C–H bond in adamantane also proceeded smoothly. In oxidation reaction, 1-adamantanol was generated in moderate yield, and as for chlorination and bromination reactions, two monohalogenation isomers were generated in good yields (products **7a-7c**). When substrate with primary, secondary and tertiary carbon (such as methyl cyclohexane) was subjected to the standard conditions, highly selective halogenation or oxidation at tertiarycarbon was observed to furnish corresponding haloalkane or alcohol (**8a-8c**). For linear alkanes including heptane, octane, the halogenation and oxidation products (**9a-9c** and**10a-10c**) were delivered in moderate to good yields, with unsatisfactory regioselectivities. When substrates with only one kind of carbonyl α sp^3 C-H or active benzyl were exposed to the conditions, their

Table 1. Optimization of oxidation and halogenation of cyclohexane by DIB[a]

entry	reagent (equiv)	DIB (equiv)	H_2O (mL)	Solvent (2.5 mL)	Time (h)	Yield[b] (%)
1	NaCl (1)	1	0.5	DCM	3	**4a** (32)
2	NaCl (1)	2	0.5	DCM	3	**4a** (35)
3	NaCl (1)	3	0.5	DCM	3	**4a** (36)
4	NaCl (1)	3.5	0.5	DCM	3	**4a** (38)
5	NaCl (1)	4	0.5	DCM	3	**4a** (39)
6	NaCl (1.5)	3.5	0.5	DCM	3	**4a** (41)
7	NaCl (1.5)	3.5	-	DCM	3	**4a** (0)
8	NaCl (3)	3.5	0.1	DCM	3	**4a** (51)
9	NaCl (3)	3.5	0.3	DCM	3	**4a** (57)
10	NaCl (3)	3.5	0.5	DCM	3	**4a** (62)
11	NaCl (3)	3.5	0.7	DCM	3	**4a** (61)
12	NaCl (3)	3.5	1	DCM	3	**4a** (56)
13	NaCl (3)	3.5	0.5	DMSO	3	**4a** (0)
14	NaCl (3)	3.5	0.5	DMF	3	**4a** (0)
15	NaCl (3)	3.5	0.5	EtOH	3	**4a** (14)
16	NaCl (3)	3.5	0.5	DCM	1	**4a** (54)
17	NaCl (3)	3.5	0.5	DCM	2	**4a** (59)
18	NaCl (3)	3.5	0.5	DCM	3	**4a** (62)
19	NaCl (3)	3.5	0.5	DCM	4	**4a** (70)
20	NaCl (3)	3.5	0.5	DCM	5	**4a** (80)
21	NaCl (3)	3.5	0.5	DCM	6	**4a** (79)
22	KCl (1.5)	3.5	0.5	DCM	5	**4a** (26)
23	$CuCl_2$(1.5)	3.5	0.5	DCM	5	**4a** (0)
24[c]	NaCl (1.5)	3.5	0.5	DCM	5	**4a** (32)
25[d]	NaCl (1.5)	3.5	0.5	DCM	5	**4a** (0)
26	KBr(1.3)	3.5	0.5	DCM	5	**4b** (64)
27[e]	-	1	0.5	DCM	14	**4c** (69)

[a] Reaction conditions: cyclohexane (0.58 mmol, 50 mg, 1 equiv), NaCl, DIB, H_2O, DCM. 18 W blue light, air, rt. [b] Yields are based on cyclohexane and detected by ^{1}H NMR analysis using CH_2Br_2 as an internal standard.[c] Purple light instead of blue light.[d] In the dark. [e] DIB (0.155 mmol, 1 equiv), **4** (0.67 mL, 40 equiv), air, rt. Yields were based on DIB and detected by ^{1}H NMR analysis using CH_2Br_2 as an internal standard.

halogenation and oxidation could proceed smoothly (**11a-11c** and**12a-12c**). Unlike halogenation, the substrate structure had remarkable effects on the oxidation results. Saturated monocyclic hydrocarbon and linear alkanes were oxidized to the corresponding alcohol and ketone, without formation of overoxidized products. Hydroxyketone **12c** was generated as the single product via α-oxidation of cyclic ketone, while substrates bearing one or more tertiary carbons were exclusively transformed into corresponding tertiary alcohols. It's worth noting that a methyltied to aromatic ring (e.g., toluene) was directly overoxidized into carboxylic acid in high yield (85%), instead of alcohol or aldehyde.

