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Tetrahedron
Tetrahedron 62 (2006) 12247–12251

Electrophilic cyclization of *N*-alkenylamides using a chloramine-T/I_2 system

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Received 28 August 2006; revised 4 October 2006; accepted 5 October 2006
Available online 27 October 2006

Abstract—A new protocol for the cyclization of *N*-alkenylamides using chloramine-T and iodine is described. When *N*-alkenylsulfonamides are treated with chloramine-T and iodine, three- to six-membered *N*-heterocycles are obtained with complete stereoselectivity. The method is compatible with the cyclization of the allylbenzamide or allylbenzthioamide to afford an oxazoline or thiazoline derivative, respectively. Mechanistic studies indicate that the chloramine-T/I_2 system functions as an effective iodonium species.
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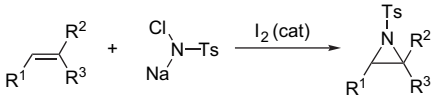
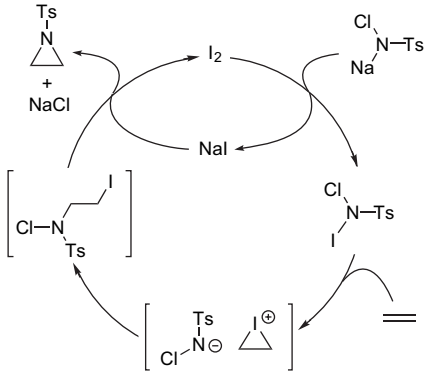
1. Introduction

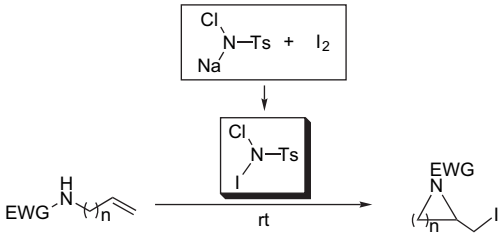
The functionalization of a double bond activated by an electrophile is one of the most useful reactions in organic synthesis. Ring formation through the reaction of a heteroatom and a cyclic onium ion is a versatile method for the stereocontrolled synthesis of heterocycles.[1] The electrophilic cyclization of nonconjugated olefinic carboxylic acids was initially exploited by Bougault.[2] Electrophiles, such as halogens, halo reagents, selenium derivatives, and certain metallic salts, for the activation of the olefinic moiety have been developed for use in this type of cyclization. Barluenga and González reported on a versatile reagent, bis(pyridine)iodine tetrafluoroborate (IPy_2BF_4), not only for the cyclization[3] but also for many other useful and unique transformations.[4] Quite recently, we reported that *tert*-butyl hypoiodite (*t*-BuOI)[5] is a powerful reagent for the cyclization of *N*-alkenylamides[6] and the aziridination of olefins with sulfonamides.[7] Since the polarity of the O–I of the reagent should be an important factor in such reactions, an N–I bond having electron-withdrawing groups on the nitrogen would be expected to act in a similar fashion. Our group (Eq. 1)[8] and the Sharpless group[9] simultaneously reported on the iodine- or bromine-catalyzed aziridination of olefins using chloramine-T. In our study, we proposed that a reactive species having N–I bond, generated from chloramine-T and iodine, is involved in the reaction path and functions as a key intermediate (Scheme 1). From these points of view, we report here on the use of inexpensive chloramine-T and I_2 as reagents for the cyclization of *N*-alkenylamides (Scheme 2).



(1)



Scheme 1. Proposed path for the I_2-catalyzed aziridination of olefins using chloramine-T.



Scheme 2. A reactive species having an N–I bond for the cyclization of *N*-alkenylamides.

