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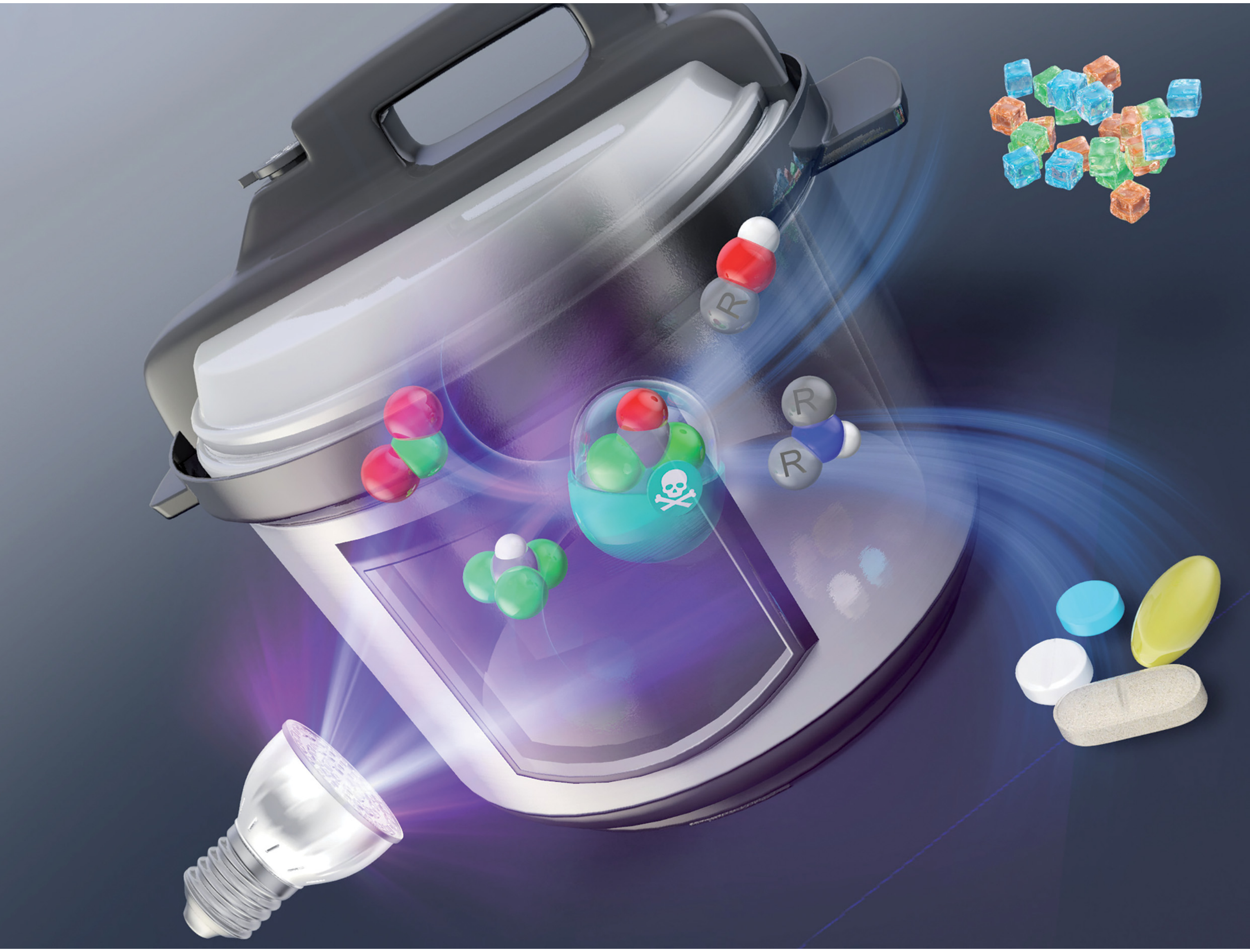

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Visible-light-induced phosgenation of amines by chloroform oxygenation using chlorine dioxide†

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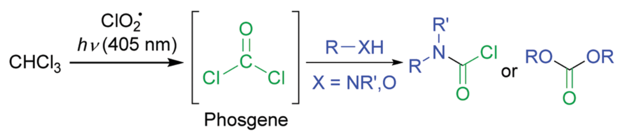
We report the visible-light-induced *in situ* preparation of $COCl_2$ through the oxygenation of chloroform in the presence of chlorine dioxide, which leads to the safe constructions of carbamoyl chlorides with good-to-high yields and wide substrate scopes. In addition, this method can also be applied to the synthesis of various carbonates.

