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Intramolecular bromine-catalyzed aziridination: a new direct access to cyclic sulfonamides

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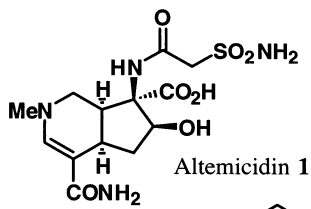
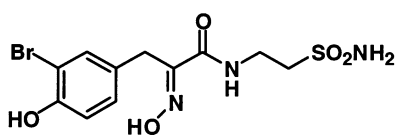
Abstract—*N*-Chloramine salts of ω-unsaturated sulfonamides have been prepared and shown to react in an intramolecular fashion in the presence of a catalytic amount of phenyltrimethylammonium tribromide to yield bicyclic aziridines. This intramolecular bromine-catalyzed aziridination procedure gave results complementary to those obtained by the copper-catalyzed methodology based on iminophenyliodinane.

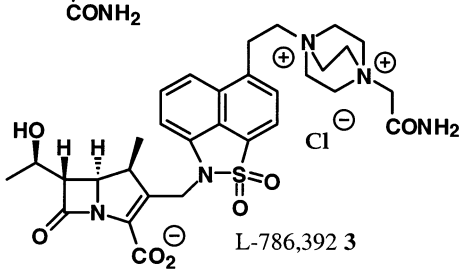
Sulfonamide-containing compounds are very rarely found in nature since only two molecules,[1] altemicidin **1**[2] and psammaplin C **2**,[3] exhibit this functionality. On the other hand, a plethora of sulfonamides have been devised by chemists which have found numerous applications in medicinal chemistry,[4a] as recently reviewed in a brief history of drug discovery.[4b] High interest has been particularly directed to the cyclic sulfonamides (sultams) which can additionally serve as chiral auxiliaries or reagents.[5] Major recent pharmaceutical applications include the carbapenem antibiotic L-786,392 **3**,[6] whose side-chain is closely implicated in its high-affinity binding to the penicillin-binding protein PBP2a as well as in its reduced immunotoxicity, and brinzolamide (Azopt™) 4[7a] introduced in 1998 for the treatment of glaucoma.[7b]



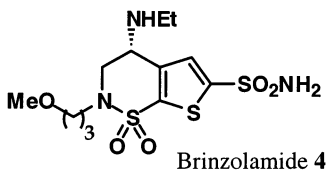
Altemicidin **1**



Psammaplin C **2**



L-786,392 **3**



Brinzolamide **4**

Keywords: aziridination; chloramine; bromine; intramolecular; sulfonamides.

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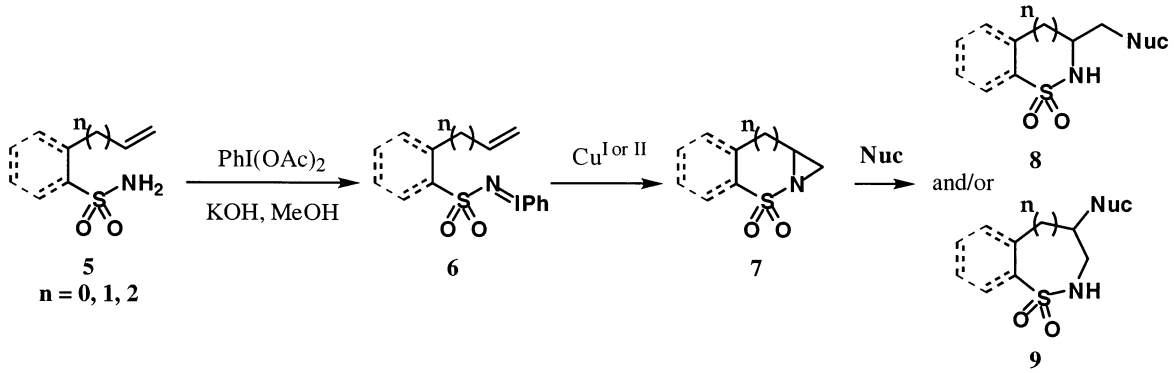


Scheme 1.