Keywords: Alkenylamides; Chloramine-T; Iodine; Heterocycles.
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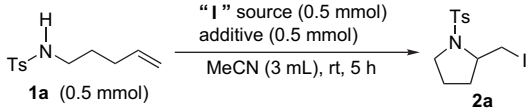
0040–4020/$ - see front matter © 2006 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2006.10.003

2. Results and discussion

To evaluate the ability of the chloramine-T/I_2 system in the electrophilic cyclization of *N*-(4-pentenyl)-*p*-toluenesulfonamide (**1a**), some related reagents were employed in the reaction (Table 1). Although the desired cyclization in the presence of the only iodine proceeded, the yield of iodomethylated *N*-tosylpyrrolidine **2a** was moderate, under the reaction conditions used. The addition of *t*-BuONa to the above conditions was ineffective. As expected, the use of a combination of iodine and chloramine-T successfully caused efficient cyclization, giving **2a** in 98% yield. The use of sodium iodide as an 'I' source instead of iodine vastly decreased the efficiency. The presence of species acting as an iodonium ion should be important to induce this cyclization.

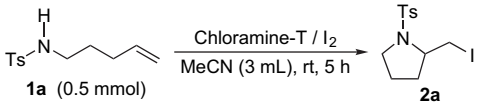
Table 1. Evaluation of iodinating reagents in the cyclization of *N*-(4-pentenyl)-*p*-toluenesulfonamide



'I' source	Additive	Yield (%)	Recovery (%)
I_2	—	61	25
I_2	*t*-BuONa	63	37
I_2	Chloramine-T	98	0
NaI	Chloramine-T	52	46

The effect of the amounts of the two reagents, iodine and chloramine-T, on cyclization was examined as shown in Table 2. Even if a half amount of either chloramine-T or iodine against **1a** was employed in the reaction, almost the same efficiency was observed, compared with the use of stoichiometric amounts of the two reagents. Interestingly, it was found that a half amount of chloramine-T and iodine is sufficient for the reaction to reach completion in almost quantitative yield (entry 4). These results indicate that both I atoms are able to serve as iodonium species.

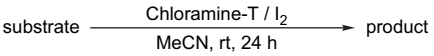
Table 2. Optimization of the amount of the reagents

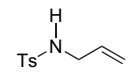
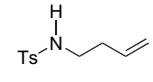
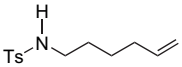
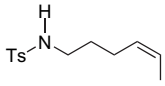
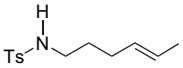


Entry	Chloramine-T (mmol)	I_2 (mmol)	Yield (%)
1	0.50	0.50	98
2	0.25	0.50	97
3	0.50	0.25	95
4	0.25	0.25	97

A variety of *N*-alkenylsulfonamides were examined using the chloramine-T/I_2 system under selected conditions (method A and B) as shown in Table 3. In method A, stoichiometric amounts of chloramine-T and I_2 were used against the *N*-alkenylsulfonamides and in method B a half amount of the reagents were used. Method A gave good results for the formation of aziridine **2b** by the cyclization of *N*-allyl-*p*-toluenesulfonamide (**1b**). The aziridination of **1b** also proceeded by method B, a rather low yield was

Table 3. Cyclization of a variety of alkenylsulfonamides using the chloramine-T/I_2 system



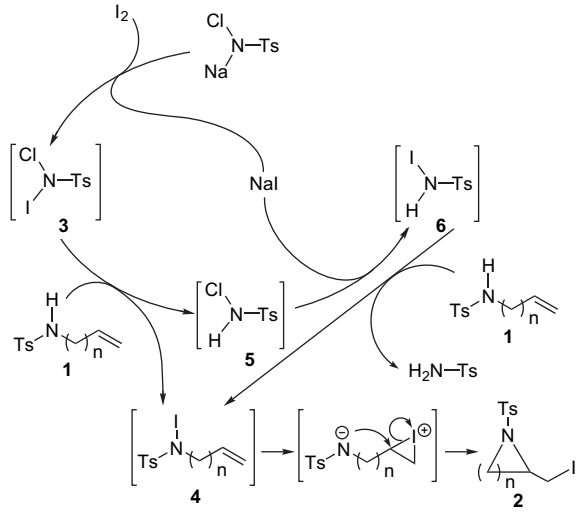
Substrate	Product	Yield (%) A[a]	Yield (%) B[b]
 (1b)	 (2b)	81	54
 (1c)	 (2c)	8	8
 (1d)	 (2d)	45	40
 (1e)	 (2e)	78[c]	37[c]
 (1f)	 (2f)	80[c]	62[c]

[a] Method A: substrate (0.50 mmol)/chloramine-T (0.50 mmol)/I_2 (0.50 mmol).
[b] Method B: substrate (0.50 mmol)/chloramine-T (0.25 mmol)/I_2 (0.25 mmol).
[c] Reaction time: 5 h.

