Hypervalent iodine-promoted aminobromination of electron-deficient olefins with Bromamine-T

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Abstract

A convenient and practical procedure for the aminobromination of electron-deficient olefins using Bromamine-T as nitrogen and bromine source promoted by (diacetoxyiodo)benzene has been developed. This metal-free protocol is highly efficient and affords the vicinal bromamines with excellent stereoselectivities.

Keywords: Aminobromination, Bromamine-T, hypervalent iodines, electron-deficient olefins

Introduction

The vicinal haloamine functionalities represent valuable synthetic intermediates of various pharmacologically active compounds and can be transformed into other useful structures via substitution reactions of the halogen atom with a wide range of nucleophiles.[1] Typically, these compounds can be obtained from the aminohalogenation of carbon-carbon double bonds. In this context, various systems employing N-halo nitrogen derivatives[2] or the combination of nitrogen source and NBS[3] have been developed.[4] Recently, palladium salts[5] and Lewis acids[6] catalyzed aminohalogenation processes have also been reported, giving the vicinal haloamines with high yield and stereoselectivity.

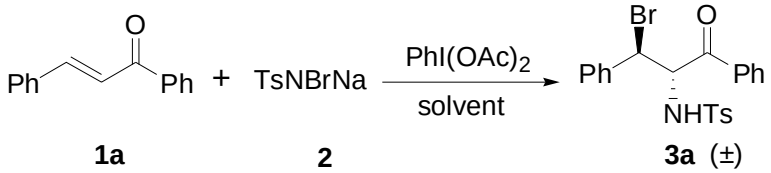
However, the aminohalogenation of electron-deficient olefins remains relatively rare probably due to the low activity of the reaction site. Very recently, elegant work focused on the copper and palladium catalyzed aminochlorination reactions have revealed that various electron-deficient olefins including α,β-unsaturated esters,[7] ketones,[8] amide,[9] nitriles,[10] and nitrostyrenes[11] can be aminochlorinated with high efficiency.[12] On the other hand, as green chemistry becomes a crucial concern in modern synthetic chemistry, avoiding metal catalysis in chemical process is

highly desirable. Delightedly, Li and coworkers reported a metal-free aminochlorination reaction of chalcones in ionic liquid.[13] At almost the same time, we discovered that the aminohalogenation of electron-deficient olefins can be promoted by (diacetoxyiodo)benzene [$PhI(OAc)_2$][14] or Brønsted acids[15] with Chloramine-T[16] or the combination of $TsNH_2$ and NBS as nitrogen and halogen sources. As an analogue of Chloramine-T, Bromamine-T has been mainly utilized as a titrant in oxidimetric estimations[17] and occasionally as an oxidant.[18] Recently, a few papers have described the employment of Bromamine-T as nitrene surrogate for the aziridination of olefins[19a-g] and the amidation of benzylic C-H bonds.[19b,h] However, using Bromamine-T as both nitrogen and bromine sources simultaneously still remains unexplored. Herein we demonstrate the aminobromination of electron-deficient olefins with Bromamine-T promoted by $PhI(OAc)_2$.

Results and Discussion

We embarked on the study of solvent and temperature effects in a test reaction of chalcone **1a** with Bromamine-T (2.0 equiv) by the action of $PhI(OAc)_2$. The results are summarized in Table 1. At 25 ^oC, the reaction was very sluggish in CH_2Cl_2 and furnished the product in low yield after 5 hours, remaining lots of chalcone **1a** uncharged (entry 1). Elevating the reaction temperature proved helpful and the bromamine **3a** was able to be isolated in 74% yield within 1.5 hour (entry 2). The hydrogen atom required in this transformation was believed to come from the atmosphere moisture. Further efforts to reduce the loading of $PhI(OAc)_2$ and Bromamine-T were unsuccessful; the yields dropped notablely even though the reaction time was prolonged (entries 3-4). The reaction performed in 1,2-dichloroethane (DCE) was disadvantageous; only give the product in 31% yield (entry 5). CH_3CN, which was used as a privileged solvent in aminohalogenation reactions,[12] afforded **3a** in 25% yield (entry 6). Other common solvents were also screened; however all of them exhibited negative activity towards this aminobromination process (entries 7-13).

Table 1. Optimizing the aminobromination reaction of chalcone **1a** with Bromamine-T promoted by $PhI(OAc)_2$[a]



1a **2** **3a** (±)

Entry	Solvent	Temp./^oC	Time/h	Yield/%[b]	Dr (*anti*/*syn*)[c]
1	CH_2Cl_2	25	5	28	92/8
2	CH_2Cl_2	reflux	1.5	74	92/8
3[d]	CH_2Cl_2	reflux	2.5	43	91/9
4[e]	CH_2Cl_2	reflux	2.5	64	92/8