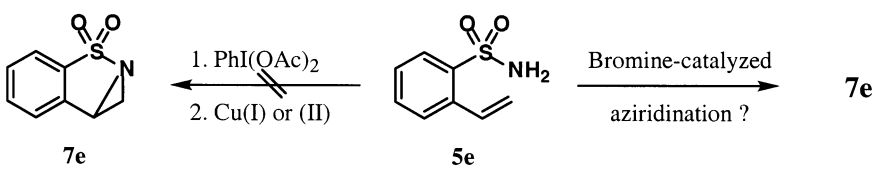
In the last few years, new methodologies involving radical processes,[8] intramolecular Diels–Alder reactions[9] or ring-closing metathesis[4a] have been applied to the synthesis of sultams. In connection with biological studies and in relation with our work on new [*N*-(alkylsulfonyl)imino]phenyliodinanes,[10] we have for our part described a new strategy for preparing cyclic sulfonamides based on copper-catalyzed aziridination.[11] Thus, iminoiodinanes **6** derived from ω-unsaturated sulfonamides **5** react intramolecularly in the presence of a catalytic quantity of copper (I) or (II) triflate to give bicyclic aziridines of type **7** which, in turn, can be opened by a variety of nucleophiles (Scheme 1).[12]

However, in the sole case of 2-vinylbenzenesulfonamide **5e**, no aziridine **7e** could be isolated using this methodology (Scheme 2). In order to demonstrate that this failure was not related to possible ring strain, we decided to explore the possibility of applying the recently reported intermolecular bromine-catalyzed aziridination of olefins using *N*-chloramine salts of sulfonamides.[13] No intramolecular aziridinations using this procedure have been reported before.

Sulfonamides **5**[12] were treated with one equivalent of *tert*-butylhypochlorite and one equivalent of sodium hydroxide in water to give the corresponding *N*-chloramine salts **10**. The latter were directly treated with a catalytic quantity of phenyltrimethylammonium tribromide (PTAB) in acetonitrile to afford aziridines **7**. Best results were obtained when a substrate concentration of 0.05 M was used. Data are summarized in Table 1.[14]

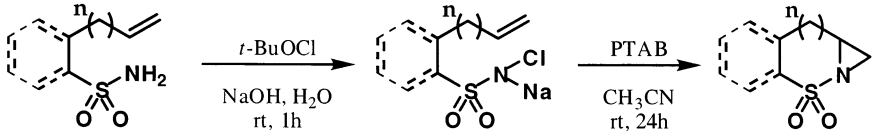
As previously observed with the copper-catalyzed procedure, no reaction took place with substrate **10a**, no doubt due to the high ring strain of the expected product **7a**. However, higher homologues **10b–d** gave rise to aziridines **7b–d**, with yields varying as a function of the chain length. Noteworthy is the observation that the *N*-chloramine salt of hex-5-ene-1-sulfonamide (**10d**) afforded the expected aziridine **7d**, albeit in low yield. This result is in sharp contrast to that obtained with the corresponding iminoiodinane, in which a C–H insertion product was exclusively formed in 51% yield.[12] Moreover, contrary to the copper-catalyzed reaction, the *N*-chloramine salt of 2-vinylbenzenesulfonamide (**10e**) allowed formation of aziridine **7e**, demonstrating that, in the case of the corresponding iminoiodinane, failure of the reaction is probably related to the high and unexplained instability of the intermediate **6e** rather than to steric considerations. Finally, the benzenesulfonamide derivatives **10f,g** also led to aziridines **7f,g**, though in lower yields than with the copper-catalyzed reaction. An overall comparison of the bromine- and copper-catalyzed aziridinations points out that both methods are complementary: in cases where one method works poorly, the other method works well.