C1 chemistry is a field of industrial organic chemistry that applies one-C compounds such as CO, CO_2, CH_4, and CH_3OH as the raw materials for transformation reactions, which involve the interconversions of C1 compounds and/or C–C bond formation reactions.[1] Among the one-C compounds, halogenated compounds play essential roles in C1 chemistry because of their high reactivities.

The phosgenation reaction, which is one of the most essential organic processes, is widely employed for fine chemical synthesis as well as resin production.[2] Among the products obtained from the phosgenation reactions of heteronucleophiles, carbamoyl chloride is an essential building block that serves as a precursor for pharmaceutical and agrochemical compounds.[3] The application of $COCl_2$,[4] a simple and traditional phosgenation reagent and reactive C1 compound, is avoided for the synthesis of these fine chemicals because of the restrictions placed on its application due to its high toxicity. Thus, triphosgene is commonly used as an alternative reagent.[5] Triphosgene exists in a stable crystalline form that is safer and easier to transport, store, and handle than $COCl_2$ gas. However, in recent years triphosgene itself has been reported to be highly toxic,[6] and an alternative method is urgently needed. The on-demand synthesis of $COCl_2$ through the UV-light irradiation of chloroform ($CHCl_3$) was recently reported,[7] which is a simple method that incorporates safe and inexpensive $CHCl_3$ as the solvent and $COCl_2$ precursor. This method requires high-energy UV light, which induces the decomposition of $COCl_2$ as the product as well as the versatility of the substrate. Although reactions with nucleophiles such as alcohols proceed efficiently, they are not suitable for the synthesis of carbamoyl chlorides from light-unstable amines.

On the other hand, we reported the C–H oxygenation reaction of methane (CH_4) through the light activation of chlorine dioxide radical ($ClO_2^\bullet$).[8] In these oxidation reactions, the chlorine radical ($Cl^\bullet$) generated from the $ClO_2^\bullet$ gas upon light activation cleaved the C–H bond. The C–H bond dissociation energy of CH_4 is 104 kcal mol^{-1}, which was higher than that of $CHCl_3$ (95.7 kcal mol^{-1}).[9] These results prompted us to investigate the generation of $COCl_2$ through the oxygenation of $CHCl_3$ with $ClO_2^\bullet$ under visible-light irradiation, because $ClO_2^\bullet$ has a strong absorption band in the visible-light region. Herein, we report the synthesis of carbamoyl chlorides with wide substrate scopes *via* phosgenation reactions using visible-light irradiation (λ > 400 nm), without decomposing $COCl_2$ (Scheme 1).

As shown in Fig. 1, an H-shaped reaction glass tube (COware) was employed as the two-chamber system.[10] One side of the system (Chamber A, 5 mL) contained an aqueous $ClO_2^\bullet$ solution prepared through the mixing of $NaClO_2$ with HCl. The other side of the system (Chamber B, 2 mL) contained a $CHCl_3$ solution with the substrate. When visible-light irradiation from an LED light (λ = 405 nm) was applied to the whole vessel, gaseous $ClO_2^\bullet$ was generated from Chamber A. The generated



Scheme 1 *In situ* $COCl_2$ preparation through $CHCl_3$ oxygenation using visible-light activated $ClO_2^\bullet$, and further reactions with heteronucleophiles to form carbamoyl chloride or carbonate products.

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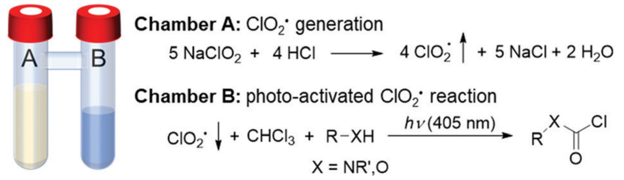


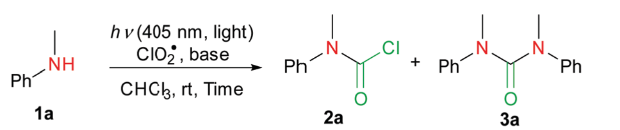
Fig. 1 Illustration of the *in situ* phosgenation process using the two-chamber system.

