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Atom-transfer radical cyclization of α-bromocarboxamides under organophotocatalytic conditions

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ABSTRACT

The atom-transfer radical cyclization (ATRC) reaction gives halogenated heterocycles from the corresponding halocarbonyls that possess a C–C double bond. In contrast, the reductive ATRC reaction gives non-halogenated heterocycles in the presence of a reductant. In this research, we successfully control the ATRC and reductive ATRC reactions of *N*-allyl-α-haloamides under visible-light irradiation in the presence/absence of the Hantzsch ester as a reductant.

Introduction

One of the most useful synthetic methodologies for the preparation of cyclic compounds is the atom-transfer radical cyclization (ATRC) reaction [1–3], which is a modification of the Kharasch-type atom-transfer radical addition (ATRA) reaction [4]. Among these processes, the ATRC reactions of *N*-allyl-α-haloamides to synthesize γ-lactams have been investigated in detail due to the number of bioactive compounds and synthetic intermediates that contain substituted γ-lactams [5]. More specifically, *N*-allyl-α-haloamides can be cyclized to give γ-lactams in the presence of organotin reagents [6], Lewis acids [7], Cu [8], Ni [9], Fe [10], Pd [11], or Ru [12].

Recently, visible-light photocatalysts have enabled a new organic reaction methodology to be developed via a single electron transfer process [13], which achieves greener organic reactions without the requirement for heating. In ATRC chemistry, Martin and co-workers were the first to report the visible light-promoted ATRC reactions of unactivated alkyl iodides (Fig. 1A) [14,15]. Under irradiation from blue light-emitting diodes (LEDs), alkyl iodides possessing C–C multiple bonds underwent the ATRC reaction in the presence of an Ir catalyst. Recent progress in the context of the ATRC reaction of *N*-allyl-α-haloamides includes the use of the ball-milling technology (Fig. 1B) [16], whereby Cu (and a Ba salt) initiate the ATRC reaction under mechanochemical conditions. These reactions are generally completed within a few hours. Despite such progress in this area, no organo-photoredox-catalyzed (PC) ATRC reaction of *N*-allyl-α-haloamides has been established (Fig. 1C).

We recently reported the organo-photoredox-catalyzed atom-transfer radical substitution reaction (ATRS) [17] between styrenes and α-halocarbonyls as the tertiary alkyl source to produce tertiary alkyl-substituted styrenes [18]. We found that an organophotoredox catalyst, *N*-Ph-phenothiazine (PTH), enabled the ATRC reaction of *N*-allyl-α-haloamide to take place to yield a γ-lactam. The corresponding reductive ATRC reaction [19] was also observed in the presence of a reductant. Thus, we herein report the ATRC and reductive ATRC reactions of *N*-allyl-α-haloamides under visible-light irradiation.

Results and discussion

We initially investigated the ATRC of α-bromocarboxamide **1a** as a standard substrate to optimize the reaction parameters (Table 1, and see also the Tables in the SI). Upon the evaluation of a variety of organophotocatalysts that are typically employed in photoredox reactions (entries 1–5), PTH was found to give the desired ATRC product **2a** in 71% yield, along with the corresponding reductive ATRC product **3a** in 6% yield (entry 1). Although DMSO, MeOH, and H_2O/*i*PrOH provided good results for this reaction (entries 1, 6, and 7), the reductive ATRC product **3** was predominantly generated when NMP (*N*-methylpyrrolidinone) was used as the solvent. It is possible that NMP acts as a hydrogen donor in this reaction system. Thus, in an attempt to improve the ATRC/reductive ATRC product ratio, $MgBr_2$ was employed as a

