Aziridination

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A Micellar Iodide-Catalyzed Synthesis of Unprotected Aziridines from Styrenes and Ammonia**

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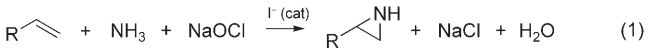
Aziridines are useful intermediates and pharmaceuticals. Therefore there is a growing need for their environmentally benign production.[1] Many olefin aziridinations rely on the addition of nitrenes, which are generated by either thermal or photochemical azide decomposition or are formed in situ from tosylimino phenyliodinane, sulfonyl azides, or chloramine-T using metal catalysts.[2] Halogens have also been proposed as catalysts in combination with chloramine-T, which is both a strong nucleophile and an oxidant.[3] In this route, pioneered by Sharpless[3a] and Komatsu,[3b] reaction of the oxidized halogen ("Br^+", "I^+") with the double bond is followed by nucleophilic attack of chloramine-T and cyclization. The main drawback of all previous reactions is the use of complex nitrogen-containing sources, which lead to N-substituted aziridines that require a subsequent deprotection step.[4] Direct routes from olefins to unprotected aziridines have only been described for α,β-unsaturated carbonyl compounds and often require complex NH donors.[5]

Ammonia, which is the most obvious nucleophilic nitrogen source, has barely been considered in aziridinations. Only the Gabriel–Cromwell aziridination uses NH_3, but the scope of this reaction is restricted to α,β-unsaturated α-halocarbonyl compounds.[5a,b] The direct incorporation of ammonia into olefins is therefore justly recognized as a top priority for catalysis.[6]

Herein we describe the first successful catalytic synthesis of unprotected aziridines from NH_3 and simple olefins. Our method resembles a halide-assisted epoxidation, in which the olefin is attacked by "Br^+" cation, which is formed in situ by oxidation of bromide, and then by water as the oxygen source.[7] The resulting bromohydrin is then cyclized to the epoxide. As will be shown, a similar concept can be applied for the N-functionalization of styrenes by replacing water with ammonia as the nucleophile: unprotected aziridines are formed in a one-pot, micellar system using iodide as a catalyst, aqueous bleach as an oxidant, and ammonia as the nitrogen source [Eq. (1)].



(1)

Styrene was used as a model olefin in our reactions. The expected product, 2-phenylaziridine, was synthesized separately as a reference by cyclization of 2-bromo-2-phenylethylamine.[8] Initial noncatalytic experiments were carried out with pre-oxidized halonium sources ("X^+"), such as *N*-halosuccinimide (NXS) or X_2 (X = Br, I). The reactions were performed under water-free conditions with NH_3 in dioxane and one equivalent of halonium ion in the presence of an additional base. Remarkably, ammonia was incorporated to give 2-phenylaziridine in a yield of around 10% (Table 1, entries 1–3). While the use of NBS led mostly to bromohydrin and dibrominated by-products, the selectivities were encouragingly high with NIS or I_2 (about 99%). Subsequent reactions were therefore performed with iodonium ion.

Table 1: Aziridination of styrene with ammonia using NXS or I_2 in the absence of surfactants.[a]

Entry	Solvent	"X^+" source	Yield [%][b]
1	dioxane	NBS	2 (7)
2	dioxane	NIS	10 (99)
3	dioxane	I_2	6 (99)
4[c]	dioxane/H_2O (9:1)	NIS	11 (99)
5[c]	dioxane/H_2O (9:1)	I_2	15 (99)
6[d]	dioxane/H_2O (9:1)	I_2	8 (98)

[a] Reaction conditions: styrene (0.5 mmol), NBS/NIS (0.5 mmol) or I_2 (0.5 mmol), NaOH (0.02 wt%), dioxane (4 mL), NH_3 in dioxane (1 mL, 0.5 M), room temperature, 2 h. [b] Selectivity given in brackets. [c] 10% (0.5 mL) H_2O added. [d] Reaction with 0.5 mL of 25% aqueous NH_3 (approx. 13 equiv) in the absence of NaOH.

Addition of water to reactions with I_2 in dioxane increased the aziridine yield to 15%, without loss of selectivity (Table 1, entry 5). Moreover, no additional base was required when excess aqueous ammonia was used (Table 1, entry 6). As long as sufficiently alkaline conditions are maintained, ammonia seems to be a more competitive nucleophile than water or hydroxide ions. The high selectivity of the reaction reflects the stability of aziridines towards the alkaline conditions.

