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Photo-on-demand Phosgenation Reactions with Chloroform Triggered by Cl_2 upon Irradiation with Visible Light: Syntheses of Chloroformates, Carbonate Esters, and Isocyanates

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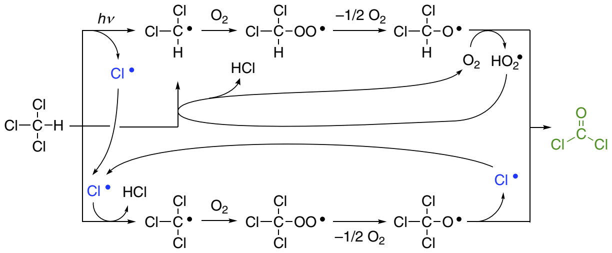
Chloroform ($CHCl_3$) upon bubbling with O_2 containing ~2% Cl_2 underwent oxidative photochemical conversion to phosgene ($COCl_2$) when exposed to a white LED light. Cl_2 may serve as a visible light-responsive radical initiator in the radical chain reactions of $CHCl_3$ and O_2. This photochemical reaction allowed both *in situ* and stepwise one-pot phosgenation reactions, which are simple and safe methods, without expensive apparatus. It can be applied to a variety of conventional organic syntheses using phosgene and phosgene oligomers.

Keywords: Visible light | Phosgenation | Chloroform

Photochemical synthesis with visible light is expected to play an important role for the design of sustainable chemical reactions with reductions of CO_2 emission and waste. It allows the use of light emitting diodes (LEDs) and sunlight as light sources, and also reduces photochemical degradation of the reaction substrates and/or products. There are a variety of photochemical reactions using visible light, most of which generally require a catalyst and/or reagent that are activated under visible light.[1–3]

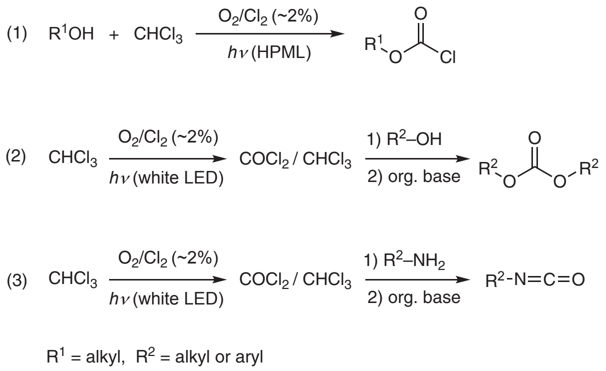
We previously reported that $CHCl_3$ under O_2 bubbling underwent oxidative photochemical conversion to produce $COCl_2$ upon exposure to UV-C light, mainly at 184.9 and 253.7 nm, generated from a low-pressure mercury lamp (LPML).[4] $COCl_2$ is a highly reactive useful C1 building block in organic synthesis, but is a highly toxic gaseous compound at room temperature.[5,6] The reaction may proceed through radical chain reactions triggered by C–Cl bond cleavage in $CHCl_3$ (Scheme 1).[4,7] The generated $Cl^•$ extracts hydrogen from another $CHCl_3$ to produce $Cl_3C^•$. It then reacts with O_2 to give $COCl_2$ with regeneration of $Cl^•$. Meanwhile, $Cl_2HC^•$ may also react with O_2 to give $COCl_2$. With this photochemical reaction, we then developed *in situ* photo-on-demand synthesis methods for chloroformates and carbonate esters from $CHCl_3$ solutions containing alcohol with or without an organic base.[8–10] Furthermore, we successfully demonstrated one-pot synthesis of isocyanates from primary amines with a prepared $CHCl_3$ solution containing $COCl_2$.[11] The substrates reacted with $COCl_2$ generated in $CHCl_3$ to give the products. These photochemical syntheses are safe, convenient, and inexpensive, but use LPML, which causes some unfavorable side reactions owing to the photo-decomposition of both reagents and products upon exposure to the high energy UV-C light. The use of mercury lamps should be avoided due to their large environmental impacts and health hazards.[12] This background motivated us to develop a novel photo-on-demand phosgenation reaction with lower-energy visible light.



Scheme 1. Proposed mechanism for oxidative photochemical conversion of $CHCl_3$ to $COCl_2$.

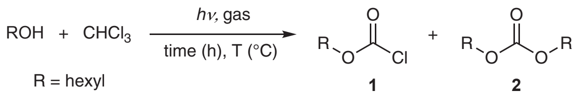
It is known that chlorine (Cl_2), having a lowest-energy absorption band at around 300–500 nm with λ_{max} at 330 nm, undergoes homolytic cleavage to give 2 $Cl^•$ upon heating or irradiation of visible light.[13,14] We expected that Cl_2 could become a visible light-responsive initiator of the radical chain reaction of $CHCl_3$,[15] and found herein that $CHCl_3$ underwent oxidative photochemical conversion to $COCl_2$ under >300 nm light when a catalytic amount of Cl_2 was added to O_2 gas.[16] In this study, we successfully applied this reaction to the *in situ* photo-on-demand synthesis of chloroformate with a mixture solution of $CHCl_3$ and alcohol (Scheme 2, reaction 1). Additionally, one-pot syntheses of carbonate esters and isocyanates were achieved with the $CHCl_3$ solution containing $COCl_2$ as prepared upon exposure to visible light (reactions 2 and 3, respectively).