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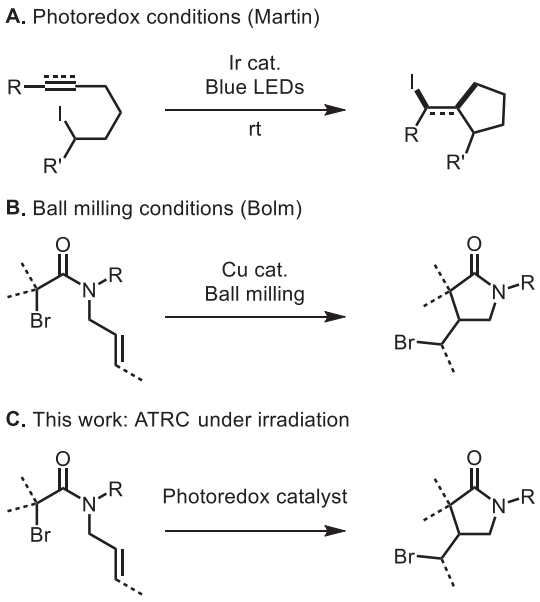
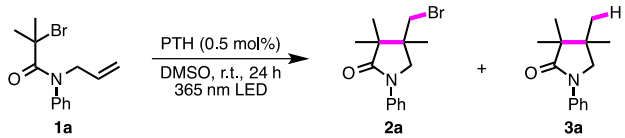


Fig. 1. ATRC reactions.

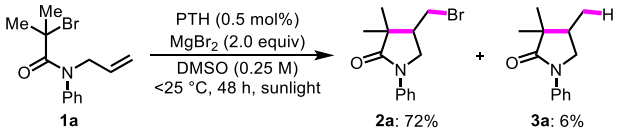
Table 1
Visible light-induced ATRC of α-bromoamides.[a]



Entry	Variation from the standard conditions (wavelength)	Yield of **2a**/**3a** (%)[b]	Ratio of **2a**/**3a**
1	None	71/6	92/8
2	PC = PDI[d], 450 nm	n.r.	–
3	PC = Eosin Y, 525 nm	n.r.	–
4	PC = Rose bengal, 525 nm	n.r.	–
5	PC = BDN[e]	64/8	89/11
6	In MeOH	63/18	78/22
7	In H_2O/*i*PrOH = 9:1	61/8	88/12
8	In NMP	16/49	25/75
9	With $MgBr_2$ (2 equiv)	82/6 (72/2)[c]	93/7
10	Without PC	n.r.	–
11	In the dark	n.r.	–
12	With Hantzsch ester (1.5 equiv)	8/80% (8/72)[c]	9/91

[a] A mixture of **1a** (0.50 mmol), 0.5 mol% of PTH, and DMSO (2 mL), was stirred at room temperature with 365 nm LEDs for 24 h under N_2.
[b] The NMR yield was determined using 1,1,2,2-tetrachloroethane as an internal standard.
[c] Isolated yield.
[d] PDI = *N*,*N*′-Bis(2,6-diisopropylphenyl)-3,4,9,10-perylenetetracarboxylic diimide.
[e] BDN = 1,4-bis(diphenylamino)naphthalene.

bromine source, although other bromine sources were also examined, including ammonium bromide. However, it was found that the ratio of products remained constant, although the overall yield was slightly improved (entry 9). In this reaction, both the PC process and the employed irradiation therefore appeared to be key in determining the outcome. Indeed, in the absence of either of these two components, the reaction did not proceed (entries 10 and 11). Moreover, when the Hantzsch ester was used as a reductant, the reductive ATRC product was predominantly obtained (entry 12). Interestingly, in this reaction, the use of sunlight instead of LEDs was found to be effective, with **2a** being obtained in 72% yield after carrying out the ATRC for 48 h under solar irradiation (Scheme 1).