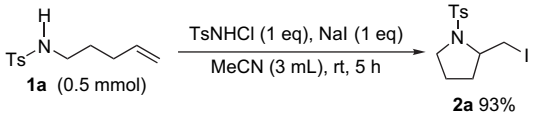
obtained, under the conditions used. Although the efficiency of cyclization of **1c** was unsatisfactory, a four-membered nitrogen heterocycle, an azetidine was obtained using these methods. In the reaction, 3-iodo-*N*-tosylpyrrolidine via 5-*endo* cyclization and ICl adduct to the C–C double bond were obtained. When *N*-(5-hexenyl)-*p*-toluenesulfonamide (**1d**) was employed in the reaction using both method A and B, moderate yields of the corresponding piperidine were obtained, in which ICl adduct was also observed. Both *trans*- and *cis*-(4-hexenyl)-*p*-toluenesulfonamides, **1e** and **1f**, were converted into the corresponding pyrrolidines in good yields with complete stereoselectivities, indicating that the present reaction proceeds through a three-membered iodonium ion intermediate.

Although the precise mechanism and the nature of the active species are unclear at present, the following findings provide support for the reaction pathway depicted in Scheme 3. As proposed in our previous work,[8] the reaction of chloramine-T with iodine is very rapid, affording *N*-chloro-*N*-iodo-*p*-toluenesulfonamide (**3**). If the active species having an N–I bond reacts with *N*-alkenylsulfonamides **1** in a manner similar to *t*-BuOI,[6] the species **3** might iodinate the nitrogen of the sulfonamides, not an olefinic moiety. In fact, when a solution of *N*-methyl-*p*-toluenesulfonamide (methyl, δ 2.41 ppm) in CD_3CN was treated with chloramine-T and I_2, a new methyl singlet at δ 3.14 ppm, identical to the peak produced in the reaction of *N*-methyl-*p*-toluenesulfonamide and *t*-BuOI,[6] appeared. The NMR study supports the formation of *N*-iodo-*N*-alkenylsulfonamides **4** by the reaction of sulfonamides with species **3** generated from chloramine-T and iodine. Cyclization of *N*-iodinated alkenylsulfonamides would be expected to proceed via a

three-membered iodonium ion, the generation of which would be confirmed by the complete stereoselectivity shown in Table 3. In order to investigate the fact that even a half amount of chloramine-T and I_2 against *N*-alkenylsulfonamides, especially **1a**, is sufficient for the cyclization, the following experiment was performed. Since it is likely that *N*-chlorinated sulfonamide **5** and NaI would be formed after the reaction of **1** and **3**, sulfonamide **1a** was treated with **5**, which was prepared separately,[10] in the presence of NaI under the reaction conditions, leading to efficient cyclization (Scheme 4). These results suggest that compound **5** might be converted into the active species **6** with NaI, after which the species would function as a source of iodonium ions for the cyclization.



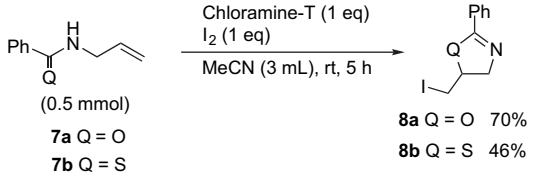
Scheme 3. Plausible reaction pathway to *N*-heterocycles.



Scheme 4. Cyclization of *N*-alkenylamide in the presence of TsNHCl and NaI.

Although the cyclization of *N*-(4-pentenyl)amides having benzoyl and Boc groups instead of tosyl group were carried out to investigate the scope and limitation of the reagents, the corresponding *N*-heterocycles were not obtained. From these results, the acidity of the tosylamide moiety would be important to perform the iodination with species **3**.