$ClO_2^{\bullet}$ gas transferred through the glass-tube bridge connecting the two chambers, to dissolve in the $CHCl_3$ solution in Chamber B.

After 40 min of visible-light irradiation, when the $CDCl_3$ was used without substrate, $COCl_2$ was generated in the $CDCl_3$ and confirmed through an observation of the characteristic signal of its carbonyl carbon at 143 ppm in its ^{13}C NMR spectrum (Fig. S3 in the ESI†).

Encouraged by this result, we commenced the study by employing *N*-methylaniline **1a** as the model amine substrate for reaction condition optimization (Table 1). The target carbamoyl chloride **2a** was obtained with an 84% NMR yield when 4 equivalents[11] of $ClO_2^{\bullet}$ and 5 equivalents of NEt_3 as the base were applied under the visible-light irradiation of 90 mW cm^{-2} LED at room temperature (entry 1). A decrease in the visible-light intensity of the reaction decreased the **2a** yield to 78% (entry 2), and the reaction did not occur under the dark condition (entry 3). An increase in $ClO_2^{\bullet}$ effectively afforded **2a** with a 93% yield (entry 4). On the other hand, the yield of **2a** decreased slightly and a small amount of the urea **3a** byproduct was obtained when the $ClO_2^{\bullet}$ decreased (entry 5). A brief base screening revealed that diisopropylethylamine (DIPEA) was optimal, and the applications of less than two equivalents of DIPEA resulted in poor yields (entries 7–10). Furthermore, we investigated the optimal conditions to obtain urea **3a**, and the best results were obtained when $ClO_2^{\bullet}$ was decreased to one equivalent and pyridine was used as the base (entry 13). It is considered that the pyridine activates the carbamoyl chloride and promotes the addition of a second amine. Because a change in the amount of $ClO_2^{\bullet}$ or a decrease in the amount of pyridine led to a decrease in the **3a** yield, entry 13 was chosen as the optimal reaction condition for urea production.

Table 1 Optimization of the reaction conditions[a]



Entry	Light (mW cm^{-2})	Time (min)	$ClO_2^{\bullet}$ (equiv.)	Base (equiv.)	NMR Yield (%) 2a	3a
1	90	40	4	NEt_3 (5)	84	0
2	30	90	4	NEt_3 (5)	78	0
3	Dark	900	4	NEt_3 (5)	0	0
4	90	60	8	NEt_3 (5)	93	0
5	90	30	2	NEt_3 (5)	74	4
6	90	60	8	Pyridine (5)	61	0
7	90	60	8	DIPEA (5)	99	0
8	90	60	8	DIPEA (3)	95	0
9	90	60	8	DIPEA (2)	63	0
10	90	40	4	DIPEA (3)	83	0
11	90	60	8	—	42	0
12	90	30	1	DIPEA (5)	16	31
13	90	30	1	Pyridine (5)	0	67
14	90	40	2	Pyridine (5)	0	47
15	90	20	0.5	Pyridine (5)	3	39
16	90	30	1	Pyridine (3)	0	34

[a] Reaction conditions: **1a** (0.2 mmol, 0.1 M), room temperature.

