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Use of Trichloroacetonitrile as a Hydrogen Chloride Generator for Ring-Opening Reactions of Aziridines

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Regioselective ring-opening reactions of 2-aryl-*N*-tosylaziridines are described, in which hydrogen chloride is generated by photodegradation of trichloroacetonitrile. HCl adducts are obtained in high yields in 1,4-dioxane, whereas methanol adducts are predominantly obtained in methanol. Trichloroacetonitrile can serve as a photoresponsive molecular storage generator for hydrogen chloride.

Halogenated alkanes, the most well-known of which is chloroform, are often used as solvents and reagents in organic synthesis. These compounds are known to undergo degradation to produce hydrogen halides by external factors such as light.[1] Thus, it may be possible to use halogenated alkanes as precursors to provide a facile method for the generation of hydrogen halides on demand. In 2012, Tsuda and co-workers reported a photochemical molecular storage strategy using $CHCl_3$ with ultraviolet (UV) irradiation under oxygen atmosphere, wherein oxidative photodecomposition of chloroform produced hydrogen chloride (HCl), chlorine (Cl_2), and phosgene ($COCl_2$) (Fig. 1a).[2] They applied a low-pressure mercury lamp (20 W) that generated UV with wavelengths of 185 and 254 nm. Since treatment of highly hazardous chemicals can be avoided, this type of application would be very attractive, but has remained underdeveloped. We therefore sought to explore other reagents as a potential storage means for HCl that conveniently respond to photoirradiation. Trichloroacetonitrile with the formula CCl_3CN has been employed in versatile organic reactions, e.g., the Overman rearrangement, preparation of benzylating or *t*-butylating agents, and glycosylation reactions.[3] Taking advantage of the strong electron-withdrawing character of the cyano group, trichloroacetonitrile serves as an alternative to carbon tetrachloride (CCl_4) in substitution reactions with triphenylphosphine.[4] Moreover, the cyano group is able to

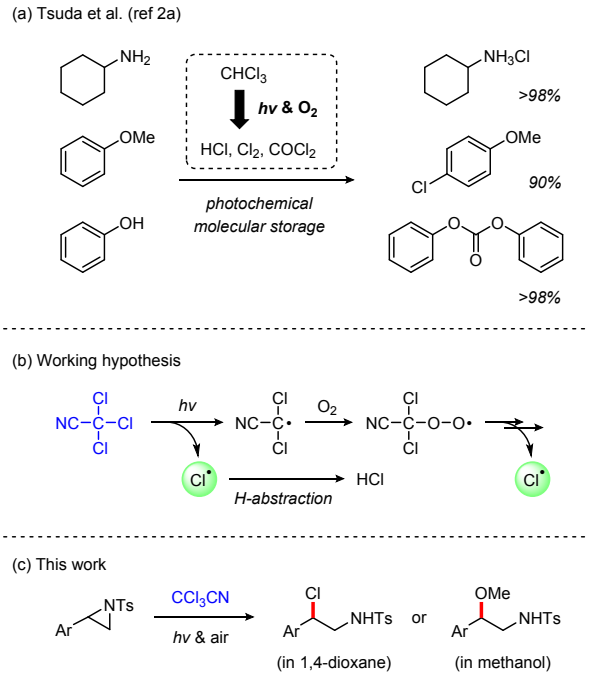

Fig 1 Trichloroacetonitrile as photoresponsive molecular storage generator of hydrogen chloride.

delocalize a carbon radical at the α-position, which lowers the energy of activation to enhance the rate of the overall reaction.[5] Thus, it is expected that trichloroacetonitrile would photodecompose under mild conditions to release a chlorine radical (Fig. 1b), which in turn, would abstract a hydrogen atom to generate HCl.[6] However, the established usage of trichloroacetonitrile for the purpose of HCl generation is still elusive.