Instead of using a solvent, we decided to try to improve the mixing of aqueous ammonia and the apolar olefin in a micellar system. Table 2 illustrates the promoting effect of surfactants on the aziridination of styrene. With non-ionic surfactants, such as ethoxylated fatty alcohols or sorbitan esters, the yield of 2-phenylaziridine increased remarkably. In

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Table 2: Aziridination of styrene with ammonia using I_2 or iodide/NaOCl.[a]

Entry	"I^+" source (equiv)	NaOCl solution [mL]	Yield [%][b]
1	I_2 (1.0)	–	67 (99)
2	I_2 (2.0)	–	88 (98)
3	–	–	0
4[c]	I_2 (1.0)	–	<0.1
5	NH_4I (1.0)	0.4	66 (99)
6	–	0.4	0

[a] Reaction conditions: styrene (0.5 mmol), I_2 (0.5 mmol) or NH_4I (0.5 mmol)/10–13% aqueous NaOCl (0.4 mL, 40 μL every 5 min), 25% aqueous NH_3 (5 mL), Brij 35 (2 wt%), room temperature, 2 h. [b] Selectivity given in brackets. [c] Reaction without Brij 35.

a typical reaction, aqueous ammonia (25%) was added to I_2 (0.1M) and Brij 35 (2 wt%).[9] After styrene addition (0.1M), the reaction yielded 67% of 2-phenylaziridine with 99% selectivity after 2 h at 298 K (Table 2, entry 1). The yield even increased to 88% with an excess of I_2 (Table 2, entry 2). No aziridine was detected in an experiment performed without I_2 (Table 2, entry 3), and only a trace of product was formed in the absence of a surfactant (Table 2, entry 4). A gradual increase of the Brij 35 concentration led to a boost in aziridine yield above 0.2 wt% of surfactant. This concentration corresponds to the critical micelle concentration in the mixture (as confirmed by dynamic light scattering (DLS) measurements) and hence leads to a dramatic increase of the interfacial area. No epoxide was formed, and traces of benzaldehyde (<2% selectivity) are the only side-product.

While previous experiments employed pre-oxidized iodonium sources, it is more desirable to use cheaper iodide salts and an oxidant. However, O_2 is not suitable as an oxidant as the use of NH_3 creates alkaline conditions and O_2 only oxidizes iodide under acidic conditions. H_2O_2 oxidizes iodide under neutral or slightly alkaline conditions but it is unstable at high pH values, especially in the presence of halides.[10] However, 2-phenylaziridine was formed in 66% yield (approximately 99% selectivity) when 0.4 mL of a 10–13% NaOCl solution was added gradually to a solution of ammonium iodide (0.1M) and styrene (0.1M) in 25% aqueous NH_3 containing 2 wt% Brij 35 (Table 2, entry 5). This yield is the same as that achieved under similar conditions with one equivalent of I_2. The degree of alkalinity in the micellar solution is also crucial as, while NH_3 needs alkaline conditions to act as a nucleophile, iodide oxidation is generally faster at low pH values.[11] When NaI was used instead of NH_4I, less aziridine was formed. The aziridine yield varied only slightly (63–77%) when using NH_3 concentrations of between 25% (ca. 13M) and 1.3M at 0.1M NH_4I. At a fixed NH_3 concentration (1.3M), a maximum 2-phenylaziridine yield of 90% was obtained using 40 mol% of NH_4I with respect to the olefin (Figure 1). Importantly, iodide is applied in substoichiometric amounts, thereby implying that it is re-oxidized repeatedly by hypochlorite.

Various olefins were tested to evaluate the reaction scope (Table 3). Moderate to excellent yields were obtained with ring-substituted styrenes, including substrates containing electron-donating or -withdrawing groups (Table 3, entries 2–8). α-Methylstyrene gave a higher aziridine yield

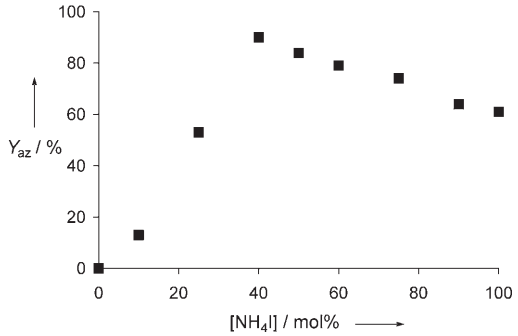
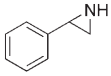
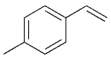
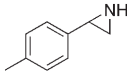
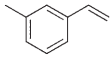
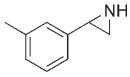
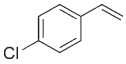
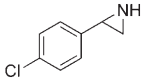
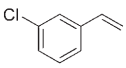
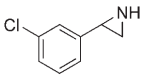
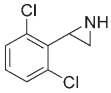
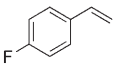
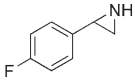
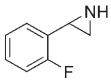
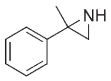
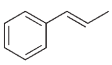
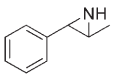


Figure 1. 2-Phenylaziridine yield with 1.3M NH_3 as a function of NH_4I concentration. Reactions were carried out according to the general conditions described in Table 2 (entry 5).