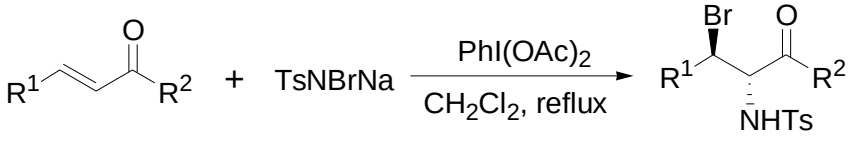
Table 1. Continued

Entry	Solvent	Temp./°C	Time/h	Yield/%[b]	Dr (*anti*/*syn*)[c]
5	DCE	reflux	4	31	92/8
6	CH_3CN	reflux	4	25	92/8
7	PhMe	80	5	trace	nd[f]
8	THF	reflux	5	trace	nd[f]
9	dioxane	reflux	5	trace	nd[f]
10	Et_2O	reflux	5	trace	nd[f]
11	DMF	80	5	0	/
13	EtOH	reflux	5	trace	nd[f]

[a] Unless otherwise specified, all reactions were performed with chalcone **1a** (0.2 mmol), Bromamine-T (0.4 mmol), and $PhI(OAc)_2$ (0.1 mmol) in the indicated solvent. [b] Isolated yields by flash column chromatography. [c] Determined by the analysis of ^1H NMR. [d] 0.06 mmol of $PhI(OAc)_2$ was employed. [e] 0.3 mmol of Bromamine-T was employed. [f] Not determined.

After a brief screening of the solvent, the use of CH_2Cl_2 was found to be optimal to attain high conversion and the substrate generality was investigated next (Table 2). It was obvious to see that irrespective of the substituent pattern and the electronic property of the aryl moiety, the products could be obtained in good yields with very good diastereoselectivities when chalcones were employed as reactants (entries 1-8). The chalcone **1i** was an exception since the strong electron withdrawing group influenced the activity of the double bond obviously. The final product was isolated in moderate yield as a single diastereomer (entry 9). Furthermore, other electron-deficient double bond systems were also examined. Enone with methyl substituent on the carbonyl side was feasible, affording the bromamine **3j** in 57% yield along with high diastereoselectivity (entry 10). To our delight, the cinnamate and cinnamide were also tolerable in the present system; both of them gave the corresponding products in moderate yields as *anti*-configuration exclusively (entries 11-12).

Table 2. $PhI(OAc)_2$-promoted aminobromination of electron-deficient olefins with Bromamine-T[a]



1 **2** **3** (±)

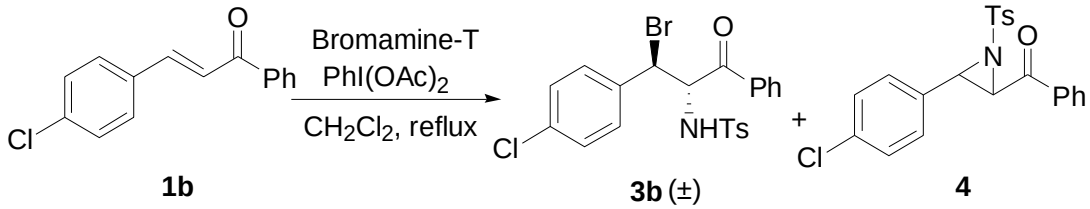
Entry	R^1	R^2	Time/h	Product	Yield%[b]	Dr (*anti*/*syn*)[c]	Mp/°C
1	Ph	Ph	1.5	**3a**	74	92/8	141-143[6b]
2	4-Cl-C_6H_4	Ph	1.5	**3b**	72	93/7	166-168[6b]

Table 2. Continued

Entry	R^1	R^2	Time/h	Product	Yield%[b]	Dr (*anti*/*syn*)[c]	Mp/°C
3	2-Cl-C_6H_4	Ph	1.5	**3c**	71	93/7	139-141[14b]
4	3,4-Cl_2-C_6H_3	Ph	2	**3d**	70	>99/1	156-158[14b]
5	Ph	4-MeO-C_6H_4	2	**3e**	70	90/10	142-144[14b]
6	4-Cl-C_6H_4	4-MeO-C_6H_4	2.5	**3f**	68	89/11	143-145[14b]
7	Ph	4-Cl-C_6H_4	2	**3g**	67	92/8	121-123[14b]
8	4-Cl-C_6H_4	4-Cl-C_6H_4	3	**3h**	66	>99/1	158-160[14b]
9[d]	4-NO_2-C_6H_4	Ph	3.5	**3i**	56	>99/1	160-162[14b]
10	Ph	Me	3	**3j**	57	93/7	123-125[14b]
11	Ph	OMe	3	**3k**	61	>99/1	137-139[6b]
12	Ph	NEt_2	3	**3l**	53	>99/1	185-187[14b]

[a] Unless otherwise specified, all reactions were performed with olefin **1** (0.2 mmol), Bromamine-T (0.4 mmol), and $PhI(OAc)_2$ (0.1 mmol) in refluxing CH_2Cl_2. [b] Isolated yields by flash column chromatography. [c] Determined by the analysis of ^1H NMR. [d] 0.6 mmol of Bromamine-T was employed.