Table 2 Activation of various C-H reagents with DIB

Substrate	Chlorination[a] (Products **a**)	Bromination[a] (Products **b**)	Oxidation[b] (Products **c**)
Cyclohexane (**4**)	80%	64%	69% (1.56:1)
Cyclopentane (**5**)	70%	62%	59% (1.46:1)
Cyclooctane (**6**)	93%	80%	99% (1:1.5)
Adamantane (**7**)	84% (1:4.3)	70% (1:4.8)	51%
Methylcyclohexane (**8**)	53% (brsm 70%)	31% (brsm 85%)	62%
Hexane (**9**)	52%	61%	55% (1:1.5)
Octane (**10**)	99%	96%	54% (1:1.4)
Toluene (**11**)	41%	59%	85%
Cyclohexanone (**12**)	24%	21%	48%

[a] Alkane (0.58 mmol, 1 equiv), DIB (2.03 mmol, 653 mg, 3.5 equiv), NaCl (1.74 mmol, 101 mg, 3.0 equiv) or KBr (0.75 mmol, 89 mg, 1.3 equiv), H_2O (0.5 mL), DCM (2.5 mL). 18 W blue light, air, rt, 5 h. Yields are based on Cyclohexane and detected by ^{1}H NMR analysis using CH_2Br_2 as an internal standard.[b] DIB (0.155 mmol, 1 equiv), alkane (40 equiv), H_2O (0.5 mL), DCM (2.5 mL) 18 W blue light, air, rt, 17 h. Yields were based on DIB and detected by ^{1}H NMR analysis using CH_2Br_2 as an internal standard.

Many experiments were carried out in order to confirm the proposed pathway of activation of alkyl sp^3 C-H bonds. As shown in scheme 2a, when TEMPO and BHT were added to the standard conditions of chlorination, bromination, and oxidation as radical scavengers, none of the corresponding products was detected, and compound **13** was detected by GC-MS, which indicated that the

transformations of chlorination, bromination, and oxidation proceed via a radical pathway.

In order to verify the source of oxygen involved in oxidation,^{18}O-labelling experiments were carried out. When $H_2{}^{16}O$ was replaced with $H_2{}^{18}O$ as the nucleophilic reagent using adamantine as the substrate, ^{18}O-labelled 1-adamantanol was obtained in 48% yields. The result shows that water acted as the oxygen source in the C-H oxidation of alkane.

Scheme 2 Study on the mechanism experiments

Finally, various concentrations of NaCl/KBr were utilized under the standard chlorination/bromination conditions with cyclohexane as substrate. An obvious linear relationship between the yield of chlorocyclohexane and the concentration of Cl^- within the tested concentration range was observed, but the increase of concentration of Br^- could not improve the yield of product and accelerate the reaction (see the Supporting Information) which showed a certain possibility for the ionic pathway in the second step of chlorination (path B).

Conclusions

In summary, we have developed a general, scalable method to activate sp^3 C-H bonds of cyclic and linear alkanes with cheap DIB, and the method exhibits good compatibility with various coupling reagents. A variety of alkyl chlorides, bromides, alcohols, and ketones can be prepared in moderate to excellent yields from readily available alkanes without the use of any toxic, volatile and explosive reagents.

Experimental

General Information

Reactions (chlorination, bromination, oxidation) were conducted in Pressure-resistant tubes. Reagents and solvents were obtained from commercial suppliers which do not require purification.^{1}H NMR and ^{13}C NMR spectra were measured on a Bruker spectrometer (at 400 and 101 MHz, respectively), and chemical shift were reported as values relative to internal TMS (δ 0.00 for ^{1}H NMR), chloroform (δ 7.26 for ^{1} H NMR), chloroform (δ 77.00 for^{13}C NMR). High-resolution mass spectrometry (HR MS) was recorded on a waters UPLC G2-XS Qt of instrument. GC-MS spectra were performed on Perkin Elmer Clarus 680 Gas Chromatograph and Clarus 600 T Mass Spectrometer (EI Source). In a general experiment, tubes were set between two 18 W blue lights and kept 2 cm away from the light source, with a fan for cooling the reaction.

General Procedure forChlorination

The DIB (2.08 mmol, 3.5 equiv, 670 mg) and NaCl (1.79 mmol, 3 equiv, 104 mg) were added in a Pressure-resistant tube. Then cyclohexane (65 μL, 1.0 equiv), H_2O (0.5 mL), DCM (2.5 mL), were added with pipetter. The tube was sealed with a stopper and positioned between two 18 W blue light (kept above 2 cm away from the light source) and stirred at room temperature (with a fan to cool the reaction down) for 5 h. After the reaction was completed, 50 μL of internal standard (CH_2Br_2) was added, then 50 μL of mixture was extracted and diluted with $CDCl_3$ to analysis by ^{1}H NMR spectroscopy after vigorous stirring.

