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COMMUNICATION

Sustainable Photoinduced Decarboxylative Chlorination Mediated by Halogen Atom Transfer

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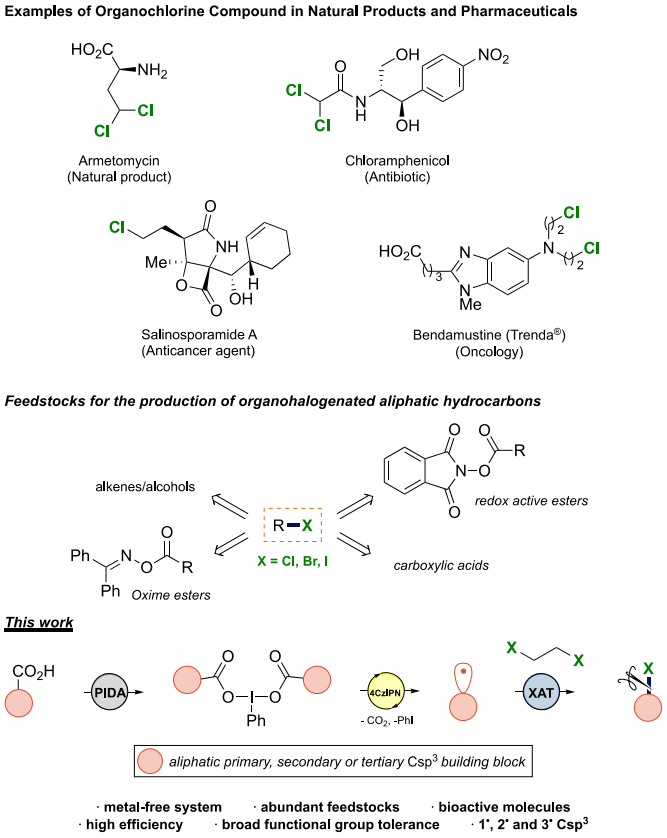
Chlorinated organic backbones constitute important components in existing biologically active chemicals, and they are extraordinary useful intermediates in organic synthesis. Herein, an operationally simple and sustainable halodecarboxylation protocol *via* halogen-atom transfer (XAT) as a key step is presented. The method merges a metal-free photoredox system with (diacetoxyiodo)benzene (PIDA) as a hypervalent iodine reagent using 1,2-dihaloethanes as halogen sources to afford haloalkanes in an efficient manner. The sustainability of this protocol is highlighted by an important waste recovery protocol as well as by atom economy and carbon efficiency parameters.

Introduction

Organochlorine compounds represent an important class of organic architectures with significant application in the agrochemical, polymer, and pharmaceutical fields.[1] Additionally, chloroalkanes are widely used intermediates for numerous organic transformations because they can be considered as cationic, radical, or anionic carbon-based synthons. Thus, the development of efficient and sustainable chlorination strategies is of great interest.[2] The selective installation of chlorine atom into hydrocarbons has traditionally used alkenes or alcohols as organic substrates. In the last 30 years, the elaboration of efficient halogenation methods from photoactive oxime esters and redox-active esters have been reported.[3] However, the development of halogenation protocols using carboxylic acids as feedstocks *via* decarboxylation has been under wider exploration given their air stability, easy handling, and broad commercial availability.[2c,4] Traditionally, halo-decarboxylative methods include the Hunsdiecker–Borodin reaction,[5] the Barton reaction,[6] or the Suarez halo-decarboxylation reaction,[7] among others.[2c] However, most of these protocols are restricted to iododecarboxylation, or they use harsh reactants or conditions. Photoredox catalysis in the development of new synthetic methods is considered an efficient and sustainable tool.[8] In this vein, Glorius and co-workers presented an efficient photocatalytic method for the halodecarboxylation of alkanes using an Ir-based photocatalyst and suitable halogen donor.[9]



Scheme 1 Organochlorinated compounds. Feedstocks for the synthesis of halogenated hydrocarbons.

