Iodoamidation of olefins with chloramine salts and iodine in aqueous media†

Satoshi Minakata* and Junpei Hayakawa

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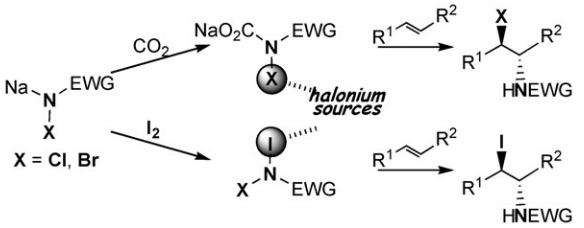
An efficient, unique, and convenient method for the iodoamidation of olefins with chloramine salts and I_2 in aqueous media is described. This method was applicable to a wide range of olefins, including aromatic, aliphatic, and electron-deficient olefins.

Amidohalogenation reactions, which are in widespread use, involve the conversion of common petroleum olefins into vicinal haloamine products *via* the addition of amide and halogen units to carbon–carbon double bonds.[1] Haloamine derivatives are versatile synthetic intermediates and can be used in the synthesis of functional materials and biologically active compounds.[2] Among the halogens, iodine is a powerful substituent for organic transformations such as transition metal-catalyzed, radical and ionic reactions. Nevertheless, only a few examples have been reported on the direct iodoamidation of olefins. Although the use of iodine azide (IN_3), prepared by reacting sodium azide with iodine monochloride, is a well-known method for the introduction of an iodine atom and a nitrogen unit into olefins,[3] azides require careful handling due to their high reactivity, explosiveness, and toxicity. Alternative methods for iodoamidation using $I(py)_2BF_4$[4a] or I_2[4b] as iodine sources were developed by Barluenga's and Corey's groups. Since the products as well as the transformations are very useful, Corey's group successfully used the method for a key step of the synthesis of the anti-influenza neuramidase inhibitor, oseltamivir.[4c] These methods are very valuable, but stoichiometric or larger amounts of HBF_4 or $SnCl_4$ are required, the nitrogen source is restricted to the reaction solvent (acetonitrile), and only cyclohexene derivatives were employed as substrates. Thus, more practical and efficient iodoamidation is desired.

We previously reported on the chloro-[5a] and bromoamidation[5b] of olefins using haloamine-T under an atmosphere of CO_2. We hypothesized that a unique reaction is induced by the insertion of CO_2 into the N–Na bond of haloamine-T, and this species then generates a cyclic halonium intermediate on the reaction with an olefin. Based on the proposed mechanism, a general and facile iodoamidation was devised as follows. Haloamine-T reacts with iodine to give *N*-halo-*N*-iodo-*p*-toluenesulfonamide.[6] Among the three substituents on the nitrogen, the iodo substituent would act as an iodonium ion because of its low electronegativity (Scheme 1). Based on this scenario, we report herein on the iodoamidation of olefins using chloramine salts and iodine in an aqueous media.[7]

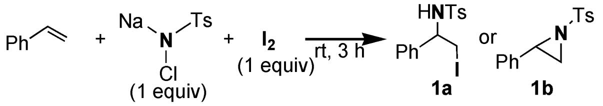


Scheme 1 Strategy for the iodoamidation of olefins.

Although we reported on the iodine-catalyzed aziridination of olefins using chloramine-T (CT) in organic or aqueous media,[8] no iodoamidated products were obtained under the reaction conditions. In order to achieve the desired iodoamidation, a stoichiometric amount of iodine was used. When styrene was treated with a stoichiometric amount of iodine and CT in an organic solvent (acetonitrile or *n*-hexane) or neat (styrene only), the corresponding aziridine was detected in the reaction mixture in all cases (Table 1, entries 1–3). On the contrary, when the reaction was conducted in water, the iodoamidated compound **1a** was obtained in 53% yield with complete regioselectivity. Iodoamidated compounds could be prepared by the ring opening of aziridines with iodide, but it is known that in the case of the ring opening of aziridine **1b** with iodide, the reverse regioisomer is produced, compared with **1a**,[9] indicating that iodoamidation in water is not involved in the formation of the aziridine. Thus, this present iodoamidation and ring opening of aziridines with iodide can be regarded as a complementary method for the formation of iodoamidated compounds. Unexpectedly, bromamine-T was not effective for the reaction.