General Procedurefor Bromination

The DIB (2.08 mmol, 3.5 equiv, 670 mg) and KBr (0.77 mmol, 1.3 equiv, 93 mg) were added in a Pressure-resistant tube. Then cyclohexane (65 μL, 1.0 equiv), H_2O (0.5 mL), DCM (2.5 mL), were added with pipetter. The tube was sealed with a stopper and positioned between two 18 W blue light (kept above 2 cm away from the light source) and stirred at room temperature (with a fan to cool the reaction down) for 5 h. After the reaction was completed, 50 μL of internal standard (CH_2Br_2) was added, then 50 μL of mixture was extracted and diluted with $CDCl_3$ to analysis by ^{1}H NMR spectroscopy after vigorous stirring.

General Procedurefor Oxidation

The DIB (0.155 mmol, 1.0 equiv, 50 mg) was added in a Pressure-resistant tube. Then cyclohexane (0.67 mL, 40 equiv), H_2O (0.5 mL), DCM (2.5 mL), were added with pipetter. The tube was sealed with a stopper and positioned between two 18 W blue light (kept above 2 cm away from the light source) and stirred at room temperature (with a fan to cool the reaction) for 14 h. After the reaction was completed, 50 μL internal standard (CH_2Br_2) was added, then 50 μL of the mixture was extracted and diluted with $CDCl_3$ to analysis by ^{1}H NMR spectroscopy.

(3s,5s,7s)-adamantan-1-ol (7c1). The adamantane (0.74 mmol, 1.0 equiv, 100 mg) and DIB (0.96 mmol, 1.3 equiv., 308 mg) were added in a Pressure-resistant tube. Then H_2O (0.5 mL) and DCM (2.5 mL) were added with pipetter. The tube was sealed with a rubber stopper and a needle to equalize the air pressure. Finally, the tubes were positioned between two 18 W blue light (kept above 2 cm away from the light source) and stirred at room temperature (with a fan to cool the reaction down) for 5 h. The target product was purified by flash column chromatography on silica eluting with ethyl acetate:petroleum ether [1:10 (v/v)]. Yield of 51%, White solid, R_f= 0.51 ethyl acetate:petroleum ether [1:4 (v/v)].^{1}H NMR (400 MHz, $CDCl_3$) δ 2.14 (t,J = 3.2 Hz, 3H), 1.71 (d, J = 2.9 Hz, 6H), 1.67 – 1.58 (m, 6H). ^{13}C NMR (101 MHz, $CDCl_3$)δ 68.3, 45.4, 36.1, 30.7. ^{1}H NMR and^{13}C NMR data correspond to the reported values.[6b]

1-oxaspiro[4.4]nonan-2-one (8c1). The target product was synthesized following general procedure for oxidation using methylcyclohexane as the substrate. The target product was purified by flash column chromatography on silica eluting with ethyl acetate:petroleum ether [1:15-1:5 (v/v)]. Yield of 62%; Colorless liquid. R_f = 0.35 ethyl acetate:petroleum ether [1:4 (v/v)]. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.60 – 1.39 (m, 9H), 1.31 – 1.23 (m, 1H), 1.19 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 70.0, 39.4, 29.5, 25.6, 22.7.^{1}H NMR and ^{13}C NMR data correspond to the reported values.[16]

(chloromethyl)benzene (12a) . The target product was synthesized following procedure for chlorination using toluene as the substrate. The target product was purified by flash column chromatography on silica eluting with ethyl acetate:petroleum ether [0:1 (v/v)]. Yield of 41%; colorless liquid. R_f = 0.50 ethyl acetate:petroleum ether [0:1 (v/v)]. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.49 – 7.30 (m, 5H), 4.62 (s, 2H).^{13}C NMR (101 MHz, $CDCl_3$) δ137.5, 128.8, 128.7, 128.5, 46.4.

(bromomethyl)benzene (12b). The target product was synthesized following general procedure for bromination using toluene as the substrate. The target product was purified by flash column chromatography on silica eluting with ethyl acetate:petroleum ether [0:1 (v/v)]. Yield of 59%; Light yellow liquid. R_f = 0.51 ethyl acetate:petroleum ether [0:1 (v/v)]. ^{1}H NMR (400 MHz, $CDCl_3$)δ 7.47 – 7.30 (m, 5H), 4.53 (s, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 137.9, 129.1, 128.9, 128.5, 33.8.

benzoic acid (12c3). The target product was synthesized following general procedure for oxidation using toluene as the substrate. The target product was purified by flash column chromatography on silica eluting with ethyl acetate:petroleum ether [1:2 (v/v)]. Yield of 85%; Light yellow solid, m.p. 121–123.°C. R_f = 0.23 ethyl acetate:petroleum ether [1:1 (v/v)]. ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.54 (s, 1H), 8.18 – 8.09 (m, 2H), 7.66 – 7.58 (m, 1H), 7.49 (t, J = 7.7 Hz, 2H).^{13}C NMR (101 MHz, $CDCl_3$) δ172.6, 133.9, 130.3, 129.3, 128.5.

Supporting Information

The supporting information for this article is available on the WWW under https://doi.org/10.1002/cjoc.2023xxxxx.

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