Since we have previously demonstrated that nucleophilic ring opening of aziridines of type **7** allows preparation of a wide variety of substituted cyclic sulfonamides,[12] the present intramolecular bromine-catalyzed aziridination procedure represents an original strategy for the synthesis of such compounds. We are currently exploring their incorporation into biologically active compounds as well as their preparation in enantiomerically pure form.

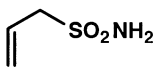
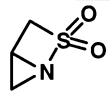
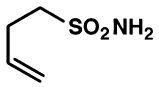
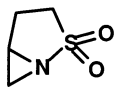
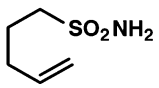
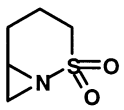
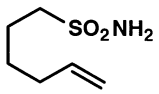
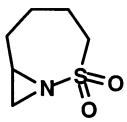
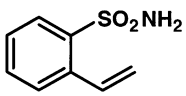
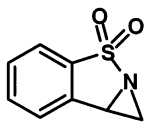
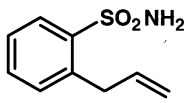
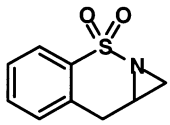
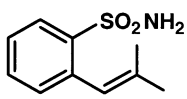
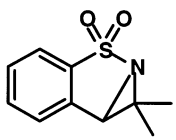


Scheme 2.

Table 1. Intramolecular bromine-catalyzed aziridination reactions



5 10 7

Substrate	% Yield[a,b]	Product
 **5a**	**7a**: 0 (0)	
 **5b**	**7b**: 70 (38)	
 **5c**	**7c**: 35 (61)	
 **5d**	**7d**: 20 (51[c])	
 **5e**	**7e**: 70 (0)	
 **5f**	**7f**: 46 (60)	
 **5g**	**7g**: 40 (80)	

[a] Non-optimized isolated yield after flash chromatography. [b] Yields in parentheses were obtained using the copper-catalyzed procedure.[12] [c] A C-H insertion product rather than an aziridine was isolated.

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14. A typical procedure was as follows: to a stirring solution of 2-vinylbenzenesulfonamide (**5e**, 203 mg, 1.10 mmol) and sodium hydroxide (45 mg, 1.0 equiv.) in water (1.2 mL) was added *tert*-butylhypochlorite (126 μL, 1.0 equiv.). The reaction was stirred at rt for 1 h before being evaporated to dryness at rt. The resulting white solid was washed with diethyl ether and then dried under vacuum for 3 h. The *N*-chloramine salt **10e** obtained in nearly quantitative yield was then reacted with a catalytic quantity of PTAB (45 mg, 10 mol%) in acetonitrile (20 mL) at rt for 24 h. The reaction mixture was then filtered on silica gel, the filtrate was evaporated to dryness under reduced pressure and the oily residue was purified by flash chromatography on silica gel (heptane–ethyl acetate 7:3) affording the corresponding aziridine **7e** (140 mg, 70%) as a white solid. mp 79–80°C; ^{1}H NMR (250 MHz, $CDCl_3$): δ 2.35 (dd, 1H, $J=1.1$ and 3.8 Hz), 2.88 (dd, 1H, $J=1.1$ and 4.9 Hz), 4.16 (pseudo t, 1H, $J=4.4$ Hz), 7.56–7.65 (m, 3H), 7.69 (d, 1H, $J=7.1$ Hz). ^{13}C NMR (62.5 MHz, $CDCl_3$): δ 43.0, 44.2, 123.5, 125.6, 130.4, 133.4, 137.0; mass spectrum (CI) m/z 182 $(M+H)^+$; Anal. Calcd for $C_8H_7NO_2S$: C, 53.03; H, 3.89; N, 7.73; S, 17.69. Found: C, 53.06; H, 3.94; N, 7.52; S, 17.57.