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Transition metal-free iodine-promoted haloamination of unfunctionalized olefins†

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A transition metal-free route to 3-halopiperidines and 2-halomethylpiperidines was described. In the presence of iodine, potassium persulfate and a suitable halogen source, intramolecular haloamination of 4-penten-1-amines and 5-hexen-1-amines proceeded readily, leading to the corresponding substituted piperidines in good isolated yields.

Vicinal haloamines such as 3-halopiperidines or 2-halomethylpiperidines have been used as important subunits in mechanism-based anti-tumour compounds,[1] they also constitute important parts in several natural products.[2]

Among the variety of methods developed, direct intramolecular haloamination of unfunctionalized 4-penten-1-amines or 5-hexen-1-amines would be one of the most straightforward routes to heterocyclic vicinal haloamines such as 3-halopiperidines or 2-halomethylpiperidines. The first generation direct haloamination of 4-penten-1-amines involved the utilization of dihalogens, and generally suffered from functional group tolerance due to the high reactivity of dihalogen.[3] The second generation chloroamination of 4-penten-1-amines developed by Göttlich *et al.* involved a Cu^{I}-catalyzed free radical cyclization of a pre-functionalized N–Cl substrate.[4] The reactions were carried out at elevated temperature, and 3-chloropiperidine products were obtained in good yields. A Lewis acid–$TiCl_3$ system was also reported to promote the free radical cyclization of N–Cl substrates at low temperature.[5] Again, functionalization of the substrates to the corresponding N–Cl derivatives was required prior to the cyclization. Later, Chemler,[6] Lu,[7] Michael,[8] Muñiz[9] and Liu[10] realized the intramolecular haloamination of *N*-sulfonamides, amides or *N*-carbamates using Pd^{II}-catalyzed cyclizations, and the corresponding 2-halomethyl heterocycles or 3-halopiperidines were obtained in good to excellent yields. In these reactions, palladium was used to activate the C=C double bonds, subsequent aminopalladation produced a C–Pd intermediate which could be cleaved by an additional molecule of copper halide to produce the final haloamination products. Recently, hypervalent iodines were also used in aminocyclization of several unfunctionalized olefins, but additional additives would generally be needed to complete the reactions.[11]

In addition to these methods, electrophile-induced cyclization of *N*-substituted alkenylimines developed by De Kimpe *et al.* was also one of the most efficient methods for the production of functionalized pyrrolidines and/or piperidines. For example, intramolecular cyclizations of *N*-substituted iminium olefins with PhSeX produced selenyl substituted cyclic iminium compounds which could be conveniently converted to the corresponding pyrrolidines or piperidines upon reductive deselenylation.[12] Cyclization of γ,δ-alkyenylimines with bromine produced the cyclic iminium bromides in good yields, and reduction of the thus obtained cyclic iminium bromides with sodium borohydride provided the corresponding bromopyrrolidines in excellent yields.[13] Pyrrolidines could also be obtained upon free radical debromination with Bu_3SnH–AIBN.[14] Cyclization of γ,δ-unsaturated aldimines with bromine produced the corresponding cyclic iminium bromides, and 5-alkoxy-1,2,3,4-tetrahydropyridines could be obtained *via* thermal rearrangement of 2,5-dialkoxypiperidines.[15] Starting from alkenylsulfinimines or alkenylsulfinamides, several functionalized cyclization products could also be obtained *via* electrophile-induced cyclization using phenylselenyl bromide, iodine and bromine as nucleophiles. Subsequent functional group transformation furnished a variety of functionalized pyrrolidines and piperidines.[16] Hydride-promoted ring expansion of 2-azaspiropyrrolinium salts produced the N-heterocyclic compounds, and alkaloids such as (−)-nitramine could be easily prepared in good overall yield using this method.[17]

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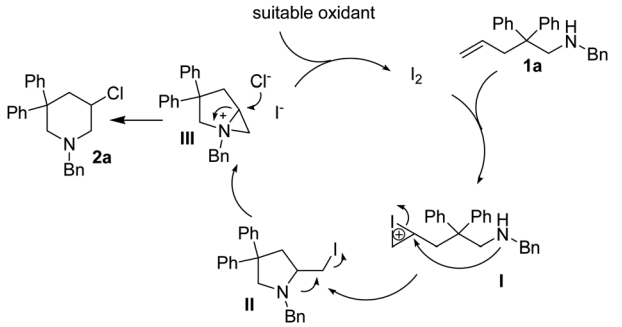
† Electronic supplementary information (ESI) available: General procedure for transition metal-free haloamination reaction, characterization of new compounds, and copies of spectra data of the compounds. See DOI: 10.1039/c4ra00383g



Scheme 1 Proposed reaction sequence for I_2-mediated chloroamination.

