



## The first diastereoselective nitroaziridination of *N*-tosylaldimines with 1-bromonitroalkanes

Lal Dhar S. Yadav\*, Garima, Ritu Kapoor

Green Synthesis Lab, Department of Chemistry, University of Allahabad, Allahabad 211 002, India

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### ABSTRACT

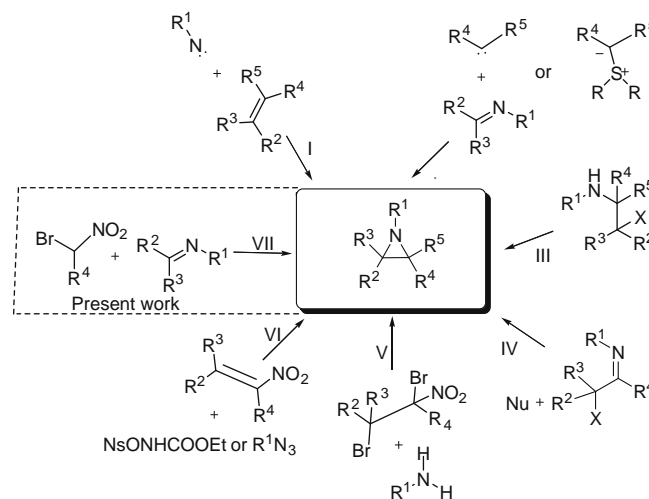
The first expeditious nitroaziridination of *N*-tosylaldimines is reported. The protocol involves operationally simple catalyst-free reaction of *N*-tosylaldimines, 1-bromonitroalkanes and NaOAc to afford 2-nitro-1-tosylaziridines in excellent yields with high *Z*-diastereoselectivity in a one-pot procedure under ambient conditions.

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Owing to their highly regio- and stereoselective ring-opening reactions,<sup>1–4</sup> aziridines are valued as important building blocks for the synthesis of a wide range of nitrogen-containing compounds such as amino acids, amino sugars and alkaloids.<sup>5</sup> Besides their importance as reactive intermediates, aziridines are also incorporated in many biologically active compounds.<sup>6</sup> Antibiotic, anticancer and antitumour activities of aziridine-containing natural products, such as azinomycins,<sup>7–9</sup> mitomycins,<sup>10,11</sup> FR-900482, FR-66979 and related compounds,<sup>12</sup> are of significant interest. The bioactivity of all these compounds lies in the role of aziridines as powerful alkylating agents.<sup>13</sup> Furthermore, several synthetic aziridines have also been reported to exhibit useful biological properties such as irreversible inhibition of glutamate racemase<sup>14</sup> and diaminopimetic acids epimerase (DAP)<sup>15</sup> and high level cytotoxicity against melanoma cell lines.<sup>16</sup>

The development of procedures leading to the stereocontrolled formation of carbon–nitrogen bond is considered a challenging research target. Numerous methods are available for differently substituted aziridines, which include aziridination of olefins<sup>17–19</sup> (Scheme 1, route I), carbene and ylide addition to imines<sup>20–22</sup> (Scheme 1, route II), cyclization of  $\beta$ -amino alcohols,<sup>23,24</sup>  $\beta$ -amino halides,<sup>23,24</sup>  $\beta$ -azido alcohols<sup>23–25</sup> (Scheme 1, route III) and halo imines<sup>26</sup> (Scheme 1, route IV). However, only a few routes for the synthesis of *C*-nitroaziridines are available in the literature.<sup>27–29</sup> All these, basically involve the same chemistry, that

is, the reaction of a nitroalkene or its derivatives with a nitrogen source, namely, ethyl [(4-nitrobenzenesulfonyl)oxy]carbamate (NsONHCOOEt), an azide or an amine (Scheme 1, routes V and VI).<sup>27–29</sup> Fioravanti et al. have recently reported an elegant synthesis of chiral nitroaziridines from optically active nitroalkenes and NsONHCOEt.<sup>29c</sup>

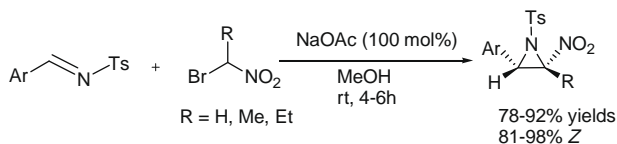


Scheme 1. General synthetic routes to aziridines.