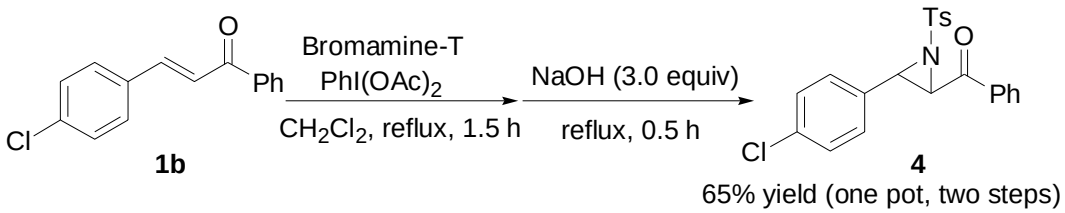
Bromamine-T was found to be an ideal nitrene source in the transition metal catalyzed aziridination of olefins.[19b] Further exploration of our aminobromination reaction revealed that when chalcone **1b**, Bromamine-T, and $PhI(OAc)_2$ was mixed in refluxing CH_2Cl_2 for 1.5 h, bromamine **3b** was isolated in 72% yield along with 5% yield of aziridine **4** (Scheme 1).



Scheme 1

It has been reported that a significant amount of bromamine product was obtained in the palladium catalyzed aziridination of electron-deficient olefins which was believed to be generated by the subsequent nucleophilic ring opening of the corresponding aziridine with bromine ion.[19c,g] To understand how the bromamine was produced in our system, extra investigation was made. We found that the yield of aziridine increased considerably when the reaction time was prolonged to 4 hours (Scheme 1). However, this conversion stopped at about

31% yield of aziridine **4** after 9 hours. Accordingly, we believed that the aziridine observed in our system was generated from the bromamine by losing hydrobromide in the presence of base[7e,20] which was released during the aminobromination process.[14,15] Actually, when excessive NaOH was added directly after the reaction mixture was refluxed in CH_2Cl_2 for 1.5 h, the bromamine **3b** disappeared and aziridine **4** was obtained in 65% yield after another 0.5 h (Scheme 2). This finding supported our hypothesis adequately.



Scheme 2

Conclusions

In conclusion, we have discovered Bromamine-T to be an efficient nitrogen and bromine source in the hypervalent iodine-promoted aminobromination of electron-deficient olefins. The reactions, which are characterized by their operational ease and high efficiency, lead to diastereoselective vicinal bromamine formation, proceed well for α,β-unsaturated ketones, cinnamate, and cinnamide.

Experimental Section

General procedure for the aminobromination of electron-deficient olefins with Bromamine-T promoted by $PhI(OAc)_2$

To a mixture of olefin **1** (0.2 mmol), Bromamine-T (0.4 mmol, 108.8 mg), and (diacetoxyiodo)benzene (0.1 mmol, 32.3 mg) in a 25 mL round-bottom flask was added CH_2Cl_2 (2 mL). This suspension was heated to reflux for the indicated time monitored by TLC. After the disappearance of the starting material, the resulting mixture was filtrated and the filtrate was separated on a silica gel column with petroleum ether/ethyl acetate 5/1 as the eluent to get the desired product **3**.

Procedure for the reaction of enone 1b with Bromamine-T

A mixture of enone **1b** (0.2 mmol, 48.5 mg), Bromamine-T (0.4 mmol, 108.8 mg), and (diacetoxyiodo)benzene (0.1 mmol, 32.3 mg) was added to a 25 mL round-bottom flask (flask A). Two same mixtures were introduced into other two parallel flasks (flask B and C)

respectively. To each flask was added CH_2Cl_2 (2 mL) and the resulting suspensions were heated to reflux for the indicated time (flask A, 1.5 h; flask B, 4 h; flask C, 9 h). The reaction mixtures were separated on a silica gel column with petroleum ether/ethyl acetate 5/1 as the eluent to get the bromamine **3b** and aziridine **4**, respectively (flask A: 70.9 mg, 72% yield of **3b** and 4.3 mg, 5% yield of **4**; flask B: 52.1 mg, 53% yield of **3b** and 14.9 mg, 18% yield of **4**; flask C: 38.5 mg, 39% yield of **3b** and 25.7 mg, 31% yield of **4**).

Procedure for the aziridination of enone 1b with Bromamine-T

To a mixture of enone **1b** (0.2 mmol, 48.5 mg), Bromamine-T (0.4 mmol, 108.8 mg), and (diacetoxyiodo)benzene (0.1 mmol, 32.3 mg) in a 25 mL round-bottom flask was added CH_2Cl_2 (2 mL). This suspension was heated to reflux for 1.5 h. Then NaOH (0.6 mmol, 24.0 mg) was added directly to the reaction mixture and the stirring was continued for another 0.5 h (monitored by TLC). After the disappearance of the bromamine **3b**, the resulting mixture was filtrated and the filtrate was separated on a silica gel column with petroleum ether/ethyl acetate 4/1 as the eluent to get the desired product **4** (53.5 mg, 65% yield).

All products reported here have previously been isolated and fully characterized, and were confirmed by comparison of their spectral data with the reported data.

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