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Photoinduced Site-Selective C(sp^3)−H Chlorination of Aliphatic Amides

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Cite This: https://dx.doi.org/10.1021/acs.orglett.0c03297 Read Online

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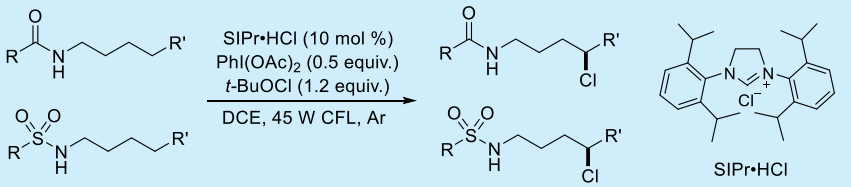


ABSTRACT: Herein, we report a new photochemical method for C(sp^3)−H chlorination of amides which employs *tert*-butyl hypochlorite as the chlorinating agent and a household compact fluorescent lamp as the light source. The reaction proceeds via N-heterocyclic carbene SIPr·HCl-promoted N−H chlorination and subsequent photoinduced Hofmann−Löffler−Freytag chlorine atom transfer. The latter process is facilitated by (diacetoxyiodo)benzene. This protocol exhibits a broad scope and is suitable for site-selective chlorination of methyl hydrogen as well as methylene and methine hydrogen.

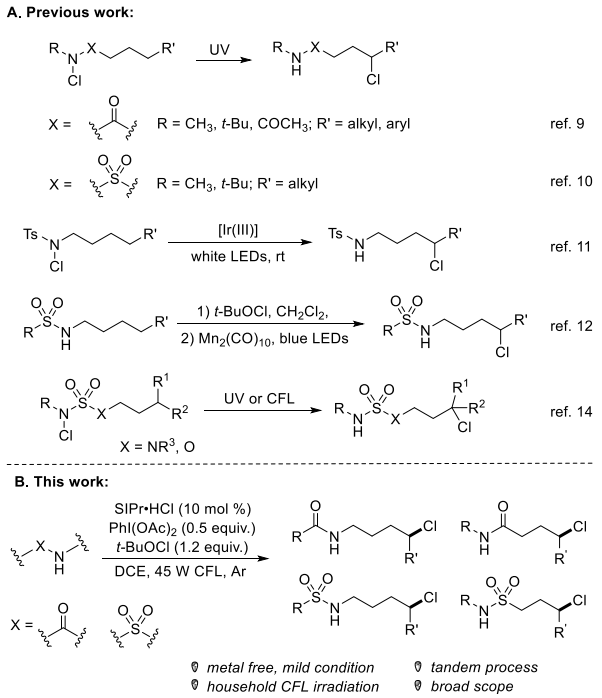
Chlorine-containing organic compounds not only are important bulk chemicals in the chemical industry[1] but also play an essential role as synthetic intermediates or designed targets in the synthesis of natural products and functional materials.[2,3] Traditionally, organic chlorides are prepared through functional group transformations from olefins, alcohols, acids, or their analogues. By comparison, installation of a chlorine atom to a C−H bond constitutes a more efficient and straightforward method for the preparation of these valuable compounds.[4] However, although numerous efforts have been made toward this goal, selective C−H chlorination of synthetic usefulness still remains a big challenge until now. It has long been known that free radical reactions are applicable to the halogenation of the C(sp^3)−H bond, but in the past, they are mostly limited to bromination and chlorination at benzyl positions.[5] Recently, several excellent methods have been developed to allow C(sp^3)−H chlorination to be implemented under mild conditions with good regioselectivity.[6] However, these methods only work well for chlorinating the methine carbon or cyclic methylene carbon, whereas the efficacy for site-selective chlorination of the acyclic methylene and methyl C(sp^3)−H has yet to be improved.