\* Corresponding author. Tel.: +91 5322500652; fax: +91 5322460533.  
E-mail address: [ldsyadav@hotmail.com](mailto:ldsyadav@hotmail.com) (Lal Dhar S. Yadav).

The literature records no report on the synthesis of 2-nitro-1-tosylaziridines. This gap and our continued efforts to develop new one-pot cyclization processes<sup>30</sup> attracted our attention to devise the first expeditious nitroaziridination of *N*-tosylaldimines with 1-bromonitroalkanes (Scheme 1, route VII). The reaction is catalyst-free, highly diastereoselective in favour of the *Z*-isomer and is performed in a one-pot procedure to afford excellent yields of hitherto unknown 2-nitro-1-tosylaziridines **3** under mild conditions (Scheme 2). Obviously, the present work is different from the work already reported<sup>29</sup> as it discloses the nitroaziridination of *N*-tosylaldimines with 1-bromonitroalkanes instead of nitroalkenes using *N*sONHCOOEt. The 2-nitro-1-tosylaziridines **3** thus obtained are promising synthetic intermediates since the nitro group offers a wide range of efficient methods for its transformation into various other functionalities.<sup>31,32</sup> Most importantly, the nitro group can be converted into a carbonyl group using the Nef reaction.<sup>33</sup> Moreover, the inherently strained aziridine ring would further enhance the synthetic potential of these nitro compounds via ring-opening reactions.

Initially, we set up a series of experiments to optimize the reaction conditions. Indeed, we used a very straightforward protocol and examined various solvent/base systems for the synthesis of representative compound **3a** (Table 1). Among all the systems tested, MeOH/NaOAc was found to be the best solvent/base system in terms of the yield as well as diastereoselectivity (Table 1, entry 1). It was noted that 100 mol % of the base was necessary to obtain the optimal yield. In order to investigate the substrate scope of the reaction, different *N*-tosylaldimines **1** were reacted with various 1-bromonitroalkanes **2** under the optimized reaction conditions. Both electron-donating and electron-withdrawing substituents are tolerated to afford the corresponding product **3** in consistently good yields and *Z*-diastereoselectivities (Table 2). The highest yield for the synthesis of **3** is 92% (Table 2, entry 5) and the highest *Z*-diastereoselectivity is 98% (Table 2, entry 4). The present optimized synthesis involves stirring of an equimolar mixture of *N*-tosylaldimine **1**, 1-bromonitroalkane **2** and NaOAc in MeOH at rt for 4–6 h to afford 2-nitro-1-tosylaziridines **3** in 78–92% yields with 81–98% diastereoselectivity in favour of the *Z*-isomer as determined by <sup>1</sup>H NMR spectroscopy (Table 2).<sup>34</sup>



Scheme 2. Diastereoselective synthesis of nitroaziridines **3**.

Table 1  
Optimization of reaction conditions for the formation of **3a**

Entry	Solvent/base system	Yield <sup>a</sup> (%) <i>Z</i> -isomer	<i>Z/E</i> <sup>b</sup>
1	MeOH/NaOAc	83	92:8
2	MeOH/Et <sub>3</sub> N	58	88:12
3	CH <sub>2</sub> Cl <sub>2</sub> /NaOAc	67	81:19
4	CH <sub>2</sub> Cl <sub>2</sub> /Et <sub>3</sub> N	42	78:22
5	MeCN/NaOAc	69	84:16
6	MeCN/Et <sub>3</sub> N	45	80:20

<sup>a</sup> Yield of isolated and purified *Z*-isomer of aziridine **3a**.

<sup>b</sup> As determined by <sup>1</sup>H NMR integration of *Z*- and *E*-isomers in the crude product.

Table 2  
One-pot synthesis of nitroaziridines **3** from *N*-tosylaldimines **1** (Scheme 2)