The reaction system for the *in situ* photo-on-demand synthesis with visible light was set up as follows. A mixture of O_2 and Cl_2 (~2%) gas was prepared in a three-necked flask (flask 1) containing $Ca(ClO)_2$ upon addition of aqueous HCl solution with a syringe pump under a steady flow of O_2 (0.1 L/min). The prepared O_2/Cl_2 gas was dried over a $CaCl_2$ column, and then injected into the next photoreactor (flask 2). A 100 W high-pressure mercury lamp (HPML) equipped with



Scheme 2. Cl_2-triggered photo-on-demand phosgenation reactions with visible light developed in this study.

Table 1. *In situ* Photochemical synthesis of chloroformate from a $CHCl_3$ solution containing 1-hexanol with a 100 W high-pressure mercury lamp (HPML).



entry	gas	1-hexanol (mmol)	$CHCl_3$ (mmol)	lamp	time (h)	T (°C)	yield (%)[a]	
							1	2
1	O_2	10	250 (20 mL)	LPML[c] (20 W)	1	10	94	–
2	O_2	10	250	HPML[d] (100 W)	1	10	–	–
3	O_2/Cl_2[b]	10	250	HPML[d]	1	10	>99	–
4	O_2/Cl_2[b]	10	250	–[e]	1	10	–	10
5	O_2/Cl_2[b]	10	250	room light	1	10	58	8
6	O_2/Cl_2[b]	30	625 (50 mL)	HPML[d]	5	20	>99	–

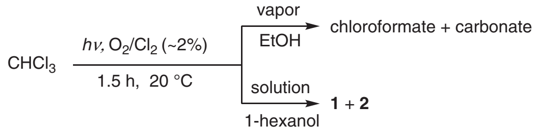
[a] Determined by ^1H NMR analysis, [b] ~2% Cl_2 content, [c] quartz glass jacket, [d] borosilicate glass jacket, [e] dark

a water cooling system was inserted into the solution via a borosilicate glass jacket (ϕ30 mm × 150 mm) fixed in the center of a cylindrical flask (ϕ46 mm × 170 mm). The system thus allows irradiation by >300 nm light with a maximum intensity at 365 nm, whose illuminance is 37.1 mW/cm^2. Alternatively, a commercially available 365 nm or white LED is attached to the outside of the cylindrical flask. The 365 LED with 2.25 W electrical power generates 355–375 nm light with a maximum intensity at $\lambda = 365$ nm, whose illuminance is 8.4 mW/cm^2. The white LED generates 400–750 nm light with a maximum intensity at $\lambda = 465$ nm, and the illuminances of the 3 and 9 W lamps are 560 and 2000 lux, respectively.

As a reference reaction, according to our previous study,[8] we demonstrated photochemical conversion of 1-hexanol to the corresponding chloroformate **1** with a 20 W LPML system (Table 1, Entry 1). When a $CHCl_3$ solution containing 1-hexanol under O_2 bubbling was exposed to the UV-C light, the chloroformate was obtained in 94% yield. The starting alcohol and/or product might undergo photo-decomposition to some extent, decreasing the product yield. With a 100 W HPML system instead of the LPML system, however, no reaction was observed (Entry 2). Interestingly, the reaction occurred upon mixing ~2% Cl_2 with the O_2 gas to give **1** in >99% yield (Entry 3). The observed increase in the product yield may result from cutting the higher energy UV light due to the borosilicate glass jacket. The reaction was then carried out in the dark, and the carbonate ester **2**, most likely formed through the reaction of **1** and alcohol, was obtained only in 10% yield (Entry 4). The reaction also proceeded under room light to give a mixture of **1** and **2** in 58 and 8% yields, respectively (Entry 5). A scale-up synthesis of **1** with the HPML was achieved by increasing the amounts of alcohol and $CHCl_3$ and raising the temperature to 20 °C (Entry 6).

To develop a more convenient simple reaction system with lower energy consumption, the HPML was then replaced by a LED, which can generate 365 nm UV-A light. Initially, we quantitatively investigated the oxidative photochemical conversion of $CHCl_3$ to $COCl_2$ by varying the LED lamp. The produced $COCl_2$ dissolved in $CHCl_3$ and that vaporized into the gas phase could be estimated separately by chemical trapping with an alcohol. When 30 mL of $CHCl_3$ under O_2/Cl_2 bubbling was exposed to 365 nm light with a 2.25 W LED at 20 °C for 1.5 h, it afforded 9.9% conversion to $COCl_2$ (Table 2, Entry 1). Furthermore, white light generated from a 3 W LED gave $COCl_2$ with 7.2% conversion (Entry 2). The observed conversion increased to 12.5% by increasing the light intensity with a 9 W LED (Entry 3). This yield is comparable to that with the 20 W LPML system (Entry 4).