In order to improve the efficiency of the iodoamidation, the reaction conditions were optimized. The use of two equivalents of CT increased the yield of the product to 73% (Table 2, entry 1). The addition of a small amount of *n*-hexane (100 μL), almost the same volume as styrene, resulted in a further improvement in the efficiency (Table 2 entry 1). The reaction of styrene derivatives containing electron-withdrawing groups afforded

Table 1 Iodoamidation of styrene with CT and I_2 in water

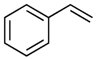
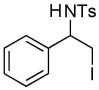
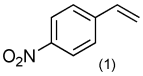
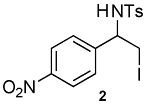
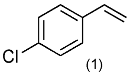
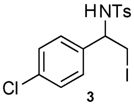
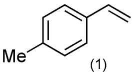
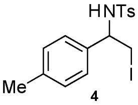
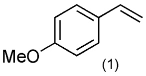
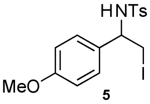
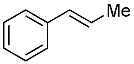
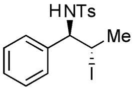
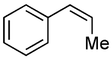
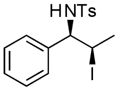
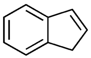
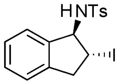
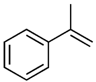
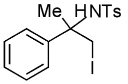


Entry	Solvent (2 mL)	Yield (%)	
		1a	**1b**
1	MeCN	0	52
2	*n*-Hexane	0	32
3	Styrene	0	65
4	H_2O	53	0

Department of Applied Chemistry, Graduate School of Engineering, Osaka University, Yamadaoka 2-1, Suita, Osaka 565-0871, Japan. E-mail: minakata@chem.eng.osaka-u.ac.jp; Fax: +81 6-6879-7402

† Electronic supplementary information (ESI) available: NMR spectra and X-ray structure analysis. CCDC 778523. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c0cc03855e

Table 2 Iodoamidation of aromatic olefins with CT and I_2 in aqueous media[a]

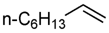
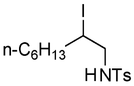
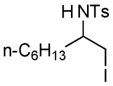
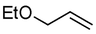
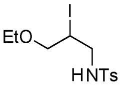
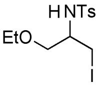
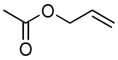
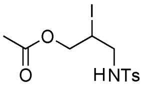
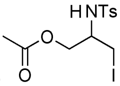
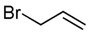
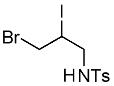
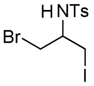
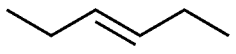
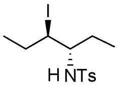
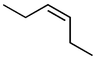
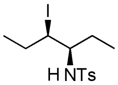
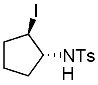
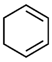
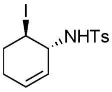
Entry	Olefin (equiv.)	Adduct	Yield (%)
1	 (1)	 **1**	73 85[b]
2	 (1)	 **2**	84
3	 (1)	 **3**	91[c]
4	 (1)	 **4**	74[b]
5	 (1)	 **5**	81[b]
6	 (1.5)	 **6**	67[c]
7	 (1.7)	 **7**	99
8	 (1)	 **8**	87[b]
9	 (1.5)	 **9**	74[b]

[a] Reaction conditions: CT (1 mmol), I_2 (0.5 mmol), olefin (0.5–0.85 mmol), H_2O (2 mL), rt, 1 h. [b] *n*-Hexane (100 μL) was added. [c] CH_2Cl_2 (100 μL) was added.

the corresponding adducts **2** and **3** in good yields (entries 2 and 3). The reaction of electron-rich styrene derivatives resulted in the production of significant amounts of oligomerized compounds. This situation could be circumvented by the addition of a small amount of organic solvent to the reaction mixture (entries 4 and 5). The iodoamidation reaction was applied to disubstituted aromatic olefins. In these cases, the use of 1.5–1.7 equivalents of the substrates afforded good yields (entries 6, 7 and 9). When *trans*- and *cis*-β-methylstyrenes were treated with CT and iodine in water, the corresponding adducts **6** and **7** were obtained with complete stereoselectivity (entries 6 and 7). Although the stereocontrol of addition reactions to *cis*-β-methylstyrene is very difficult, it is noteworthy that the stereoselectivity of the present iodoamidation reactions was completely controlled. Indene was converted into the *trans* iodoamidated product **8** in high yield. The X-ray structure of the product confirmed that the stereochemistry of the iodoamidated compound **8** was *trans* adduct (entry 8).[10] The formation of oligomers (entries 4 and 5) and the complete stereoselectivity of the reaction (entries 6–8) suggest that cyclic iodonium intermediates are likely involved in the reaction. The iodoamidation of α-methylstyrene produced the iodoamidated compound **9** containing a quaternary carbon center (entry 9).