Entry	Aziridines <b>3</b>		Time <sup>a</sup> (h)	Yield <sup>b,c</sup> (%) <i>Z</i> -isomer	<i>Z/E</i> <sup>d</sup>
	Ar	R			
1	Ph	H	5	83	92:8
2	2-ClC <sub>6</sub> H <sub>4</sub>	H	5	85	95:5
3	4-ClC <sub>6</sub> H <sub>4</sub>	H	4	88	94:6
4	4-MeOC <sub>6</sub> H <sub>4</sub>	H	6	82	98:2
5	4-O <sub>2</sub> NC <sub>6</sub> H <sub>4</sub>	H	4	92	96:4
6	Ph	Me	6	81	89:11
7	2-ClC <sub>6</sub> H <sub>4</sub>	Me	5	83	91:9
8	4-ClC <sub>6</sub> H <sub>4</sub>	Me	5	85	90:10
9	4-MeOC <sub>6</sub> H <sub>4</sub>	Me	6	80	96:4
10	4-O <sub>2</sub> NC <sub>6</sub> H <sub>4</sub>	Me	4	89	93:7
11	Ph	Et	6	79	81:19
12	2-ClC <sub>6</sub> H <sub>4</sub>	Et	6	80	85:15
13	4-ClC <sub>6</sub> H <sub>4</sub>	Et	6	81	83:17
14	4-MeOC <sub>6</sub> H <sub>4</sub>	Et	5	78	92:8
15	4-O <sub>2</sub> NC <sub>6</sub> H <sub>4</sub>	Et	5	87	89:11

<sup>a</sup> Time for completion of the reaction as indicated by TLC.

<sup>b</sup> Yield of isolated and purified products.

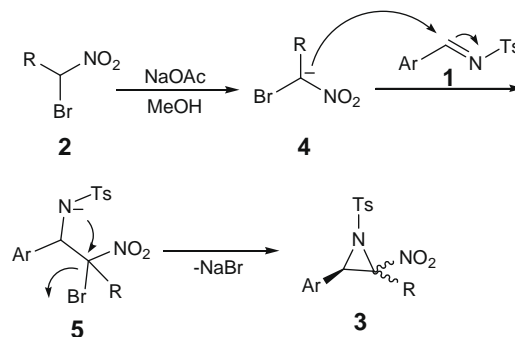
<sup>c</sup> All compounds gave C, H and N analyses within ±0.38% and satisfactory <sup>1</sup>H NMR, <sup>13</sup>C NMR and EIMS data.

<sup>d</sup> As determined by <sup>1</sup>H NMR integration of *Z*- and *E*-isomers in the crude product.

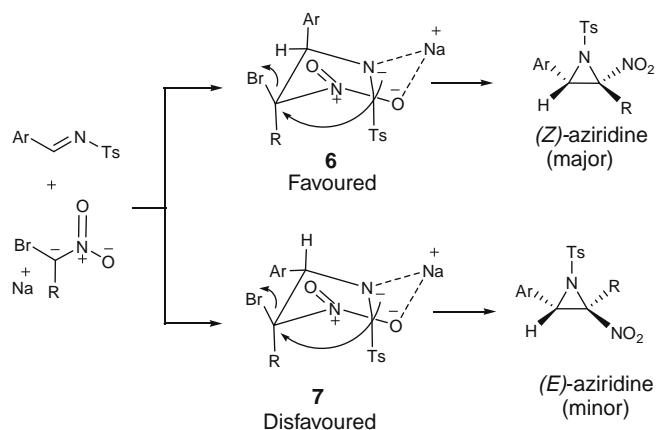
The formation of 2-nitroaziridines **3** plausibly involves nucleophilic addition of carbanion **4** generated from 1-bromonitroalkane **2** followed by intramolecular cyclization via nucleophilic substitution of tosylamide anion **5** to afford **3** with high *Z*-diastereoselectivity (Scheme 3). The observed diastereoselectivity in the formation of 2-nitroaziridines **3** may be explained by comparing the two metal-chelated chair-like intermediates **6** and **7** (Scheme 4). The intermediate **6** having the bulky groups Ar and Ts *trans* to each other is more stable (favoured) than **7** where these groups are *cis*. Thus, (*Z*)-aziridines are selectively formed through the intermediate **6** (Scheme 4).<sup>35</sup>

The *Z*-stereochemistry of aziridines **3** was assigned on the basis of higher *J*-values (9.6–9.8 Hz) of 2-H and 3-H than those for (*E*)-aziridines (6.7–6.8 Hz). This is in conformity with the earlier observations for aziridines reported in the literature.<sup>36–38</sup> Furthermore, strong NOEs, were observed between 2-H/3-H and 2-Me (or 2-Et)/3-H of aziridine **3**, which conclusively demonstrate that these protons are on the same face of the molecule and thus, prove their *Z*-stereochemistry (Fig. 1). On the other hand, in the case of *E*-isomer of **3** no appreciable NOEs were observed between 2-H/3-H and 2-Me (or 2-Et)/3-H, which indicate that these protons are on the opposite faces of the molecule.