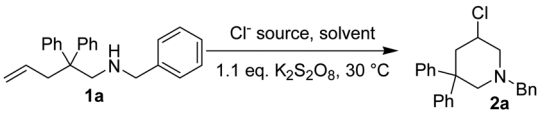
We have shown that $CuCl_2$ alone could act as both reaction promoter and the chlorine source, and Markovnikov vicinal chloroamines such as 2-chloromethylpyrrolidines could be obtained as the major products for intramolecular chloroamination of *N*-substituted 4-penten-1-amines.[18] The reaction could be carried out under mild conditions. However, it was difficult to get regiospecific products, and an additional step was generally required to fully convert the initially formed 2-chloromethylpyrrolidines to 3-chloropiperidines.[19] In this communication, we wish to report our recent progress on transition metal-free intramolecular haloamination of 4-penten-1-amine and 5-hexen-1-amine substrates. High regioselectivity was realized, and the corresponding halogenated piperidines could be isolated in good yields.

In our course of searching for new reagents for intramolecular haloamination of 4-penten-1-amines, we found that intramolecular iodoamination products could be observed when zinc iodide was used. However, it was difficult to completely reproduce the results in follow-up studies. After a thorough work, we found that the reaction could take place when the reaction was carried out in untreated ethereal solvents such as crude THF or crude diethyl ether, but failed in sodium dried solvents. We reasoned that the reaction was induced by molecular iodine formed *via* the oxidation of zinc iodide by dissolved oxygen or possible peroxides formed during long time storage of the solvents.

We then proposed a new route to 3-chloropiperidines as shown in Scheme 1. At first, iodine would react with the C=C double bond of substrate **1a** through normal electrophilic addition reaction, an iodonium 3-membered ring intermediate **I** was formed. Intramolecular nucleophilic attack of the nitrogen atom on the 3-membered ring of **I** produced the iodomethylpyrrolidine **II** as a temporary product. It was further converted to aziridinium intermediate **III** due to the good nucleophilicity of nitrogen atom and the good leaving property of I^-. In the presence of excess amount of Cl^-, nucleophilic ring opening of **III** by Cl^- produced 3-chloropiperidine as the final products.[12,13,16,17,20] Oxidation of I^- with a suitable oxidant would regenerate iodine and complete the reaction cycle.

Several issues will have to be considered in order for chloroamination of substrate **1a** to proceed successfully. The first issue is the iodine source. It could either be molecular iodine or other metal iodides. The second issue is the oxidant. The

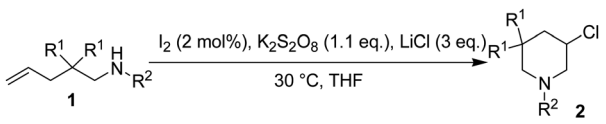
Table 1 Optimization of reaction conditions

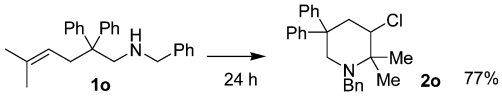
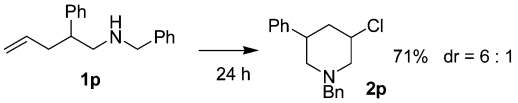
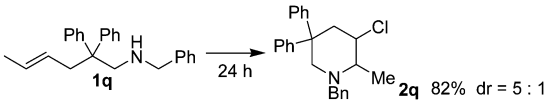


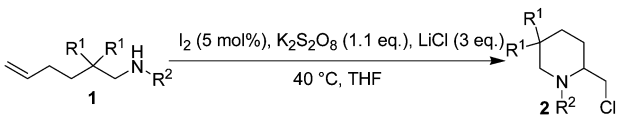
Entry	Catalyst (mol%)	Chlorine source	Solvent	Time (h)	Isolated yield (%)
1	I_2 (5)	LiCl (3 eq.)	THF	7	84
2	NaI (10)	LiCl (3 eq.)	THF	48	78
3	ZnI_2 (10)	LiCl (3 eq.)	THF	48	76
4	I_2 (2)	LiCl (3 eq.)	THF	12	83
5	I_2 (1)	LiCl (3 eq.)	THF	48	56
6	I_2 (2)	LiCl (3 eq.)	THF	12	80[a]
7	I_2 (2)	$CaCl_2$ (3 eq.)	THF	24	80
8	I_2 (2)	LiCl (3 eq.)	THF	12	83
9	I_2 (2)	LiCl (3 eq.)	DCM	12	18
10	I_2 (2)	LiCl (3 eq.)	EA	12	51
11	I_2 (2)	LiCl (3 eq.)	CH_3CN	12	26
12	I_2 (2)	LiCl (3 eq.)	Toluene	12	5
13	I_2 (2)	LiCl (3 eq.)	EtOH	12	6
14	I_2 (2)	LiCl (3 eq.)	DMF	12	22
15	I_2 (2)	LiCl (3 eq.)	DMSO	12	1
16	I_2 (2)	LiCl (3 eq.)	Acetone	12	20
17	I_2 (2)	LiCl (3 eq.)	1,4-Dioxane	12	19