Using the optimized reaction conditions, we investigated the substrate scopes of the phosgenation reactions of *N*-nucleophiles (Fig. 2). First, the scopes of different aromatic amine (aniline) derivatives were examined. Both anilines with electron-withdrawing and electron-donating substituents afforded their corresponding carbamoyl chlorides (**2b** and **2c**) in good yields. Interestingly, allyl-substituted aniline **1d** and iminostilbene **1e** underwent phosgenation reactions to afford their desired products in moderate yields and without side reactions such as chlorination of the double alkenyl C═C bond. However, trace amounts of the product were detected when the diphenylamine **1f** was used as the substrate. This is partly owing to the lower nucleophilicity of the **1f** compared with those of the *N*-methyl anilines **1a–c**.[12] In the case of the conformationally-restricted cyclic derivatives, an unknown byproduct was observed and was likely because of its higher reactivity. Hence, the desired products **2g** and **2h** were obtained in high yields through a decrease of $ClO_2^{\bullet}$ to 4 equivalents. We also obtained **2g** in good yields when 365 nm LED or sunlight as light source, respectively. Aliphatic amines were compatible in the reactions and afforded the related products in moderate-to-good yields. The phosgenation reactions of dibutyl amine **1i** and the cyclic amines **1j** and **1k** achieved 99, 83, and 58% yields, respectively.[13] The proline derivative **1l** also afforded the desired product in a moderate yield. The benzyl-substituted amine **1m** and the tetrahydroisoquinoline derivatives **1n** and **1o** were well tolerated under the reaction conditions, and provided the desired products in excellent yields. Notably, the **2o** product formed through this method is a key precursor of solifenacin, a competitive cholinergic receptor antagonist. In addition, we tested this method during the late-stage phosgenation reactions of structurally complex pharmaceutical samples. Both of the fluoroquinolone antibiotics, norfloxacin and gatifloxacin, afforded the desired products in high yields and without any detectable side products. When the substrates with nitrogen and oxygen nucleophiles in the same molecule were used, the corresponding cyclic products with inserted carbonyl groups **4–6** were obtained in high yields. The heterocyclic skeletons obtained have been investigated extensively for the developments of various pharmaceuticals and pesticides.[14] On the other hand, reactions were complicated when primary amine (toluidine) was used. The expected products, isocyanate or urea, could not be obtained in this reaction conditions.

We also explored the scopes of these reactions by replacing the nitrogen nucleophiles with oxygen nucleophiles (phenols and alcohols, Fig. 3). The process for the *N*-methyl aniline was applied to the phenols, and for all their cases, the carbonates