However, *N*-allylbenzamide or *N*-allylbenzthioamide derivatives were found to be employed in the cyclization (Scheme 5). The reaction of *N*-(2-propenyl)benzamide (**7a**) with stoichiometric amounts of chloramine-T and iodine in acetonitrile at room temperature gave the iodomethylated oxazoline **8a** in 70% yield. The thioamide derivative **7b** was allowed to react under the reaction conditions, affording the corresponding thiazoline **8b** in moderate yield.



Scheme 5. Cyclization of *N*-allylbenz(thio)amides.

3. Conclusions

A simple and efficient method for the cyclization of various alkenylamides using chloramine-T and I_2 was developed. The precise mechanism of this reaction is presently unclear, but auxiliary experiments suggest that *N*-iodo-*N*-alkenylamides are generated as intermediates. Since the cyclization pathway involves a cyclic iodonium ion, the stereochemistry could be completely controlled. Chloramine-T and iodine are both readily available, inexpensive and easily handled, and the combination of these reagents enabled both I atoms of iodine to function as iodonium species. Applications of the system to other organic synthesis are currently in progress.

4. Experimental

4.1. General experimental method

All reactions were carried out under an atmosphere of nitrogen. Acetonitrile was freshly distilled over CaH_2. ^1H and ^{13}C NMR spectra were recorded at 270 and 68 MHz or 400 and 100 MHz, respectively. Flash column chromatography (FCC) was performed using silica gel FL60D (Fuji Silysia Chemical Co.). Analytical thin layer chromatography was performed using EM reagent and 0.25 mm silica gel 60-F plates. Visualization was accomplished with UV light and spraying with an ethanolic phosphomolybdic acid solution followed by heating.

4.2. General procedure for the preparation of *N*-alkenylamides

Following the general procedure of Ing's method,[11] a mixture of an alkenyl halide (50 mmol), potassium phthalimide (100 mmol), and dimethylformamide (50 mL) was heated at 85 °C for 3 h. After cooling to room temperature, Et_2O (100 mL) and H_2O (100 mL) were added to the reaction mixture. The aqueous layer was extracted with Et_2O (50 mL×2). The combined organic layer was washed successively with water (100 mL×2) and brine (100 mL) and dried over K_2CO_3, and the solvent was removed under reduced pressure to give the white solid. A slurry of the given phthalimide derivative (50 mmol), EtOH (50 mL) and hydrazine hydrate (100 mmol) was heated to reflux for 30 min. After cooling to room temperature, the reaction mixture was filtered through a paper filter, and the solid was washed with dichloromethane (250 mL) to give an alkenylamine. Triethylamine (20 mL) and an acid chloride (50 mmol) was added to the solution of the amine obtained at 0 °C. The solution was allowed to warm to room temperature over the course of 12 h. After washing with 1 N hydrochloric acid (100 mL), 1 N aqueous K_2CO_3 (100 mL), water (100 mL×2), and brine (100 mL) and dried over K_2CO_3, and the solvent was removed under reduced pressure to give the yellow oil.

Purification by flash chromatography (hexane/ethyl acetate, 9:1) led to isolation of desired *N*-alkenylamide as a colorless oil.

4.3. General procedure for cyclization of *N*-alkenylamides

Method A: chloramine-T (0.5 mmol) and iodine (0.5 mmol) were added to a solution of *N*-alkenylamides (0.5 mmol) in acetonitrile (3 mL). The mixture was allowed to stir in the dark at room temperature for the indicated times under an atmosphere of nitrogen, quenched with 0.3 M aqueous $Na_2S_2O_3$ (3 mL), extracted with CH_2Cl_2, dried over $MgSO_4$, and the extract was then concentrated under vacuum. The residue was purified by flash column chromatography on silica gel (eluent: hexane/ethyl acetate).

Method B: chloramine-T (0.5 mmol) and iodine (0.5 mmol) of method A was changed to chloramine-T (0.25 mmol) and iodine (0.25 mmol).