[a] In argon atmosphere.

Table 2 I_2-catalyzed intramolecular chloroamination



Entry		Substrate R^1	Substrate R^2	Reaction time (h)	Isolated yield (%)
1	**1a**	Ph	Bn	12	83
2	**1b**	Ph	*p*-MeBn	12	78
3	**1c**	Ph	*p*-MeOBn	12	81
4	**1d**	Ph	*p*-FBn	18	80
5	**1e**	Ph	*p*-O_2NBn	18	52
6	**1f**	Ph	*i*Bu	18	61
7	**1g**	Ph	*n*Bu	18	69
8	**1h**	Me	Bn	24	30
9	**1i**	Me	*n*Bu	24	62
10	**1j**	$-(CH_2)_5-$		24	36
11	**1k**	Allyl	Bn	24	71
12	**1l**	H	Bn	24	26
13[a]	**1m**	Ts	Bn	24	N. R.
14[a]	**1n**	Ac	Bn	24	N. R.
15					
16					
17					
18	**1r**	Ph	Bn	48	71
19	**1s**	Ph	*p*-MeBn	48	66
20	**1t**	Ph	*p*-MeOBn	48	69
21	**1u**	Ph	*p*-FBn	48	62
22	**1v**	Ph	*p*-ClBn	48	74
23	**1w**	$-(CH_2)_5-$	Bn	48	65
24	**1x**	CH_3	Bn	48	57



[a] NR. = no reaction.

oxidant should meet the criteria such that it should be able to oxidize iodide to regenerate molecular iodine, but should not overoxidize iodide to OI^- or IO_2^-. The third issue is a suitable chlorine source. It should be chosen such that it could gradually release Cl^- to ensure a reasonable chloroamination, but should not participate any other reactions. The final issue is the reaction medium. It should have a reasonable solubility for both the oxidant and the chlorine source, no need to mention its ease of removal or handling.

Several easily available oxidants such as hydrogen peroxide, *tert*-butyl hydrogen peroxide (TBHP) and potassium persulfate were first tested. Hydrogen peroxide or TBHP failed to give good results possibly due to their overstrong oxidizing ability, and potassium persulfate was proven to be an ideal oxidant for the reaction. This was also in good agreement with the general knowledge that I^- could be oxidized to molecular iodine in the presence of potassium persulfate.[21] Potassium or zinc iodide gave similar results, and molecular iodine was proved to be more suitable for the reaction due to its good solubility in organic solvents.

After the screening of a suitable oxidant, other conditions such as iodine source, chlorine source and solvents were tested to optimize the reaction conditions, and the results are summarized in Table 1.

As indicated in Table 1, THF was more superior to other solvents, and lithium chloride gave better results than calcium chloride did. The former was chosen as the chlorine source due to its slightly better solubility in THF. Other reason for using inorganic salts as chlorine source was their ease of removal. The amount of iodine was reduced to 2 mol% to avoid the possible formation of I_3^-. Reducing the amount of iodine will also suppress the possible formation of 3-iodopiperidine.

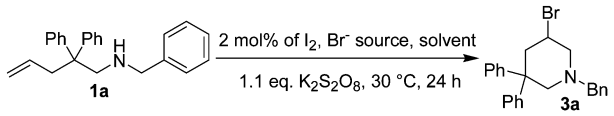
After establishing a general procedure for intramolecular chloroamination of **1a**, other 4-penten-1-amines and 5-hexen-1-amines were tested to study the scope of the substrates, and the results are presented in Table 2.