At the same time, hypervalent iodine(III) reagents have received enormous attention by synthetic chemists because they represent an attractive alternative to toxic heavy metal-based oxidants.[10] As such, they also have been used for halogenation of organic architectures.[11] Regarding halodecarboxylative hypervalent iodine-mediated transformations, the Suarez iododecarboxylation reaction combines the PIDA [(diacetoxyiodo)benzene]/I_2 system with light and thermal conditions,[12] but this method is efficient only for iododecarboxylation; bromo- and chlorodecarboxylation are much less effectual. Recently, Miyamoto and Uchiyama[13]

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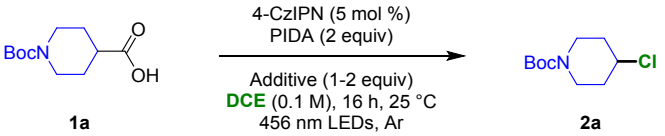
presented the hypervalent iodine/KBr combination for the bromodecarboxylation of sterically hindered carboxylic acids. The photoredox/hypervalent iodine dual combination has been demonstrated to be a powerful strategy for the development of organic transformations in a mild and sustainable fashion.[14] Herein, we merge a metal-free photoredox/hypervalent iodine system for the chlorodecarboxylation of Csp^3-based architectures *via* halogen-atom transfer (XAT) as a key step using readily available 1,2-dichloroethane (Scheme 1) as a halogen source. A photo-mediated XAT halogenation from 1,2-dihaloethanes of this type appears to be underdeveloped.[15] The method presented herein thus expands the toolbox for the efficient and sustainable synthesis of halogenated products.

Results and Discussion

To evaluate the viability of the decarboxylative chlorination mediated by a hypervalent iodine/photoredox system and search for suitable reaction conditions (See details in ESI), we selected 1-Boc-piperidine-4-carboxylic acid (**1a**) as a model substrate and 1,2-dichloroethane (DCE) as the chlorine source. After systematically surveying various reaction parameters, we were pleased to obtain the desired product **2a** in 62% ^{1}H NMR yield when using 1,2,3,5-tetrakis(carbazol-9-yl)-4,6-dicyanobenzene (4-CzIPN, 5 mol %) as photocatalyst (PC), PIDA (2 equiv) as hypervalent iodine partner, under nitrogen with irradiation with blue LED strips (λ_{max} = 456 nm) at 25 °C for 16 h (Table 1, entry 1). Notably, in sharp contrast to all previously reported decarboxylative halogenation protocols, the present reaction did not require the addition of an external chlorine source. To improve the yield of the reaction, we also performed the reaction in the presence of a base, such as 2,6-lutidine or Cs_2CO_3. However, only 60% and 15% yields, respectively, were obtained (Table1, entry 2). In addition, we noticed that the chlorinated product **2a** was obtained in lower yield when using the transition metal-based photocatalyst $[Ir[dF(CF_3)ppy]_2(dtbpy)]PF_6$ (Table 1, entry 3). Interestingly, the addition of external chlorine sources such as *t*-BuOCl or *N*-chlorosuccinimide (NCS) did not improve the yield (Table 1, entry 4). The established conditions thus provide a metal-, base- and external halogen-free alternative approach to the Suárez and Hunsdiecker halodecarboxylation methods. Subsequently, other hypervalent iodine derivatives were tested (Table 1, entry 5). Only the presence of PIDA, the most readily available reagent, provided good yields. We also checked the efficacy of the reaction using other chlorinated solvents, such as CH_2Cl_2 and $CHCl_3$. However, lower yields or trace amounts of product **2a** were observed (Table 1, entry 6). Additionally, we tried the reaction with DCE as a stoichiometric amount in presence of MeCN as solvent, but only slight traces of the product were detected. Subsequently, a critical survey of light sources revealed that the wavelength of the LED had a significant impact on the reaction efficiency, and other light sources such as purple Kessil (λ_{max} = 390 nm) gave a significant drop in yield of **2a** (Table 1, entry 7). Finally, as expected, no reaction took place in the absence of hypervalent iodine, photocatalyst, or visible-light irradiation (Table 1, entries 8 and 9), confirming the essential role of these three parameters for developing this reaction.