Extensive studies have been conducted on ring-opening reactions of aziridines with various nucleophiles,[7] because the transformations afford synthetically valuable products including 1,2-aminoalcohol derivatives.[8] Although several methods, especially catalytic processes with Lewis acids, have

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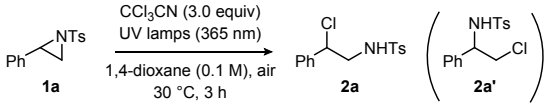
been developed to date, the regioselectivity of the adducts can be problematic depending on the nucleophiles or the substituents of the aziridines.[9,10] We envisaged that the photochemical molecular storage strategy might be suitable to provide practical access to aziridine ring-opening reactions, because the electrophilic activation of a substrate by a Brønsted acid is one of the most common approaches to promote a reaction. Herein, we demonstrate HCl and methanol addition to 2-aryl-*N*-tosylaziridines by employing a fragment of photodecomposed trichloroacetonitrile, leading to the synthesis of both β-chloroamines and β-methoxyethylamines (Fig. 1c).

At the outset of our study, we tested the HCl addition to 2-phenyl-*N*-tosylaziridine (**1a**) with the use of 3.0 equiv of trichloroacetonitrile (Table 1). The initial experiment was performed in 0.1 M 1,4-dioxane with 365 nm UV irradiation[11] under air atmosphere at ambient temperature for 3 h (Table 1, entry 1). To our delight, the desired β-chloroamine **2a** was obtained in high yield, and no regioisomer **2a'** was observed. A control experiment under dark conditions resulted in no consumption of starting material **1a** (Table 1, entry 2). Notably, the privileged reactivity of trichloroacetonitrile was proven by comparison of chloroalkanes $CHCl_3$ and CCl_4, neither of which provided **2a** (Table 1, entries 3 and 4). As expected, the use of HCl solution in 1,4-dioxane led to a similar result as entry 1 (Table 1, entry 5). Interestingly, *air* atmosphere was important for the efficient conversion, which was revealed by reactions under argon and oxygen atmospheres (Table 1, entries 6 and 7). Although oxygen is necessary on the basis of the reported mechanism (cf. Fig. 1b),[1m,2a] a high concentration of oxygen seems to suppress the free radical reaction. Furthermore, solvent screening showed an intriguing tendency (Table 1, entries 8-16). In all cases of ether-type solvents, complete conversion of aziridine **1a** was observed. The reaction in tetrahydrofuran afforded **2a** in moderate yield, but significant amounts of by-products were observed, probably due to decomposition of tetrahydrofuran (Table 1, entry 8). Switching to 2-methyltetrahydrofuran improved the yield of **2a** up to 83%, and the reaction in diethyl ether achieved a yield comparable to that in 1,4-dioxane (Table 1, entries 9 and 10). Use of toluene, dichloromethane, acetonitrile, and dimethyl sulfoxide resulted in recovery of **1a** (Table 1, entries 11-14). Regioisomer **2a'** was obtained, albeit with low conversion, in high polar solvents such as dimethylformamide and dimethylacetamide (Table 1, entries 15 and 16).

Subsequently, we attempted the methanol addition to aziridine **1a**, and identified the optimal conditions shown in entry 1 of Table 2. The reaction of **1a** with methanol under air afforded the corresponding adduct **3a** in 98% isolated yield within 30 min (standard conditions). Almost no conversion of **1a** was observed without light or without trichloroacetonitrile (Table 2, entries 2 and 3). Even a catalytic amount (5 mol %) of trichloroacetonitrile provided **3a** in high yield, although 24 h was needed for the consumption of starting material **1a** (Table 2, entry 4). The reaction using a HCl solution in methanol led to decreased yield due to formation of HCl adduct **2a** (Table 2, entry 5). $CHCl_3$ and CCl_4 were less effective, revealing the merit of trichloroacetonitrile photodecomposition (Table 2, entries 6 and 7). Lastly, the amount of HCl in the reaction mixture was estimated by Mohr's method (see ESI for details). It should be noted that the HCl generation in 1,4-dioxane (ca. 0.3 equiv of