Intramolecular hydrogen atom transfer (HAT) from a C(sp^3) atom to an electrophilic heteroatom-centered radical is a facile process for the generation of carbon radicals. The intramolecular HAT is highly regioselective (1,5-HAT in most cases) and thus provides a viable solution for the selective C(sp^3)−H functionalization of organic compounds.[7] In this regard, much attention has been paid to the N-radical-directed C(sp^3)−H functionalization reactions (generally referred to as Hofmann−Löffler−Freytag (HLF) reaction).[8] Whereas aliphatic *N*-halogen amines were initially used for the HLF reaction, amides are more commonly used precursors of N-radicals because of the activating effect of carbonyl and sulfonyl groups. In view of the importance of halogenated amides, HLF C(sp^3)−H chlorination of amides has been much investigated since the 1960s. In early studies, UV light irradiation was employed to convert *N*-chloroamides to the corresponding amidyl radicals (Scheme 1A).[9,10] Although this protocol is straightforward and has the merit of simplicity, its scope in synthesis is rather limited because of the harshness of UV light. Recently, Yu,[11] Zhang,[12] and our group[13] applied visible light photoredox catalysis to effect the 1,5-chloro transfer of *N*-chlorosulfonamides. Photoinduced site-selective chlorination of sulfamate esters and sulfamides via 1,6-HAT was achieved by Roizen.[14] Moreover, two novel methods for C(sp^3)−H chlorination of amides with *N*-allylsulfonamides and *N*-alkyloxy amides as precursors were reported by Studer[15] and Leonori.[16] Despite these achievements, however, it is still highly desirable to develop new methods which can enable the remote chlorination of both amides and sulfonamides in a simple and highly efficient way. In this concern, herein, we report a simple metal-free photochemical protocol for HLF chlorination of amides and sulfonamides with *tert*-butyl hypochlorite as the chlorinating reagent (Scheme 1B). This method exhibits a wide scope; both amides and sulfonamides can be chlorinated at the δ-position in good yield and high regioselectivity. Notably, the reaction can be implemented under the irradiation of a

Received: October 1, 2020

https://dx.doi.org/10.1021/acs.orglett.0c03297
Org. Lett. XXXX, XXX, XXX−XXX

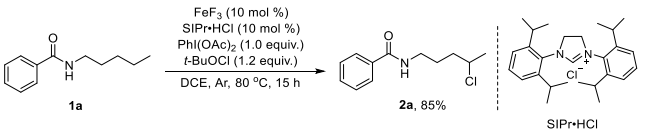
Scheme 1. Photoinduced Remote C(sp^3)−H Chlorination of Amides



household compact fluorescent lamp (CFL) in a tandem pattern of N-chlorination and 1,5-chlorine atom transfer, which are enabled by N-heterocyclic carbene (NHC)·SIPr·HCl and (diacetoxyiodo)benzene (DIB), respectively.

At the initial stage of this study, we envisioned that carboxamides would be chlorinated at the δ-position with an electrophilic chlorinating agent. As the previously developed photocatalytic protocol[13] cannot effect the anticipated conversion of carboxamides, iron catalysis under thermal conditions was explored next. After extensive screening of the reaction conditions, we found that by using *t*-BuOCl as the chlorinating reagent, FeF_3 as catalyst, SIPr·HCl and DIB as the additive, compound **1a** can be transformed into the desired product **2a** in good yield in dichloroethane (DCE) at increased temperature (Scheme 2). A subsequent control experiment indicated that the

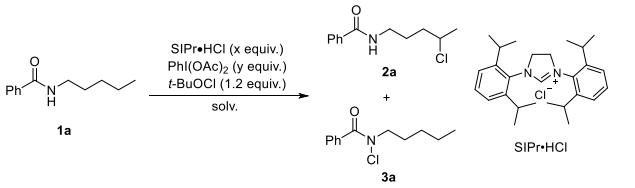
Scheme 2. FeF_3-Catalyzed C(sp^3)−H Chlorination of Carboxamide 1a



reaction took place as well in the absence of FeF_3. On the basis of this result, more conditions were explored without using iron, and the results are presented in Table 1.