Table 1 **Screening of the reaction conditions**



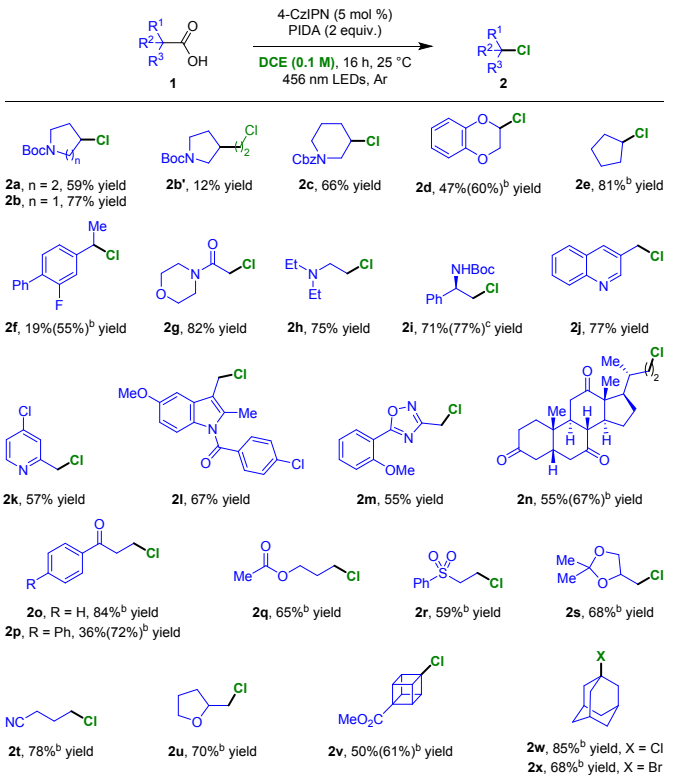
1a **2a**

Entry	Modification of conditions[a]	Yield (%)[b]
1	None (without additive)	62(59)[c]
2	Adding 2,6-lutidine, Cs_2CO_3 (1.5 equiv)	60, 15
3	$[Ir[dF(CF_3)ppy]_2(dtbpy)]PF_6$ as photocatalyst	33
4	Adding *t*-BuOCl or NCS (1 equiv)	53, 50
5	$MesI(OAc)_2$, [BI-OAC] instead of PIDA	25, 24
6	CH_2Cl_2, $CHCl_3$, MeCN as solvent	34, 24, *n.d.*[d]
7	390 nm instead of 456 nm irradiation	25
8	No PIDA	*n.r.*
9	Dark conditions or no photocatalyst	*n.r.* <4

[a] Reaction conditions: **1a** (0.1 mmol, 1 equiv), 4-CzIPN (0.005 mmol, 5 mol %), PIDA (0.2 mmol, 2 equiv), Additive (0.1 to 0.2 mmol, 1 to 2 equiv), $ClCH_2CH_2Cl$ (1 mL), 25 °C, nitrogen atmosphere, λ_{max} = 456 nm LEDs, 16 h. [b] The yield was determined by crude ^{1}H NMR using 1,3,5-trimethoxybenzene. [c] Isolated Yield. [d] Reaction carried out with MeCN as solvent (1 mL) and DCE (0.1 mmol, 1 equiv). *n.r.* no reaction. *n.d.* not determined.

With suitable conditions in hand (Table 1, entry 1), the scope of this photocatalytic decarboxylative chlorination was investigated (Table 2). As shown in Table 2, we began the exploration with a variety of carboxylic acids.