4.3.1. 2-Iodomethyl-1-(*p*-toluenesulfonyl)pyrrolidine (2a). Spectroscopic data were in agreement with those of previously published material.[12] Colorless crystalline solid; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.50–1.55 (m, 1H), 1.76–1.90 (m, 3H), 2.44 (s, 3H), 3.14–3.26 (m, 2H), 3.46–3.51 (m, 1H), 3.61 (dd, 1H, J=2.8, 9.6 Hz), 3.70–3.76 (m, 1H), 7.34 (d, 2H, J=8.0 Hz), 7.72 (d, 2H, J=8.0 Hz); ^{13}C NMR ($CDCl_3$, 68 MHz): δ 11.5, 21.5, 23.8, 32.0, 50.1, 60.7, 127.5, 129.8, 134.2, 143.7.

4.3.2. 2-Iodomethyl-1-(*p*-toluenesulfonyl)aziridine (2b). Spectroscopic data were in agreement with those of previously published material.[13] Colorless solid; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 2.18 (d, 1H, J=3.2 Hz), 2.45 (s, 3H), 2.83 (d, 1H, J=6.8 Hz), 3.01–3.12 (m, 3H), 7.36 (d, 2H, J=8.2 Hz), 7.84 (d, 2H, J=8.2 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 2.5, 21.8, 36.3, 41.1, 128.1, 129.5, 134.3, 144.7.

4.3.3. 2-Iodomethyl-1-(*p*-toluenesulfonyl)azetidine (2c). Spectroscopic data were in agreement with those of previously published material.[6] Colorless crystalline solid; ^{1}H NMR ($CDCl_3$, 270 MHz): δ 1.85–1.99 (m, 1H), 2.03–2.15 (m, 1H), 2.47 (s, 3H), 3.28 (dd, 1H, J=9.9, 10.0 Hz), 3.42 (dt, 1H, J=8.3, 8.3 Hz), 3.54 (dd, 1H, J=3.8, 9.9 Hz), 3.65 (dt, 1H, J=3.7, 8.3 Hz), 3.89–4.00 (m, 1H), 7.38 (d, 2H, J=8.2 Hz), 7.72 (d, 2H, J=8.2 Hz); ^{13}C NMR ($CDCl_3$, 68 MHz): δ 9.8, 21.7, 24.1, 45.9, 62.9, 128.2, 129.8, 131.7, 144.2.

4.3.4. 2-Iodomethyl-1-(*p*-toluenesulfonyl)piperidine (2d). Spectroscopic data were in agreement with those of previously published material.[12] Colorless oil; ^{1}H NMR ($CDCl_3$, 270 MHz): δ 1.25–1.58 (m, 5H), 2.03–2.12 (m, 1H), 2.43 (s, 3H), 2.94 (dt, 1H, J=2.3, 14.2 Hz), 3.22 (dd, 1H, J=5.0, 10.0 Hz), 3.36 (dd, 1H, J=10.0, 10.0 Hz), 3.71 (dd, 1H, J=3.5, 14.2 Hz), 4.24–4.28 (m, 1H), 7.30 (d, 2H, J=8.1 Hz), 7.72 (d, 2H, J=8.1 Hz); ^{13}C NMR ($CDCl_3$, 68 MHz): δ 4.0, 17.7, 21.5, 24.3, 26.2, 40.6, 53.8, 127.0, 129.8, 137.9, 143.3.

4.3.5. *erythro*-2-(1-Iodoethyl)-1-(*p*-toluenesulfonyl)pyrrolidine (2e). Spectroscopic data were in agreement with those of previously published material.[12] Colorless crystalline solid; ^{1}H NMR ($CDCl_3$, 270 MHz): δ 1.31–1.44 (m, 1H), 1.68–2.06 (m, 3H), 1.83 (d, 3H, J=7.0 Hz), 2.45 (s, 3H), 3.27–3.36 (m, 1H), 3.44–3.53 (m, 1H), 3.96–4.02 (m, 1H), 4.75 (dq, 1H, J=3.8, 7.0 Hz), 7.34 (d, 2H, J=8.1 Hz), 7.72 (d, 2H, J=8.1 Hz); ^{13}C NMR ($CDCl_3$, 68 MHz): δ 21.5, 24.4, 25.1, 30.4, 36.8, 49.3, 65.5, 127.5, 129.7, 135.1, 143.6.