As shown in Table 1, **1a** was transformed into **2a** in 60% in DCE at 80 °C under an argon atmosphere with assistance of 0.1 equiv of SIPr·HCl and 1.0 equiv of DIB. N-Chlorination product **3a** was generated in 21% at the same time. The reaction was greatly improved by irradiation with a 45 W white CFL at ambient temperature. The yield of **2a** increased considerably, and the reaction time was shortened to 6 h. The reaction took place as well with blue LEDs (10 W) as the light source, although

Table 1. Screening of the Reaction Conditions[a]



entry	*x*/*y*	solvent	conditions	yield (%)[b] **2a**/**3a**
1	0.1/1.0	DCE	80 °C, 15 h	60/21
2	0.1/1.0	DCE	CFL, rt, 6 h	91/0
3	0.1/1.0	DCM	CFL, rt, 6 h	76/7
4	0.1/1.0	CH_3CN	CFL, rt, 6 h	80/11
5	0.1/1.0	THF	CFL, rt, 6 h	0/0[c,d]
6	0.1/1.0	CH_3OH	CFL, rt, 6 h	0/0
7	***0.1/0.5***	***DCE***	***CFL, rt, 6 h***	***93/0***
8	0.1/0.2	DCE	CFL, rt, 6 h	32/0
9	0.05/0.5	DCE	CFL, rt, 6 h	90/0
10	0.1/0	DCE	CFL, rt, 6 h	11/0
11	0/0.5	DCE	CFL, rt, 6 h	0/0[c,d]
12	0.1/0.5	DCE	in dark, rt, 6 h	0/96
13[e]	0.1/0.5	DCE	CFL, rt, 6 h	trace/trace
14[f]	0.1/0.5	DCE	CFL, rt, 6 h	87/0
15	0.1/0.5	DCE	blue LEDs, rt, 6 h	78/10
16	0.1/0.5	DCE	blue LEDs, rt, 18 h	89/0
17	0.1/0.5	DCE	white LEDs, rt, 6 h	43/48

[a]The reactions were conducted on a 0.2 mmol scale in 2.0 mL of solvent under an argon atmosphere unless otherwise specified. DCE, dichloroethane; DCM, dichloromethane. [b]Isolated yield. [c]No reaction took place. [d]Most of **1a** was recovered. [e]The reaction was performed under an aerobic atmosphere. [f]The reaction was conducted on a 8 mmol scale.

a longer reaction time is needed for a complete conversion (entries 15 and 16). White LEDs (10 W), on the other hand, were less effective as the light source (entry 17). DCE proved to be the optimal solvent. The reaction can be implemented on gram scale without much loss in yield (entry 14). Control experiment shows that **1a** did not react without SIPr·HCl (entry 11), and only a small conversion was observed when DIB was absent (entry 10). Air inhibited the reaction completely (entry 13). When the reaction was conducted in the dark under the otherwise same conditions, **3a** was generated as the only product (entry 12). We also tested the effectiveness of several other NHCs as well as hypervalent iodine reagents, and the result is presented in Supporting Information (Tables S1 and S2).

The optimized conditions (Table 1, entry 7) were then applied to a wide variety of differently substituted carboxamides, and the result is presented in Scheme 3. This protocol works well for *N*-aryl-substituted carboxamides, and δ-chlorination products **2** were obtained in good yield and high selectivity whatever the electronic nature of the aryl ring. The methyl hydrogen was chlorinated as well as the methylene and methine hydrogen. This method is also applicable to *N*-alkyl-substituted carboxamides. It should be noted that in the case of compound **1ac**, which has δ-methylene hydrogen atoms at both the carbonyl side and the aminyl side, only **2ac** was obtained in a yield of 80%.