Table 3: Scope of the catalytic aziridination with aqueous NH_3 in the presence of iodide.[a]

Entry	Olefin	Aziridine	Yield [%][b]
1			84 (99)
2			75 (99)
3			56 (99)
4			74 (99)
5			71 (99)
6			30 (98)
7			74 (99)
8			70 (99)
9			92 (99)
10			56 (98)

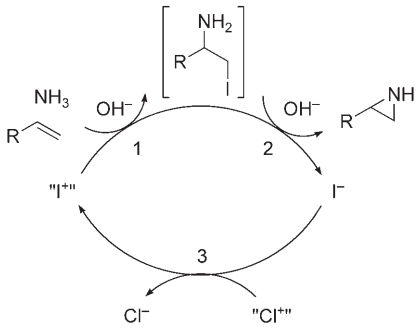
[a] Reaction conditions: olefin (0.5 mmol), NH_4I (50 mol%), 10–13% aqueous NaOCl (0.4 mL, 40 μL every 5 min), Brij 35 (2 wt%), H_2O (4.5 mL), 25% aqueous NH_3 (0.5 mL), room temperature, 2 h. [b] Selectivity given in brackets.

(92%) than styrene itself, while β-methylstyrene provided a lower yield (56%; Table 3, entries 1, 9, and 10). This situation suggests that the electrophilic iodonium species attacks the olefin and that the positive charge on the α-carbon atom in the reaction of α-methylstyrene is stabilized to a greater extent than in the other two reactions.

Aziridine yields were much lower for aliphatic olefins with various substitution patterns, despite varying the time,

temperature, and reactant and surfactant concentrations. A likely explanation for this is that the iodonium ion disproportionates into iodide and iodate in alkaline solutions if its reaction with the olefins is slow.[12] Indeed, it is known that aliphatic olefins react less readily than styrenes with iodonium ions,[3e,f] although iodonium ions can be activated by Lewis acids in an approach that is currently being elaborated.[13] Nevertheless, the selective formation of small amounts of unprotected aziridines from aliphatic olefins proves that the reaction is, in principle, possible.

A proposal for a full reaction cycle is depicted in Scheme 1. Support for catalysis by the iodonium ion comes from the observation that no aziridine is formed in the absence of an oxidized iodine species. Alkaline conditions are required for ammonia incorporation and ring closure after the initial electrophilic attack (Scheme 1, steps 1 and 2). Cyclization of the putative 2-iodo-1-phenylethylamine intermediate is assumed to proceed rapidly as the less-reactive reference 2-bromo-1-phenylethylamine is completely converted into 2-phenylaziridine under similar alkaline conditions (step 2). The fact that iodide can be applied in sub-stoichiometric amounts demonstrates that re-oxidation of iodide by ClO^- ions closes the catalytic cycle (step 3).



Scheme 1. Proposed reaction mechanism for the iodide-catalyzed aziridination.

In conclusion, a new method has been demonstrated for incorporating ammonia into olefins under very mild, micellar conditions. To our knowledge, this is the first report of the direct catalytic aziridination of styrenes with ammonia that does not rely on the use of protecting groups.[14] The catalytic use of iodide in combination with bleach as an oxidant represents an environmentally benign and cheap alternative to other oxidants, such as *t*BuOI, which was recently proposed by Minakata's group for the preparation of tosylated aziridines.[3f] A similar substitution of organic oxidants by bleach has previously been demonstrated for epoxidations[15] and dihydroxylations.[16] We are currently investigating the full scope of the substrate range.

Experimental Section

Reaction products were identified by GC-MS analysis and by comparison with reference aziridines synthesized by cyclization of bromoamines.[8] Yields and selectivities were determined by GC analysis.

Aziridination using iodide/NaOCl: Brij 35 (90 mg, 2 wt%) and NH_4I (37 mg, 0.05 M, 0.5 equiv) were dissolved in water (4.5 mL). After addition of styrene (57 μL, 0.1 M) and 25% aqueous NH_3 (0.5 mL; approx. 1.3 M), NaOCl (0.4 mL of a 10–13% aqueous solution) was added gradually (40 μL every 5 min). After stirring for 2 h at 298 K, the reaction mixture was carefully extracted with diethyl ether. The organic layer was dried with anhydrous $MgSO_4$ and analyzed by GC. The identity of 2-phenylaziridine was also confirmed by the formation of 2-chloro-2-phenylethylamine after ring-opening with aqueous HCl. EI-MS data for 2-phenylaziridine: *m*/*z* (%): 119 (10), 118 (100), 117 (14), 91 (22), 89 (12), 77 (5), 63 (9), 51 (7), 36 (6).

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[9] The use of ionic surfactants, such as SDA or quaternary ammonium compounds, did not provide aziridines under the applied conditions. Nonionic, TWEEN- and LUTENSOL-type surfactants led to similar results as Brij 35. Brij 35 (polyoxyethylene lauryl ether, $CH_3(CH_2)_{11}$–$O(CH_2CH_2O)_{23}$–H, 1198 g mol^{-1}) is a registered trademark of ICI Americas, Inc.

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