4.3.6. *threo*-2-(1-Iodoethyl)-1-(*p*-toluenesulfonyl)pyrrolidine (2f). Spectroscopic data were in agreement with those of previously published material.[12] Colorless crystalline solid; ^{1}H NMR ($CDCl_3$, 270 MHz): δ 1.33–1.43 (m, 1H), 1.78–1.93 (m, 3H), 1.87 (d, 3H, J=7.0 Hz), 2.44 (s, 3H), 3.10–3.17 (m, 1H), 3.34–3.39 (m, 2H), 4.71–4.81 (m, 1H), 7.32 (d, 2H, J=8.3 Hz), 7.74 (d, 2H, J=8.3 Hz); ^{13}C NMR ($CDCl_3$, 68 MHz): δ 20.4, 21.6, 24.4, 28.5, 30.2, 51.4, 65.4, 127.6, 129.8, 133.7, 143.8.

4.3.7. 5-Iodomethyl-2-phenyl-2-oxazoline (8a). Spectroscopic data were in agreement with those of previously published material.[6] Colorless oil; ^{1}H NMR ($CDCl_3$, 270 MHz): δ 3.28–3.42 (m, 2H), 3.80 (dd, 1H, J=6.6, 15.1 Hz), 4.17 (dd, 1H, J=8.1, 15.1 Hz), 4.75–4.86 (m, 1H), 7.38–7.51 (m, 3H), 7.92–7.95 (m, 2H); ^{13}C NMR ($CDCl_3$, 68 MHz): δ 7.8, 60.7, 78.2, 127.3, 128.0, 128.2, 131.3, 163.2.

4.3.8. 5-Iodomethyl-2-phenyl-2-thiazoline (8b). Spectroscopic data were in agreement with those of previously published material.[6] Yellow oil; ^{1}H NMR ($CDCl_3$, 270 MHz): δ 3.23 (dd, 1H, J=10.0, 10.1 Hz), 3.38 (dd, 1H, J=5.3, 10.0 Hz), 4.17–4.25 (m, 1H), 4.26 (dd, 1H, J=8.1, 19.5 Hz), 4.62 (dd, 1H, J=1.5, 19.5 Hz), 7.38–7.50 (m, 3H), 7.79–7.82 (m, 2H); ^{13}C NMR ($CDCl_3$, 68 MHz): δ 9.9, 51.5, 69.8, 128.4, 128.8, 131.4, 132.8, 166.3.

4.3.9. 3-Iodo-1-(*p*-toluenesulfonyl)pyrrolidine. Colorless crystalline solid; mp 99–103 °C; TLC R_f 0.17 (hexane/EtOAc, 4:1); IR (KBr): 1345, 1159 cm^{-1}; ^{1}H NMR ($CDCl_3$, 270 MHz): δ 2.07–2.33 (m, 2H, –NCH_2CHCH_2–), 2.44 (s, 3H, ArCH_3), 3.44 (t, 2H, J=6.8 Hz, –$CHCH_2CH_2N$–), 3.56 (dd, 1H, J=4.7, 11.5 Hz, –NC*H*HCH–), 3.90 (dd, 1H, J=5.8, 11.5 Hz, –NCH*H*CH–), 4.13–4.21 (m, 1H, –NCH_2CHCH_2–), 7.34 (d, 2H, J=8.0 Hz, Ar*H*), 7.73 (d, 2H, J=8.0 Hz, Ar*H*); ^{13}C NMR ($CDCl_3$, 68 MHz): δ 17.3, 21.5, 38.1, 46.9, 58.6, 127.5, 129.8, 133.8, 143.8; MS (CI, methane): 352 ([M+1]$^+$, 100), 224 ([M−I]$^+$, 14), 196 ([M−Ts]$^+$, 10), 184 (18), 155 (13); Anal. Calcd for $C_{11}H_{14}INO_2S$: C, 37.62; H, 4.02; N, 3.99. Found: C, 37.84; H, 3.90; N, 3.92.