However, for compounds lacking δ-hydrogen at the aminyl side, the chlorination can take place as well at the carbonyl side. As such, compounds **2al**−**2ao** were generated in moderate to good yields from the corresponding amide precursors (Figure 1).

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Scheme 3. Reaction Scope-1

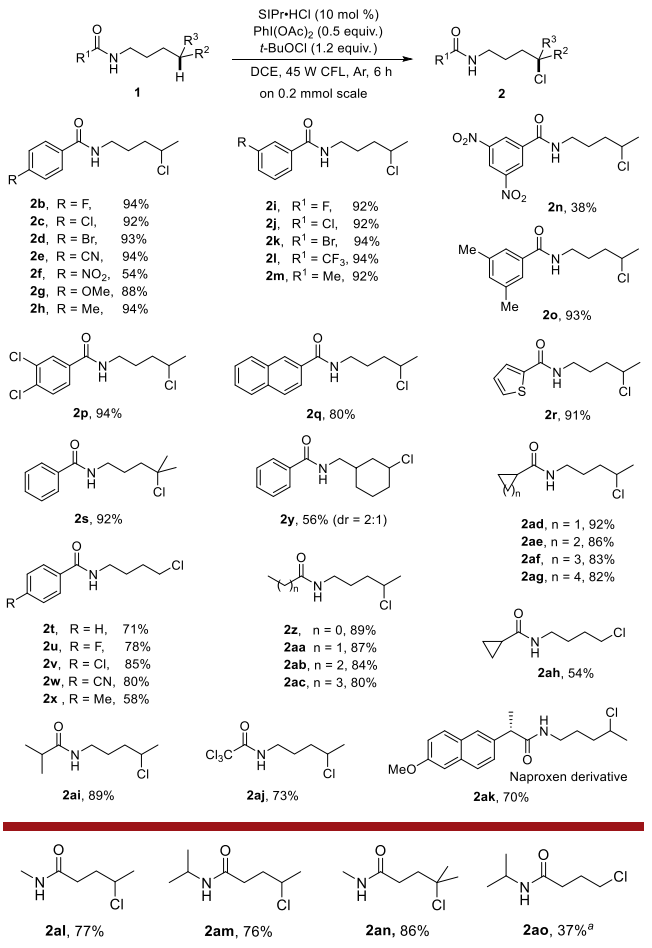


Figure 1. Reaction scope-2. [a]1.5 equiv of *t*-BuOCl was used, and the reaction time was 12 h.

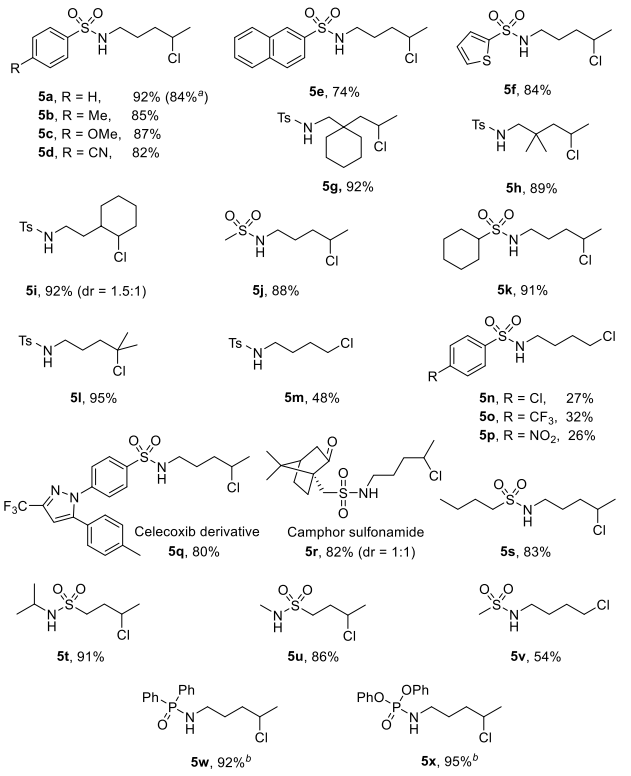
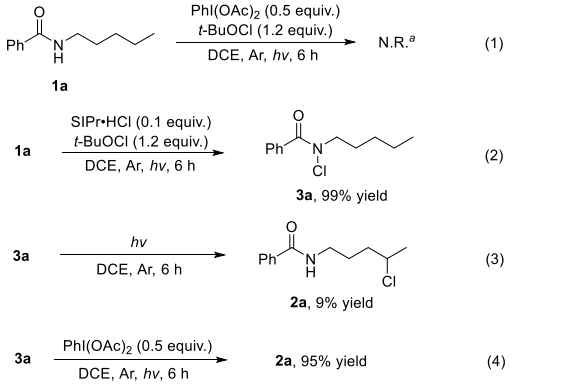