Table 2[a] Scope of decarboxylative halogenation



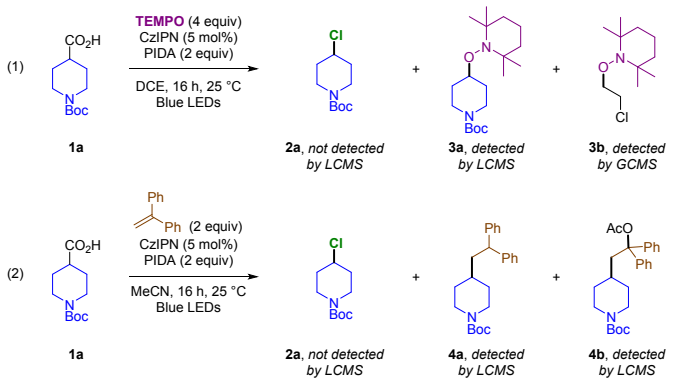
[a] Reaction conditions: **1** (0.1 mmol, 1 equiv), 4-CzIPN (0.005 mmol, 5 mol %), PIDA (0.2 mmol, 2 equiv), DCE (1 mL), 25 °C, nitrogen atmosphere, λ_{max} = 456 nm LEDs, 16 h. [b] Addition of 2,6-lutidine (1.5 equiv). [c] 0.5 mmol scale of **1**.

Various secondary alkyl carboxylic acids incorporating nitrogen- and oxygen heterocycles were perfectly tolerated under these reaction conditions (**2a**-**2d**). Notably, neither the position of the heteroatom on the ring nor the protecting group of the amine (Boc or Cbz) have a major influence on the yield. Note that the five-membered ring product **2b** was isolated as a mixture (85/15) with a by-product **2b'** from the addition of the chloroethyl radical **9**. Subsequently, we showed that the presence of other heteroatoms (**2d**) allowed the formation of the corresponding chlorinated product in moderate yield (47%). Then, to demonstrate the potential impact of this method on medicinal chemistry, several bioactive secondary acids were used. For example, the use of a Doxazosin related compound D and flurbiprofen[16a,b] provided access to the corresponding chlorine derivatives **2d** and **2f** respectively.

After having explored the activity of secondary carboxylic acids, we continued our investigations with the study of primary carboxylic acids (Table 2). The challenge perceived with these substrates was related to their generally lower reactivities as well as the greater instability of the reaction intermediate formed during the reaction. However, a wide range of primary carboxylic acids with a variety of functional groups was very well-tolerated with good to excellent yields. Many nitrogenated derivatives were particularly effective under these conditions, including an amide (**2g**), an amine (**2h**) and an *N*-carbamate (**2i**). Moreover, the installation of a chlorine atom in heterocyclic units such as quinoline (**2j**), pyridine (**2k**), indole (**2l**),[17] and 1,2,4-oxadiazole (**2m**) was performed under the standard conditions, thus providing access to these less-seen chlorinated molecules *via* a decarboxylative chlorination reaction. Finally, the formation of compound **2n** containing a steroidal scaffold was carried out efficiently. Here again, several naturally occurring molecules or molecules with various biological activities were accommodated. As examples, amino acid derivative *beta*-phenylalanine (**1i**), and the nonsteroidal anti-inflammatory indomethacin (**1l**),[18,19] were suitable substrates for chlorination. However, at this stage we noticed that the reaction was less efficient in some examples, and the desired products could not be easily isolated (e.g., **2p**, condition A). To overcome this limitation and provide broader generality, further optimization of the reaction was carried out (See Table S5 in SI). Thus, we determined that the addition of 2,6-lutidine as a base allowed the formation of chlorinated products in better yields. Indeed, under these conditions the chlorinated product **2p** was isolated a very good yield of 72%. With these new conditions in hand, we were able to expand the scope to a wider variety of 1°, 2° and 3° carboxylic acids (Table 2).