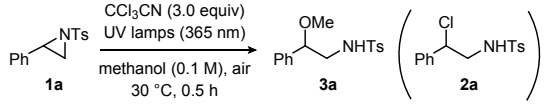
Table 1 Optimization of reaction conditions[a]



entry	variation from standard conditions	**2a** (%)[b]
1	none	>98 (95)
2	no light	<5
3	$CHCl_3$ instead of CCl_3CN	<5
4	CCl_4 instead of CCl_3CN	<5
5	HCl instead of CCl_3CN	98
6	under Ar	<5
7	under O_2	26[c]
8	in THF	54[d]
9	in 2-MeTHF	83[d]
10	in Et_2O	>98
11	in toluene	<5
12	in CH_2Cl_2	<5
13	in CH_3CN	<5
14	in DMSO	<5
15	in DMF	<5[e]
16	in DMA	13[e]

[a]Unless otherwise noted, all reactions were carried out on a 0.10 mmol scale using aziridine **1a** and 3.0 equiv of trichloroacetonitrile with 365 nm UV lamps under air atmosphere at 30 °C for 3 h. [b]Determined by ^{1}H NMR analysis using 1,1,2,2-tetrachloroethane as an internal standard (isolated yield is shown in parentheses). [c]Recovery of **1a**; entry 6: 91%; entry 7: 70%. [d]Complete conversion of **1a**. [e]Yield of **2a'** (%); entry 15: trace; entry 16: 17%.

Table 2 Optimization of reaction conditions[a]



entry	variation from standard conditions	**3a** (%)[b]
1	none	>98 (98)
2	no light	<5
3	no CCl_3CN	<5
4	0.05 equiv of CCl_3CN (24 h)	97
5	HCl instead of CCl_3CN	70[c]
6	$CHCl_3$ instead of CCl_3CN	<5[d]
7	CCl_4 instead of CCl_3CN	41[d]

[a]Unless otherwise noted, all reactions were carried out on a 0.10 mmol scale using aziridine **1a** and 3.0 equiv of trichloroacetonitrile with 365 nm UV lamps in a 0.1 M of methanol under air atmosphere at 30 °C for 0.5 h. [b]Determined by ^{1}H NMR analysis using 1,1,2,2-tetrachloroethane as an internal standard (isolated yield is shown in parentheses). [c]HCl adduct **2a** was obtained in 26% yield. [d]Recovery of **1a**; entry 6: 97%; entry 7: 56%.

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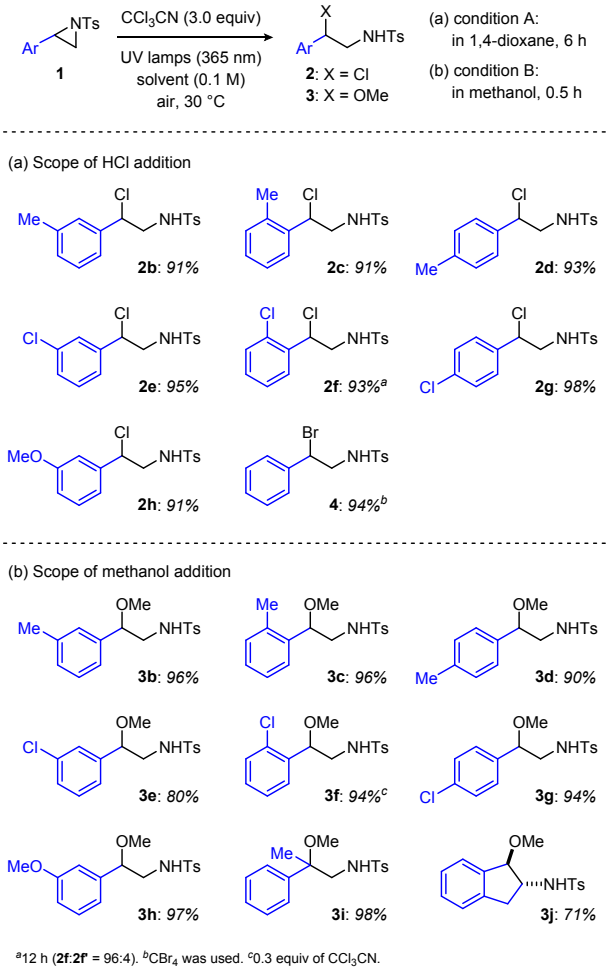
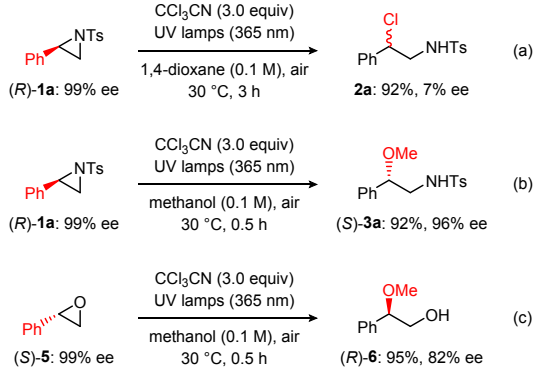