Table 2. Chemical estimation of $COCl_2$ generated from $CHCl_3$ under bubbling with O_2 containing Cl_2 (~2%) upon photo-irradiation with 365 nm and white LED.

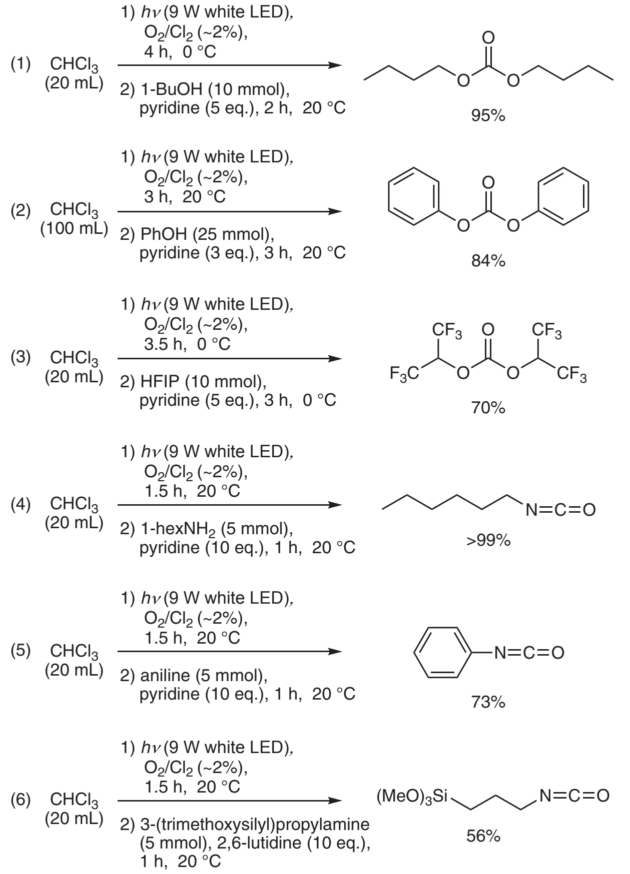


entry	lamp	$CHCl_3$ (mmol)	Estimated $COCl_2$ (mmol)		conversion (%)[a]
			solution	vapor	
1	365 nm LED (2.25 W)	375 (30 mL)	26	11	9.9
2	white LED (3 W)	375 (30 mL)	16	11	7.2
3	white LED (9 W)	375 (30 mL)	26	21	12.5
4	LPML[b] (20 W)	375 (30 mL)	26	25	13.6

[a] Determined by ^1H NMR analysis, [b] quartz glass jacket

Next, the above *in situ* photochemical conversion of $CHCl_3$ to $COCl_2$ was applied to the one-pot syntheses of carbonate esters and isocyanates (Scheme 3).[17] When a 1:5 mixture of 1-BuOH and pyridine was added to the as-prepared $CHCl_3$ solution containing $COCl_2$, dibutyl carbonate was obtained in 95% yield. PhOH, a lower nucleophilic aromatic alcohol, also reacted to give diphenyl carbonate in 84% yield. Hexafluoroisopropyl alcohol (HFIP), which is expected to have lower nucleophilicity than PhOH judging from their pK_a values (9.3 and 10.0, respectively),[18,19] provided the corresponding carbonate ester in 70% yield. This method was further available to the synthesis of isocyanates. A sequential addition of hexylamine and pyridine to the as-prepared $CHCl_3$ solution containing $COCl_2$ resulted in formation of the isocyanate in >99% yield. With the same procedure, aniline, an aromatic amine, was converted to the corresponding isocyanate in 73% yield. 3-(Trimethoxysilyl)propylamine, which readily undergoes hydrolysis condensation with water under acidic conditions, also provided the corresponding isocyanates in 56% yield.

In this study, we found that oxidative photochemical conversion of $CHCl_3$ to $COCl_2$ occurred upon exposure to visible light while bubbling with O_2 containing ~2% Cl_2. The visible light caused Cl–Cl bond cleavage to generate $Cl^\bullet$, which may be an initiator to trigger the radical chain reactions of $CHCl_3$ and O_2. This reaction allows photo-on-demand generation of $COCl_2$ in $CHCl_3$, which is practically applicable to *in situ* and stepwise one-pot phosgenation reactions. It is expected to replace a variety of conventional organic synthetic



Scheme 3. Stepwise one-pot photochemical syntheses of carbonate esters and isocyanates with $CHCl_3$ and alcohols or primary amines with a 9 W white LED.

reactions using phosgene and phosgene oligomers, and reduce the environmental impacts.

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