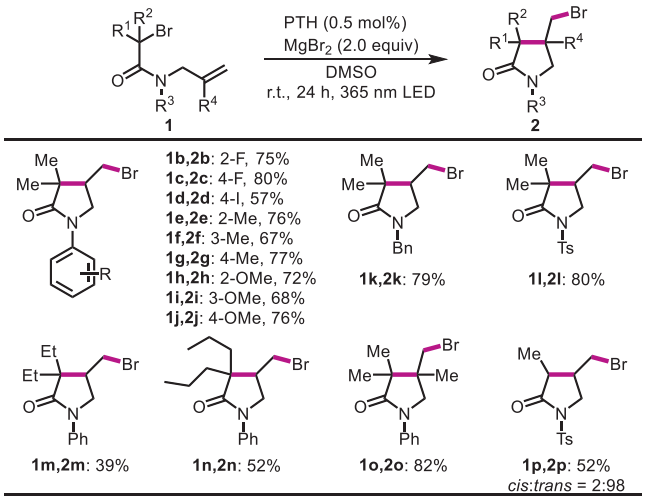


Scheme 1. Sunlight-induced ATRC of α-bromoamides.

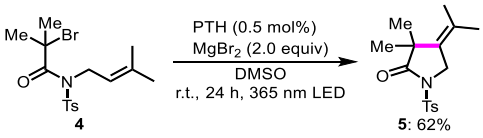
Using the optimized conditions (Table 1, entry 9), the substrate scopes for the ATRC and reductive ATRC reactions were examined (Table 2). In the case of the ATRC, α-bromocarboxamides possessing halogen atoms (i.e., **1b**, **1c**, and **1d**) and electron-donating substituents (**1e**–**1j**) on their aryl groups were examined. Overall, yields ranging from 67 to 80% were achieved, although iodoarene **1d** gave a lower 57% yield. In this case, unidentified products were detected, which suggested that C–I cleavage may take place to promote radical side-reactions. In addition, the presence of *N*-benzyl and tosyl groups (**1k** and **1l**) resulted in smooth reactions under the optimized conditions, although sterically-hindered bromides (**1m–1o**) underwent the ATRC reaction to give only low to good yields of **2m–2o**. For example, **1n**, which possesses long alkyl chains at the position α to the carbonyl group resulted in a 52% yield of **2n**, while diethyl-substituted **1m** gave only a 39% yield of the corresponding product. In addition, the sterically-congested *N*-methallyl-substituted **1o** smoothly underwent the ATRC to give **2o** in 82% yield, while α-bromocarboxamide (**4**) possessing an *N*-3-methyl-crotyl group gave the corresponding elimination product (**5**) in 62% yield (Scheme 2). Moreover, an α-bromocarboxamide possessing a *sec*-alkyl moiety at the carbonyl α-position (**1p**) gave the expected ATRC product **2p** in 52% yield with 2:98 (*cis:trans*) selectivity.

We then examined the functional-group compatibility of the reductive ATRC process (Table 3). More specifically, α-bromocar-

Table 2
Substrate scope for the ATRC reaction.[a]

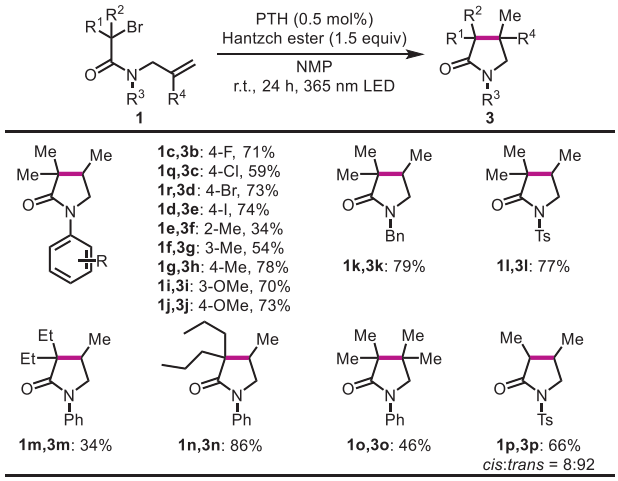


[a] A mixture of α-bromoamide **1** (0.50 mmol), PTH (0.5 mol%), $MgBr_2$ (2.0 equiv), and DMSO (2.0 mL), was stirred at room temperature with 365 nm LEDs for 24 h under N_2.