Figure 2. Reaction scope-3. The reaction was carried out on 0.2 mmol scale. Reaction time: 2.5 h. [a]The reaction was carried out on an 8 mmol scale. [b]Reaction time: 6 h.

This procedure was equally suitable to chlorinate the sulfonamides. As shown in Figure 2, variously substituted sulfonamides (**4**) reacted under the standard conditions to afford the corresponding sulfonamides (**5**) in moderate to excellent yields. The reaction also took place without using SIPr·HCl, but the yield was considerably lower (**5b**, 37%) under the otherwise same conditions. The chlorination can take place at the sulfonyl side as well as at the aminyl side. In the case that both positions have available hydrogen atoms, the hydrogen δ to the nitrogen atom at the aminyl chain was chlorinated exclusively (**5s**), consistent with the observed selectivity for carboxamides. Phosphamides can react in the same way like carboxamides and sulfonamides (**5w** and **5x**).

As shown in Table 1, SIPr·HCl and DIB play a crucial role in the reaction. To elucidate the function of SIPr·HCl and DIB, a control experiment was conducted, which is illustrated in Scheme 4. The result demonstrates that SIPr·HCl is essential for initial chlorination of the nitrogen atom in **1a** (Scheme 4, (1) and (2)), whereas DIB has no effect in this step. The catalytic effect of SIPr·HCl is closely related to the chloride anion. In addition to SIPr·HCl, we also tested several other NHCs, among which only those with a chloride counteranion (NHC·HCl) can enable the reaction (Table S1). We presume that SIPr·HCl might react with *t*-BuOCl to generate a small amount of Cl_2, which is a more powerful chlorinating agent than *t*-BuOCl. Indeed, we detected the formation of Cl_2 (with KI-starch test paper and wet blue litmus paper) when SIPr·HCl was mixed with *t*-BuOCl in DCE and found that when *n*-Bu_4NCl was used in place of SIPr·HCl, **2a** was generated from **1a** in a yield of 84% (Scheme S1). The beneficial effect of DIB lies in that it can facilitate the second HLF chlorination step. Irradiation of **3a** in the presence of DIB resulted in the formation of **2a** in excellent yield (Scheme 4, (4)), whereas only a small amount of **2a** was produced when DIB was removed from the reaction condition (Scheme 4, (3)).

Scheme 4. Control Experiment



[a]Trace of **2a** was detected.

To gain more insight into the reaction mechanism, a radical-inhibiting experiment was conducted with **1a** (Scheme 5). It was found that the reaction was completely inhibited by 2,2,6,6-tetramethylpiperidine-1-oxyl (TEMPO) or 2,6-di-*tert*-butyl-4-methylphenol (BHT). Moreover, when **1ap** and **4y** were used as the substrates, the reaction only afforded **2ap** and **5y**,