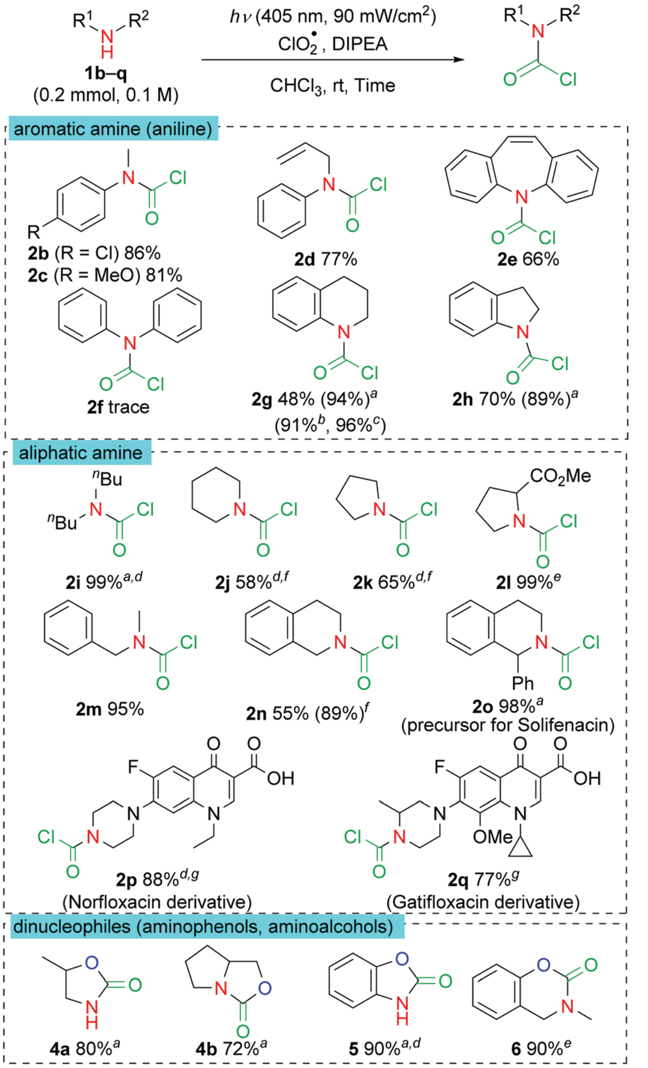


Fig. 2 Substrate scopes of the phosgenation reactions of *N*-nucleophiles. The reactions conditions: amine **1** 0.2 mmol (0.1 M), $ClO_2^•$ (8 equiv.), DIPEA (3 equiv.) at room temperature for 60 min. Isolated yields. [a] $ClO_2^•$ (4 equiv.), 40 min. [b] 365 nm, $ClO_2^•$ (4 equiv.), 20 min. [c] Sunlight, $ClO_2^•$ (4 equiv.), 2 h. [d] Reactions conducted in $CDCl_3$ instead of $CHCl_3$. ^{1}H NMR yields obtained based on the internal standard of 1,1,2,2-tetrachloroethane. [e] $ClO_2^•$ (4 equiv.), DIPEA (5 equiv.), 40 min. [f] Amine **1** 0.1 mmol (0.02 M), 40 min. [g] Amine **1** 0.1 mmol (0.05 M), $ClO_2^•$ (4 equiv.), 30 min.

8a–d were obtained in quantitative yields. In addition, the desired carbonates were obtained using the fluorine substituted alcohols as the substrates, although their yields were slightly lower. In the case of *n*-propanol, carbonate **8g** was obtained in moderate yield. It is interesting to note that we also successfully obtained chloroformate **8g′** when 2,6-lutidine was used as a base. This is an important result, although further studies are needed. Diols such as the ethylene glycol, propylene glycol, and catechol derivatives also afforded their cyclic carbonates (**9a,b**, and **10**) at high yields. Different types of carbonates, including diaryl, dialkyl, and cyclic carbonates, are essential in industry and are employed in a broad range of applications[15] such as their employments as the starting

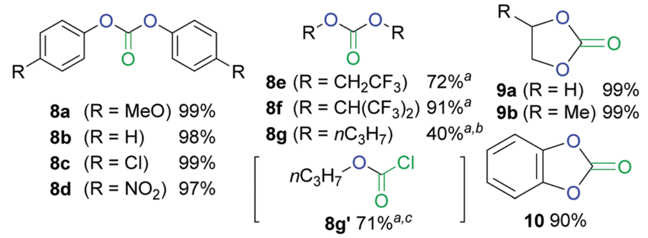


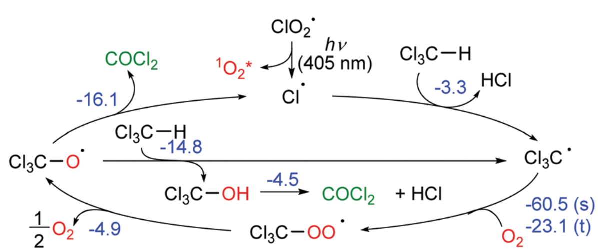
Fig. 3 Substrate scopes of the phosgenation reactions of *O*-nucleophiles. The reactions conditions: phenols or alcohols **7** 0.2 mmol (0.1 M), $ClO_2^•$ (4 equiv.), DIPEA (5 equiv.) at room temperature for 40 min.[a] Reactions conducted in $CDCl_3$ instead of $CHCl_3$. ^{1}H NMR yields obtained based on the internal standard of 1,1,2,2-tetrachloroethane. [b] Alcohol **7** 0.4 mmol (0.4 M), $ClO_2^•$ (2 equiv.), pyridine (5 equiv.). [c] Alcohol **7** 0.1 mmol (0.02 M), $ClO_2^•$ (8 equiv.), 2,6-lutidine (5 equiv.).

materials for resin (polycarbonates and polyurethanes) manufacturing, and have recently attracted considerable attention as sustainable process feedstocks.[16]

To investigate the reaction mechanism of the generation of $COCl_2$ from chloroform by our method, we conducted a control experiment (Scheme S1(a), ESI†). Ethylene glycol, which reacts with $COCl_2$ at a 1 : 1 ratio, was employed as the substrate and reacted with $ClO_2^•$ (0.5 equiv.) to afford a cyclic carbonate with a 61% yield. This result indicates that an equivalent amount of $ClO_2^•$ is not required for $COCl_2$ formation.

Furthermore, the product yields of carbonate **9a** were determined (Fig. S4, ESI†) with respect to the reaction times in $CHCl_3$ and $CDCl_3$ under the same reaction conditions. It is worth noting that a significant induction period was observed when the reaction was conducted in $CDCl_3$. It has been reported that the difference in bond energies between Cl_3C–H and Cl_3C–D is 6.0 kcal mol^{-1}.[17] These results indicate that hydrogen abstraction from Cl_3CH is the rate-limiting step in this reaction.