As shown in Table 2, Thorpe–Ingold effect was observed for the reaction. Substrates with diphenyl groups on the main chain (entries 1 to 7) gave good isolated yields, and substrates bearing small substituents (entries 8 to 11) or lacking of substituents on the main chain (entry 12) showed poor reactivity. In the case of substrate **1l**, most of the starting material could be recovered after reacting for 24 hours. Sulfonamide or acetamide substrates (entries 13 and 14) failed to react due to low nucleophilicity of the nitrogen atom. Substrates with substituents on C=C double bonds (entries 15 to 17) could also be converted, and acceptable diastereoselectivity was observed. 5-Hexen-1-amine substrates (entries 18 to 24) generally showed poor reactivity possibly due to the unfavorable entropy feature of the reaction. Increasing the amount of iodine, elevating the reaction temperature and elongating the reaction time led to the increase of isolated yields. Again, the course of the reaction was affected by the substituents on the main chain. Further, this type of substrates produced 2-chloromethylpiperidines instead of the 3-chloro-1-azacycloheptanes due to the stability of the six-member ring compounds.

In addition of the application of vicinal chloroamines in medicinal chemistry and organic chemistry, cyclic vicinal bromoamines were also found widespread applications in organic synthesis of a variety of N-heterocyclic compounds.[22] To this end, bromoamination of substrate **1a** was also tested to extend the application scope of the reaction. Conditions for chloroamination were first adopted, and results for screening of bromine source and reaction medium were summarized in Table 3.

In contrast to chloroamination in which LiCl could be used as chlorine source, inorganic salts were not ideal bromine sources for the bromoamination reactions (Table 3, entries 1 to

Table 3 Bromoamination of **1a** under different condition



Entry	Bromide	Solvent	NMR yield[a]
1	LiBr	THF	<5
2	$MnBr_2$	THF	11
3	$ZnBr_2$	THF	<5
4	TBAB	THF	<5
5	NBS	THF	36
6	Py·HBr	THF	57
7	Py·HBr	CH_2Cl_2	87 (73)[b]
8	Py·HBr	MeOH	<5
9	Py·HBr	EtOAc	30
10	Py·HBr	CH_2Cl_2–EtOAc	55
11[c]	Py·HBr	CH_2Cl_2	>99 (88)[b]

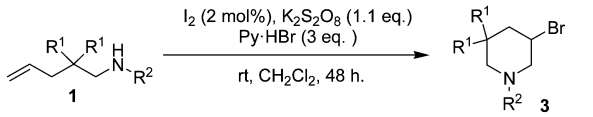
[a] Determined by crude ^{1}H NMR. [b] Data in parentheses are isolated yield. [c] Reaction time = 48 hours.

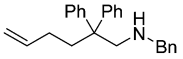
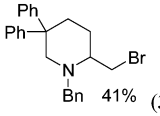
3) possibly due the poor solubility of these metal bromides in reaction media. Conventional bromine sources such as TBAB or NBS (entries 4 and 5) also failed to give satisfactory results. Finally, pyridinium bromide was chosen as the bromine source. Good result was observed when the reaction was carried out in dichloromethane, possibly due to its good solubility in haloalkanes (entry 7). Complete conversion and excellent isolated yield was observed after 48 hours (entry 11).

After establishing a general procedure for bromoamination of substrate **1a**, other substrates were also subjected to the same reaction to extend the application scope of the reaction, and the results were summarized in Table 4.As shown in Table 4, good to excellent results were obtained for substituted 4-penten-1-amine substrates (entries 1 to 8), and substrates lacking of efficient Thorpe–Ingold functional groups generally gave poor isolated yields at specified reaction time (entries 9 to 11). 5-Hexen-1-amine substrate gave low yield (entry 12) possibly due to the unfavourable entropy feather of the cyclization reaction.

In summary, catalytic amount of molecular iodine can be used to promote intramolecular haloamination of unfunctionalized olefins. Good isolated yields were obtained for substituted 3-halopiperidines and 2-halomethylpiperidines. The reaction requires the presence of a suitable oxidant to regenerate the iodine. The current study provided an easy entry to a variety of substituted piperidines which could be used as important intermediates for both medicinal chemistry and organic synthesis.

Table 4 I_2-mediated bromoamination of unfunctionalized olefins



Entry	Substrate R^1	Substrate R^2	Isolated yield (%)
1	Ph	Bn	86 (**3a**)
2	Ph	*p*-MeBn	90 (**3b**)
3	Ph	*p*-MeOBn	86 (**3c**)
4	Ph	*p*-FBn	83 (**3d**)
5	Ph	*p*-ClBn	80 (**3e**)
6	Ph	*p*-O_2NBn	82 (**3f**)
7	Ph	*i*Pr	65 (**3g**)
8	Ph	*i*Bu	72 (**3h**)
9	Me	Bn	63 (**3i**)
10	–$(CH_2)_5$–	Bn	66 (**3j**)
11	H	Bn	39 (**3k**)
12			 41% (**3l**)

Acknowledgements

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