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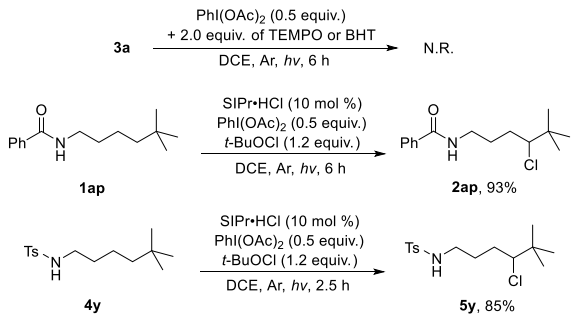
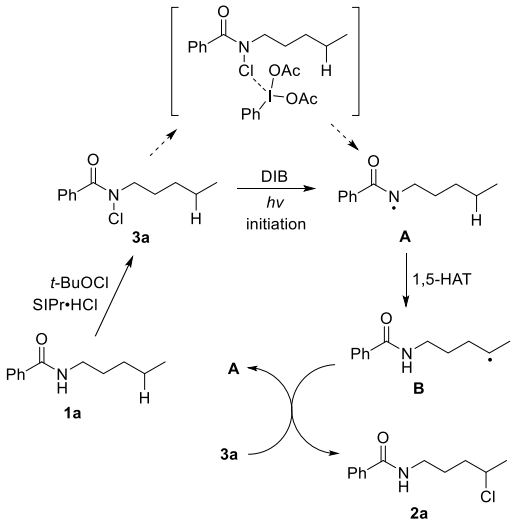
Scheme 5. Mechanistic Investigation



respectively; no methyl migration was observed. This result is consistent with a radical chain mechanism for the observed chlorine atom transfer.[13,14]

On the basis of the above-mentioned results, a plausible mechanism is proposed to account for the present chlorination reactions (Scheme 6). Taking **1a** as an example, the reaction is

Scheme 6. Proposed Mechanism



initiated by the N-chlorination of **1a** through assistance of SIPr·HCl. The thus-formed **3a** undergoes N−Cl cleavage under irradiation to give amidyl radical **A**. The cleavage of the N−Cl bond, which generally requires UV light, is greatly assisted by DIB. The beneficial effect of DIB might be caused by its interaction with **3a** through halogen bonding between Cl···I,[17] which would result in weakening of the N−Cl bond. That the UV−vis spectrum of the mixture of **3a** and $PhI(OAc)_2$ is red-shifted to some extent relative to those of **3a** and $PhI(OAc)_2$ lends support to this hypothesis (Figure S3). It is also possible that DIB acted as the radical initiator through photoinduced O−I cleavage, but this initiation is not expected to be efficient as strong UV light is still needed to break the O−I bond.[18] Moreover, this latter mechanism seems contradictory to the fact that iodosylbenzene exhibited a similar beneficial effect like DIB (Table S2).

Following the initiation step, a radical chain mechanism would operate for the formation of C−H chlorination product **2a**. Thus, amidyl radical **A** undergoes 1,5-HAT to give rise to carbon radical **B**. From the latter, **2a** is formed via chlorine atom transfer with **3a**, with **A** being regenerated at the same time.

In conclusion, we have developed a new photochemical method for the site-selective chlorination of amides by employing *tert*-butyl hypochlorite as the chlorinating agent and a household CFL as the light source. The reaction takes place via N−H chlorination of amides followed by photoinduced HLF chlorine atom transfer. The success of the present protocol hinges on the use of SIPr·HCl to promote the N−H chlorination and (diacetoxyiodo)benzene to facilitate the generation of the amidyl radical via N−Cl cleavage. A wide variety of carboxamides and sulfonamides can be chlorinated under the present conditions in good yield and high efficiency. We hope that this method will find applications in practical synthesis.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.0c03297.

Methods and experimental procedures; UV−vis absorption spectroscopy measurement; optimization of reaction conditions; characterization data; NMR spectra (PDF)

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

The authors thank the National Natural Science Foundation of China (No. 21772077) and State Key Laboratory of Applied Organic Chemistry for financial support.

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