Scheme 2. Reaction using **4**.

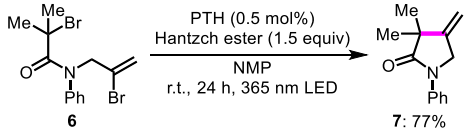
Table 3
Substrate scope for the reductive ATRC reaction.[a]



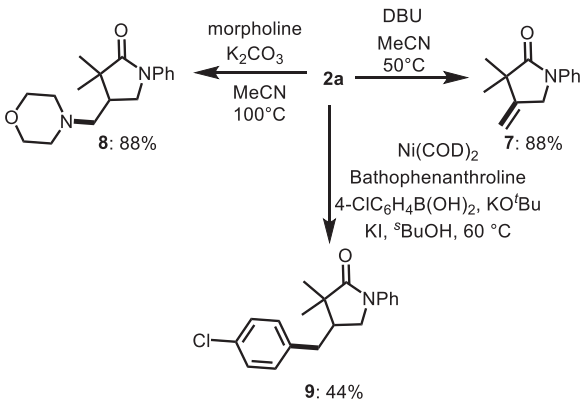
[a] A mixture of α-bromoamide 1 (0.50 mmol), PTH (0.5 mol%), Hantzch ester (1.5 equiv), and NMP (2.0 mL), was stirred at room temperature with 365 nm LEDs for 24 h under N_2.

boxamides possessing halogen atoms (**1c**, **1d**, **1r**, and **1q**) or electron donating substituents (**1e**–**1j**) on their aryl groups were examined. Overall, yields ranging from 70 to 78% were obtained, although the presence of Cl- and methyl-substituted aryl groups (**1e**, **1f**, and **1q**) gave low yields. Similar to the case of the ATRA process, α-bromocarboxamides bearing *N*-benzyl and tosyl groups (**1k** and **1l**) smoothly reacted under the optimized conditions. We also examined α-bromocarboxamides possessing various lengths of alkyl chains. More specifically, when the *n*-ethyl-substituted **1m** was used, **3m** was produced in a low 34% yield. In contrast, *n*-propyl-substituted **1n** gave the corresponding product in 86% yield. Subsequently, to produce reductive ATRC products possessing vicinal quaternary carbon centers, we tested an α-bromocarboxamide possessing a sterically-congested *N*-methallyl group (**1o**), and the expected product **3o** was obtained in 46% yield. When the reaction was carried out using **1p**, which possesses a *sec*-alkyl moiety at the carbonyl α-position, lactam **3p** was obtained in 66% yield with a high stereoselectivity. Interestingly, the reactivity of 2-bromoallyl substituted **6** differed from those of substrate **1**. More specifically, this substrate underwent the ATRC reaction, but the subsequent HBr elimination was rapid, resulting in the formation of **7** in 77% yield (Scheme 3).

We then moved on to demonstrate that **2a** can undergo three different chemical transformations, as outlined in Scheme 4. More specifically, the reaction of **2a** in the presence of morpholine resulted in the formation of aminated product **8** in 88% yield, while the elimination reaction of **2a** with DBU gave the corresponding olefin **7** in 88% yield. Furthermore, the reaction of **2a** with arylboronic acid in the presence of a Ni catalyst resulted in a primary-alkylative cross-coupling reaction to afford **9** in 44% yield.