a12 h (**2f**:**2f'** = 96:4). bCBr_4 was used. c0.3 equiv of CCl_3CN.

Scheme 1 Substrate scope of the ring-opening reactions of aziridines with photodecomposed trichloroacetonitrile.

HCl upon aziridine **1**) was more than four times as fast as that in methanol (ca. 0.07 equiv). In addition, less than 120 mol % of HCl based on trichloroacetonitrile was observed even at a longer irradiation time of 12 h in 1,4-dioxane.

The scope of substrates is summarized in Scheme 1. The HCl addition to **1** was first examined by varying the aziridine component (Scheme 1a, upper half). Steric effects of the aryl group of **1** were investigated, but there was no significant difference between *meta*-, *ortho*-, and *para*-tolyl groups (**2b**: 91%; **2c**: 91%; **2d**: 93%). Aziridines bearing electron-deficient and electron-rich aryl groups afforded **2e**, **2g**, and **2h** in high yields (91-98%). We observed less than 5% of regioisomer **2f'** in the case of *ortho*-chloro-substituted **1f**. CBr_4 was also applicable to give the HBr adduct **4** in 94% yield. Next, the scope of the methanol addition was investigated (Scheme 1b, lower half). A series of aziridines **1b–1h** furnished the corresponding methanol adducts **3b–3h** in good to high yields (80-97%) under the optimal reaction conditions except for *ortho*-chlorophenyl **1f**. Although a competitive HCl addition took place to form **2f** when **1f** was employed with 3.0 equiv of trichloroacetonitrile, a decreased amount of



Scheme 2 Reactions of optically active aziridine **1a** and epoxide **5**.

trichloroacetonitrile (0.3 equiv) enabled selective formation of **3f**. 1,1-Disubstituted aziridine **1i** was cleanly converted to the product **3i**, but a 1,2-disubstitution pattern was challenging. Indene-derived **1j** formed not only **3j** (71%) but also its regioisomer (18%).

To expand the applicability of our methodology, optically active aziridine (*R*)-**1a** was submitted to the optimized reaction conditions. Mechanistically, it is of interest that contrasting results were obtained as shown in Scheme 2a and 2b. Serious stereochemical erosion occurred during the course of the HCl addition (7% ee), indicating an S_N1-like pathway that involved a carbocationic intermediate. On the other hand, the methanol addition to (*R*)-**1a** yielded enantio-enriched and stereoinverted product (*S*)-**3a** with 96% ee, wherein an S_N2-type ring-opening could proceed. Furthermore, styrene oxide (**5**) was tested as an analogue of 3-membered heterocycles. To our delight, enantiopure (*S*)-**5** was smoothly converted to the methanol adduct (*R*)-**6** in high yield with perfect regioselectivity, but partial loss of enantiomeric excess was observed (Scheme 2c).

In summary, we have demonstrated regioselective ring-opening reactions of 2-aryl-*N*-tosylaziridines **1** for the synthesis of β-chloroamines **2** and β-methoxyethylamines **3**. HCl addition to **1** afforded **2** in a solution of 1,4-dioxane, whereas switching the solvent to methanol efficiently formed the corresponding adduct **3**. In this strategy, HCl is generated by photodegradation of trichloroacetonitrile that functions as a UV-light responsive molecular storage generator of HCl. Further applications of this methodology will be performed in due course.

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Conflicts of interest

There are no conflicts to declare.

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