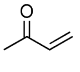
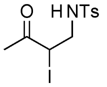
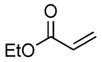
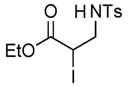
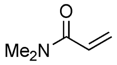
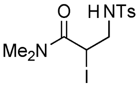
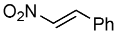
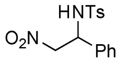
The successful transformation of aromatic olefins into iodoamidated compounds in an aqueous medium prompted us to investigate the use of aliphatic olefins as substrates (Table 3). The simple aliphatic olefin, 1-octene, was subjected to the above conditions and produced iodoamidated compounds with a mixture of regioisomers (entry 1). Functional groups such as ethers, esters and halogens were compatible with this addition reaction (entries 2–4). Complete stereoselectivity was observed in the reaction of internal and cyclic olefins (entries 5–7). The reaction of a cyclic olefin was particularly fast, and prolonging the reaction time afforded the corresponding aziridine *via* cyclization of the iodoamidated compound **16**. A conjugated cyclic olefin, cyclohexadiene, was transformed to compound **17** as a sole product with stereo-, regio-, and chemoselectivity.

Table 3 Iodoamidation of aliphatic olefins with CT and I_2 in aqueous media[a]

Entry	Olefin	Adducts	Yield (%)
1		 **10a**  **10b** (56 : 44)	85
2		 **11a**  **11b** (63 : 37)	84
3		 **12a**  **12b** (87 : 13)	82
4		 **13a**  **13b** (81 : 19)	73
5		 **14**	61[b]
6		 **15**	92[b]
7		 **16**	83[c]
8		 **17**	64

[a] Reaction conditions: CT (1 mmol), I_2 (0.5 mmol), olefin (1 mmol), H_2O (2 mL), rt, 1 h. [b] CH_2Cl_2 (100 μL) was added. [c] Reaction time: 2 min.

Table 4 Iodoamidation of electron-deficient olefins with CT and I_2 in aqueous media[a]

Entry	Olefin (equiv.)	Adduct	Yield (%)
1	 (2)	 **18**	68
2	 (1)	 **19**	95
3	 (2)	 **20**	83[b]
4	 (1.5)	 **21**	99[c]

[a] Reaction conditions: CT (1 mmol), I_2 (0.5 mmol), olefin (0.5–1 mmol), H_2O (2 mL), rt, 1 h. [b] CH_2Cl_2 (100 μL) was added. [c] Et_2O (400 μL) was added.

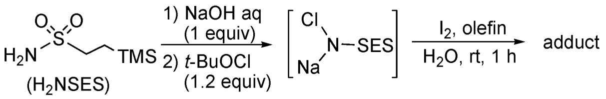
The method was also found to be applicable to electron-deficient olefins (Table 4). When methyl vinyl ketone was treated with CT and iodine in water, the α-iodo-β-amidated ketone **18** was obtained with complete regioselectivity (entry 1). The reaction of an α,β-unsaturated ester with CT and iodine proceeded in high yield (entry 2). An α,β-unsaturated amide was also converted into an iodoamidated compound (entry 3). The reaction of *trans*-β-nitrostyrene gave an α-amidated compound **21**, which contained no iodine substituent, by treatment with aqueous $Na_2S_2O_3$ as a work-up process[11] (entry 4). On the other hand, the reaction of an electron-rich olefin[12] such as butyl vinyl ether gave a complicated mixture.

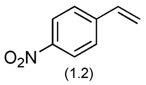
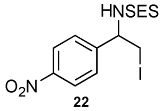
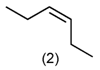
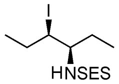
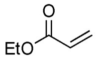
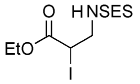
While the above findings demonstrate that the present method can be used in reactions with wide range of olefins, the nitrogen source was restricted to the use of chloramine-T. To extend the scope of the reaction, the one pot iodoamidation from a simple amide involving the *in situ* generation of a chloramine salt was examined, as shown in Table 5. To obtain primary amines more readily, the introduction of trimethylsilylethanesulfonamide was investigated. The sulfonamide was treated with aqueous NaOH and *t*-BuOCl to generate the chloramine salt *in situ*. The unstable intermediate, without isolation, was subjected to the present iodoamidation reaction using three types of olefins, and the desired adducts **22–24** were obtained in good to excellent yields.

Although the precise mechanism of the reaction is unclear at present, a proposed mechanism is shown in ESI.†

From the results of the present study, an efficient and convenient method was developed, which represents a new and general procedure for the iodoamination of olefins. The method has a very broad scope in terms of aromatic, aliphatic, and electron-deficient olefins that can be used, thus allowing access to a wide range of iodoamidated compounds. Moreover, the iodo substituent is a versatile functional group that can be used in further transformations. This reaction proceeds under extremely mild conditions with high selectivity and efficiency.

Table 5 One pot iodoamidation from sulfonamide



Entry	Olefin (equiv.)	Adduct	Yield (%)
1	 (1.2)	 **22**	82
2	 (2)	 **23**	97[a]
3	 (2)	 **24**	73

[a] CH_2Cl_2 (100 μL) was added.

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Notes and references

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