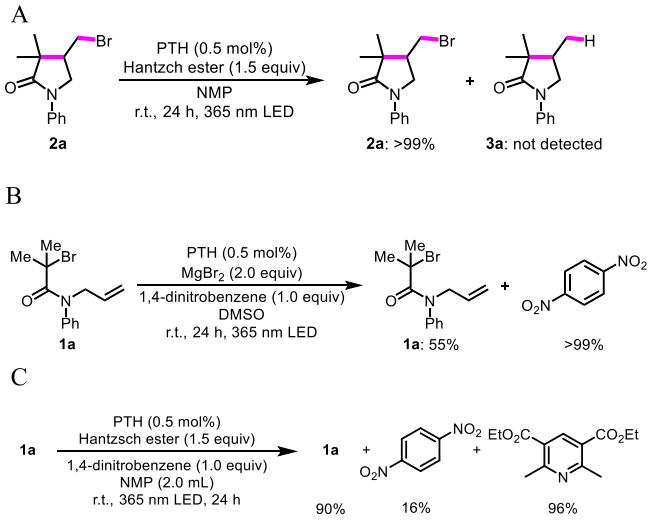


Scheme 3. Reaction of **6**.



Scheme 4. Derivatization of **2a**.

Finally, we carried out a number of control experiments to understand the reaction mechanism involved in this process. Interestingly, we found that the reductive ATRC product was not directly generated from the reaction of **1a** in the presence of the Hantzsch ester (Scheme 5A). This result indicated that no primary-alkyl radical species was generated from **2a** under the reaction conditions examined herein, and that an intermediate radical was directly captured by the reductant. To confirm the involvement of a single-electron transfer process, the reaction of **1a** was carried out in the presence of 1,4-dinitrobenzene (Scheme 5B). No trace of product **2a** was obtained, and instead, substrate **1a** was recovered in 55% yield (Other products were not able to identified), along with the 1,4-dinitrobenzene reagent (>99% yield, <1% conversion). This reaction was also carried out in the presence of the Hantzsch ester (Scheme 5C), and a similar result was obtained (i.e., 90% **1a**, no product). But 1,4-dinitrobenzene was reduced to the corresponding amine, and Hantzsch ester was converted to the pyridine derivatives. These results supported the fact that the single-electron reduction of **1a** could proceed via a PC process. To verify the effect of photoirradiation, the ATRC reaction of **1a** was monitored over time (Fig. 2). The reaction was found to be particularly efficient, with 56% of product **2a** forming within 1 h. Importantly, when the LED light was switched off, the reaction stopped, and when it was switched back on again, the reaction restarted. This observation strongly suggests that PC plays a critical role in this ATRC reaction, and that no radical chain transfer is involved.



Scheme 5. Control experiments.

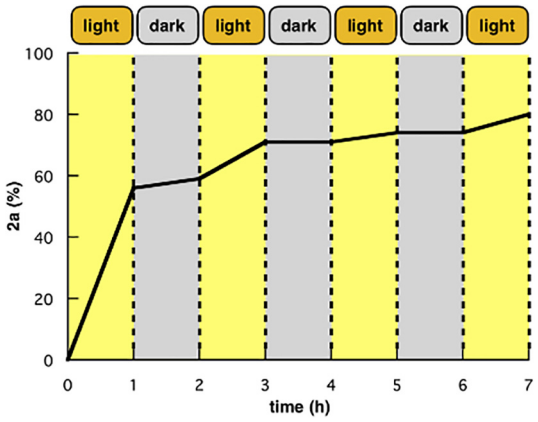


Fig. 2. Time course of the reaction with on/off switching of the photoirradiation source. The yields were determined by ^{1}H NMR spectroscopy using 1,1,2,2-tetrachloroethane as an internal standard.

Conclusion

In summary, we successfully developed ATRC and reductive ATRC reactions using α-bromocarboxamides possessing an allylic fragment, whereby PTH was employed as a photocatalyst. Under the irradiation conditions employed herein, cyclized products were obtained, while reductive products were obtained in the presence of the Hantzsch ester as a reductant. These results are of importance since they provide an expansion of the scope of the ATRC reaction, and give additional insight into the reductive ATRC process.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgments

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Appendix A. Supplementary data

Supplementary data (experimental procedures, analytical data and copies of the ^{1}H and ^{13}C NMR spectra and copies of the 1H and 13C NMR spectra) to this article can be found online at https://doi.org/10.1016/j.tetlet.2021.152952.

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