Based on the experimental results obtained, the DFT calculations performed (M06-2x/6-311 + +G(d,p) level of theory; (see ESI† for detailed protocol), and previous reports,[17] a plausible reaction mechanism is presented in Scheme 2. The visible-light activation of $ClO_2^•$ yields chlorine radicals ($Cl^•$) and singlet oxygen molecules ($^1O_2$*) through bond rearrangements from Cl–O–Cl to Cl–O–O bonds.[8] The generated $Cl^•$ abstracts hydrogen from Cl_3C–H to form a trichloromethyl radical ($Cl_3C^•$) and HCl.[18] This process proceeds more easily than methane oxidation,



Scheme 2 Plausible radical chain mechanism for the generation of phosgene. The blue numbers indicate the ΔE values (kcal mol^{-1}) estimated using DFT calculations.

as indicated by the C–H bond energies (H_3C–H: 104 kcal mol^{-1}, Cl_3C–H: 95.7 kcal mol^{-1}).[9] In fact, the energy difference (ΔE) for this process estimated from DFT calculations is negative (−3.3 kcal mol^{-1}). However, this reaction step is energetically unfavourable for $CDCl_3$ compared with $CHCl_3$, because of its relatively higher bond energy. This could have resulted in a remarkable induction period. The radical intermediate $Cl_3C^\bullet$ then combines with oxygen to produce the peroxyl radical $Cl_3COO^\bullet$.[19] The calculated ΔE values for the formations of $CCl_3OO^\bullet$ from the singlet and triplet O_2 are −60.5 and −23.1 kcal mol^{-1}, respectively. Hence, once $Cl_3C^\bullet$ is formed, it can rapidly react with both the singlet and triplet O_2 to produce the peroxyl radical. $Cl_3COO^\bullet$ gives an alkoxy radical ($Cl_3CO^\bullet$) through the desorption of O_2 *via* a Russel-type mechanism, and the ΔE value for this process is estimated to be −4.9 kcal mol^{-1}. There are two possible reaction pathways for the $Cl_3CO^\bullet$; the first pathway is $COCl_2$ formation through the regeneration of $Cl^\bullet$, and the second pathway is the mechanism of hydrogen abstraction from $CHCl_3$ to form $Cl_3C^\bullet$. Both pathways are estimated to be exothermic with ΔE values of −16.1 and −14.8 kcal mol^{-1}, respectively. The regenerated $Cl^\bullet$ and $Cl_3C^\bullet$ are recycled to produce $COCl_2$ until the radical chain is terminated. In addition, the generated CCl_3OH yields $COCl_2$ along with HCl, and the ΔE value for this step is also negative (−4.5 kcal mol^{-1}). Thus, all the steps after the photochemical generation of $Cl^\bullet$, as shown in Scheme 2, are exothermic in nature and energetically favourable as a radical chain reaction.[20]

The stoichiometric equation for this oxygenation reaction is given by eqn (1). Two $CHCl_3$ molecules react with one O_2 molecule to produce two $COCl_2$ molecules. This means that the $ClO_2^\bullet$ acts as an initiator in the radical chain cycle and as an O_2 source for $COCl_2$ formation.

$$2CHCl_3 + O_2 \rightarrow 2COCl_2 + 2HCl \qquad (1)$$

We have developed a visible-light-induced $COCl_2$ generation method using $CHCl_3$ and sodium chlorite as the starting materials, which are inexpensive and easy to handle. Various carbamoyl chlorides can be synthesized safely and efficiently *via* the phosgenation reactions of amines using $COCl_2$ generated *in situ*. This is an excellent method that can be applied to a wide range of substrates, including anilines and aliphatic amines, as well as pharmaceutical compounds with nucleophilic nitrogen atoms. In addition, this phosgenation method was successfully applied to carbonate synthesis from phenols and alcohols. This novel phosgenation system is an alternative to the classical method that involves the use of a hazardous reagent.

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Conflicts of interest

The authors declare no conflict of interest.

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20 When light irradiation was turned off 5 minutes after the reaction started, an increase in product (10 to 35%) was observed even under shielded light (see Fig. S4 in ESI†).