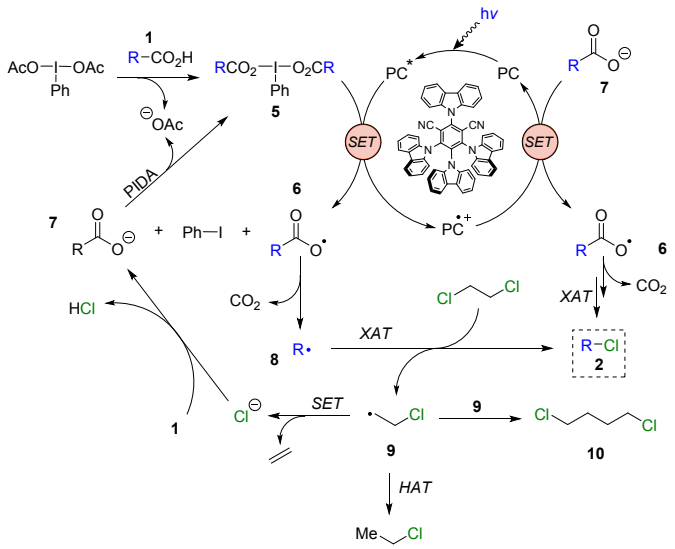
Gratifyingly, new functionalized primary chlorinated products containing other functional groups, such as ketones (**2o** and **2p**), ester (**2q**), sulfone (**2r**), ketal (**2s**) or nitrile (**2t**) were efficiently synthesized. Notably, the presence of the furan heterocycle was perfectly well tolerated, allowing the isolation of **2u** in 70% yield. Additionally, the production of **2n** was improved to 67% yield with these new conditions. Concerning the secondary acids, the product **2d** was obtained in an improved yield of 60%. Thereafter, to explore the limits of this strategy, simple carboxylic or acyclic secondary carboxylic acids were tested (**2e** and **2f**). For these examples, the addition of 2,6-lutidine as base was necessary to produce the corresponding chlorides in good yields. Also, we showed that the synthesis of tertiary chlorinated products was possible with the synthesis of **2v** and **2w** in 61% and 85% yields, respectively. In the same way as before, several naturally occurring molecules or molecules with various biological activities were used during this last study. For example, product derived from the analgesic and anti-inflammatory Fenbufen (**1p**),[20] and dehydrocholic acid (**1n**)[21] were accessed in reasonable yields. As last examples, the incorporation of a chlorine on tertiary structures such as adamantane (**2w**) and cubane (**2v**), a bioisostere of arenes,[22] was successfully achieved. Finally, to extend the possible applications of this method further, the synthesis of other alkyl halides, specifically bromides, was carried out. The bromination reaction was performed by simply switching the solvent from DCE to 1,2-dibromoethane (DBE). Of note, this transformation furnished the brominated product **2x** in good yield, showing the feasibility of a bromodecarboxylative synthesis using 1,2-dibromoethane. Overall, a wide range of 1°, 2° and 3° carboxylic acids were compatible with this transformation, affording the desired alkyl halide products in good to excellent yields (55–85%, **2a**–**2x**) without any obvious major reactivity differences between the substrates.

To shed light on the mechanism of the above reactions, we designed the experiments described in Scheme 2. In this regard, 2,2,6,6-tetramethylpiperidineoxy (TEMPO) or 1,1-diphenylethylene were added as radical scavengers under the optimized conditions to trap potential radical intermediates. The presence of these scavengers totally inhibited the formation of chlorinated product **2a**. The carbon-centered radical was trapped in both experiments (**3a** and **4a** in Scheme 2) and detected by LCMS (see the ESI). Additionally, although TEMPO-Cl was not detected, TEMPO-CH_2CH_2Cl **3b** was observed by GCMS (see the ESI) from the crude reaction mixture. In addition to the formation of product **2b'**, mentioned earlier, this result provides evidence that the $\bullet CH_2CH_2Cl$ radical is generated during the reaction. These key experiments highlight that the reaction proceeds *via* radical intermediates. Further control experiments (*vide infra*) demonstrated that in the absence of either light or photocatalyst no reaction takes place (Table 1, entry 9).



Scheme 2 Mechanistic investigations.

Based on these experiments, a mechanism for a photo-mediated process based on Halogen-Atom Transfer (XAT) is proposed in Scheme 3.[15,23]

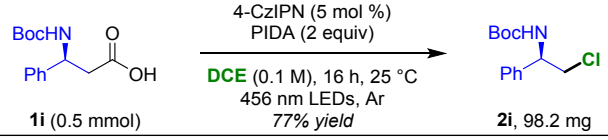


Scheme 3 Proposed reaction pathway.