4.3.10. *N*-(3-Chloro-4-iodobutyl)-*p*-toluenesulfonamide (A) and *N*-(4-chloro-3-iodobutyl)-*p*-toluenesulfonamide (B). Compounds **A** and **B** obtained as an inseparable mixture, 79:21 in 23% yield. Yellow oil; ^{1}H NMR (270 MHz, $CDCl_3$) (**A**+**B**): δ 1.76–1.93 (m, 2H, –C*H*HCH_2NHTs, **A**+**B**), 2.14–2.30 (m, 2H, –CH*H*CH_2NHTs, **A**+**B**), 3.01–3.26 (m, 4H, –CH_2CH_2NHTs, **A**+**B**), 3.36 (dd, 1H, J=8.2, 10.3 Hz, **B**),[†] 3.55 (dd, 1H, J=4.6, 10.3 Hz, **B**),[†] 3.76 (dd, 1H, J=9.9, 11.1 Hz, **A**),[†] 3.95–4.06 (m, 1H,

[†] Identification of the chemical shifts was determined by the comparison of those of the similar compounds.[14]

$ClCH_2CHICH_2$–, **B**),[†] 4.00 (dd, 1H, J=4.3, 11.1 Hz, **A**),[†] 4.16–4.26 (m, 1H, $ICH_2CHClCH_2$–, **A**),[†] 7.37 (d, 4H, Ar*H*, J=8.2 Hz, **A+B**), 7.76 (d, 4H, Ar*H*, J=8.2 Hz, **A+B**); MS (CI, isobutane): *m*/*z* (relative intensity, %) (**A** and **B**): 388 ($[M+1]^+$, 13), 352 ($[M-Cl]^+$, 19), 260 ($[M-I]^+$, 44), 184 ($[CH_2NHTs]^+$, 100), 155 ($[ArSO_2]$, 27).

4.3.11. *N*-(5-Chloro-6-iodobutyl)-*p*-toluenesulfonamide (C) and *N*-(6-chloro-5-iodobutyl)-*p*-toluenesulfonamide (D). Compounds **C** and **D** obtained as an inseparable mixture, 47:53 in 32% yield. Yellow oil; ^{1}H NMR (270 MHz, $CDCl_3$) (**C+D**): δ 1.25–1.60 (m, 8H, $-CH_2CH_2CH_2NHTs$, **C+D**), 1.60–1.80 (m, 2H, $-CHHCH_2NHTs$, **C+D**), 1.80–2.05 (m, 2H, $-CHHCH_2NHTs$, **C+D**), 2.86–3.02 (m, 4H, $-CH_2CH_2NHTs$, **C+D**), 3.35 (dd, 1H, J=8.4, 9.9 Hz, **D**),[†] 3.52 (dd, 1H, J=4.9, 9.9 Hz, **D**),[†] 3.74 (dd, 1H, J=10.1, 11.0 Hz, **C**),[†] 3.81–3.94 (m, 1H, $ClCH_2CHICH_2$–, **D**),[†] 3.99 (dd, 1H, J=4.6, 11.0 Hz, **C**),[†] 4.04–4.17 (m, 1H, $ICH_2CHClCH_2$–, **C**),[†] 7.32 (d, 4H, Ar*H*, J=8.2 Hz, **C+D**), 7.76 (d, 4H, Ar*H*, J=8.2 Hz, **C+D**); MS (CI, isobutane): *m*/*z* (relative intensity, %) (**C** and **D**): 416 ($[M+1]^+$, 13), 380 ($[M-Cl]^+$, 74), 288 ($[M-I]^+$, 7), 254 (100).

4.4. The NMR study of the iodination of *N*-methyl-*p*-toluenesulfonamide

Chloramine-T (0.02 mmol) and iodine (0.02 mmol) were added to a solution of *N*-methyl-*p*-toluenesulfonamide (0.02 mmol) in CD_3CN (0.5 mL). After 10 min, ^{1}H NMR of the mixture was measured. The conversion of 13% of *N*-methyl-*p*-toluenesulfonamide to *N*-iodo-*N*-methyl-*p*-toluenesulfonamide was observed.[6]

Acknowledgements

This work was supported by a Grant-in-Aid for Scientific Research from Ministry of Education, Culture, Sports, Science and Technology, Japan. Y.M. expresses his special thanks for the 21st century center of excellence (21COE) program, 'Creation of Integrated EcoChemistry of Osaka University'. We also wish to acknowledge the Instrumental Analysis Center, Faculty of Engineering, Osaka University.

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