Photoexcitation of 4-CzIPN under blue-light irradiation generates a potent excited state PC* complex.[24] At the same time, PIDA generates a (diacyloxyiodo)arene complex **5** *in situ*, thus activating the carboxylic acid substrate. An initial single electron transfer (SET) with PC* generates the oxidized PC$^{\bullet+}$ and induces a photochemical decomposition of the hypervalent I–O bond. This step generates a reactive radical **6** that undergoes a decarboxylation event to afford the corresponding alkyl radical **8**. At this point, the newly formed radical reacts with the halogen donor DCE *via* a XAT to form the desired chlorinated product **2** and the chlorinated radical **9**. The formed carboxylate **7** can be reduced by the oxidized photocatalyst (PC$^{\bullet+}$), allowing the formation of another carboxyl radical **6** and return of the photocatalyst to the initial ground state. The fate of **9** cannot be definitively determined, but reasonable possibilities include hydrogen atom transfer (HAT) to form chloroethane, dimerization to generate **10**, or SET to form an ion, inducing a beta elimination of chloride to generate ethylene and chloride ion. Finally, although the exact role of the base, 2,6-lutidine is not clearly identified, we can envisage that it may contribute to the neutralization of the acidic reaction mixture (pH 2-3). This last point would favor displacement of the equilibrium toward the formation of carboxylate **7**.

To demonstrate the practicality of this method and its impact on the environment, a scaled-up reaction was examined with **1i** (0.5 mmol), and we evaluated green chemistry metrics[24] for the synthesis of the corresponding chlorinated derivative **2i** (see Table 3 and SI for calculations).

Table 3 **Evaluation of green chemistry metrics**



1i (0.5 mmol) **2i**, 98.2 mg

Entry	Name	m (mg)	M (g/mol)
1	**1i**	132.7	265.30
2	4-CzIPN	19.7	788.89
3	PIDA	322.10	322.10
4	Recycled PhI	172.6	204.01
5	Solvent	6.25 g	98.96
6	Recycled solvent	4.6 g	
7	**2i**	98.2	255.74

cEF = 18.9 kg waste per kg product - Solvent included

tEF = 8.4 kg waste per kg product - 90% of solvent recycled

sEF = 2.1 kg waste per kg product - Solvent not included

Atom Economy (AE) = 70%

Atom Efficiency = 54%

Carbon Efficiency = 81%

To evaluate the *E*-factor, the actual amount of waste produced in the process, it is often assumed that 90% of the solvent could be recovered and re-used. With this in mind, we calculated a "traditional *E*-factor" (tEF) of 8.4 kg waste per kg of product. However, this may have been too optimistic. More recently, Sheldon and co-workers suggested the use of simple *E*-factors (sEF) and complete *E*-factors (cEF).[26] The sEF does not take solvents and water into account, whereas the cEF accounts for all process materials, including solvents. In general, the true commercial *E*-factor will fall somewhere between the sEF and cEF. Therefore, in the present case, the sEF is 2.1 kg waste per kg of product and the cEF is 18.9 kg waste per kg of product (See SI). An important point for this study was that the main by-product formed during the reaction, iodobenzene, can easily be

recovered for reuse, after oxidation,[27] in another cycle. To complete the evaluation of the green chemistry metrics we also determined an atom economy of 70%, 54% of atom efficiency and 81% of carbon efficiency. Based on recent publications, these results are very competitive and contribute to the classification of this approach as one of the more sustainable decarboxylative chlorination methods.

Conclusions

In summary, we have devised a sustainable photo-mediated decarboxylative chlorination method for the synthesis of a wide range of primary, secondary, and tertiary chlorinated compounds from the corresponding commercially available carboxylic acids. The PIDA/photocatalyst combination in the presence of 1,2-dihaloethanes promotes this transformation *via* halogen-atom transfer as a key step. This photochemical approach offers high atom economy with a low *E*-factor under mild reaction conditions. Furthermore, the reactions demonstrated high functional group tolerance and broad substrate scope, including halogenation of natural products and bioactive molecules in a mild and efficient manner.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

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