In summary, we have developed a one-pot, general and efficient protocol for a convenient and diastereoselective synthesis of various chemically and pharmaceutically relevant 2-nitro-1-tosylaziridines from readily and widely available *N*-tosylaldimines



Scheme 3. A plausible mechanism for the formation of nitroaziridines **3**.



Scheme 4. A rationale for the Z-diastereoselectivity of nitroaziridination.

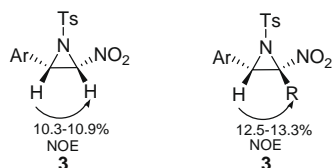


Figure 1. NOE experiment on aziridines 3.

and 1-bromonitroalkanes. The synthesis is operationally simple, high yielding and performed under mild conditions.

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## Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2009.07.054.

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- General procedure for the synthesis of 3-aryl-2-nitro-1-tosylaziridines **3**: A mixture of sodium acetate (1 mmol), 1-bromonitroalkane **2** (1 mmol) and N-tosylaldimine **1** (1 mmol) in methanol (5 mL) was stirred at rt for 4–6 h (Table 2). After completion of the reaction (monitored by TLC), water (5 mL) was added and the product was extracted with diethyl ether (3 × 10 mL). The combined extract was dried over MgSO<sub>4</sub>, filtered, concentrated under reduced pressure, and the crude product thus obtained was purified by silica gel chromatography using ethyl acetate-*n*-hexane (2:8) as eluent to afford an analytically pure sample of **3**. Physical data of representative compounds: Compound **3** (Table 2, entry 3, Ar = 4-ClC<sub>6</sub>H<sub>4</sub>, R = H), Z-isomer: Yellowish solid, yield 88%, mp 148–150 °C. IR (KBr)  $\nu_{\max}$  3043, 2831, 1601, 1568, 1511, 1465, 1330, 1164, 857, 835 cm<sup>-1</sup>. <sup>1</sup>H NMR (400 MHz; CDCl<sub>3</sub>/TMS)  $\delta$ : 2.35 (s, 3H, TsCH<sub>3</sub>), 4.99 (d, 1H, *J* = 9.8 Hz, 3-H), 6.10 (d, 1H, *J* = 9.8 Hz, 2-H), 7.00–7.23 (m, 4H, 4-ClC<sub>6</sub>H<sub>4</sub>), 7.34 (d, 2H, *J* = 8.1 Hz, Ts), 7.81 (d, 2H, *J* = 8.1 Hz, Ts) <sup>13</sup>C NMR (100 MHz; CDCl<sub>3</sub>/TMS)  $\delta$ : 24.0, 48.4, 76.7, 127.2, 128.1, 129.0, 130.0, 132.2, 134.3, 136.8, 144.7. EIMS (*m/z*): 352 (M<sup>+</sup>). Anal. Calcd for C<sub>15</sub>H<sub>13</sub>ClN<sub>2</sub>O<sub>4</sub>S: C, 51.07; H, 3.71; N, 7.94. Found: C, 50.74; H, 3.47; N, 8.30. Compound **3** (Table 2, entry 8, Ar = 4-ClC<sub>6</sub>H<sub>4</sub>, R = Me) Z-isomer: Yellowish solid, yield 85%, mp 161–163 °C. IR (KBr)  $\nu_{\max}$  3040, 2825, 1605, 1560, 1515, 1460, 1335, 1160, 860, 840 cm<sup>-1</sup>. <sup>1</sup>H NMR (400 MHz; CDCl<sub>3</sub>/TMS)  $\delta$ : 1.64 (s, 3H, CH<sub>3</sub>), 2.35 (s, 3H, TsCH<sub>3</sub>), 4.98 (s, 1H, 3-H), 7.00–7.22 (m, 4H, 4-ClC<sub>6</sub>H<sub>4</sub>), 7.33 (d, 2H, *J* = 8.1 Hz, Ts), 7.80 (d, 2H, *J* = 8.1 Hz, Ts) <sup>13</sup>C NMR (100 MHz; CDCl<sub>3</sub>/TMS)  $\delta$ : 19.0, 24.2, 49.0, 80.0, 127.0, 128.2, 129.1, 130.1, 132.0, 134.2, 136.9, 144.6. EIMS (*m/z*): 366 (M<sup>+</sup>). Anal. Calcd for C<sub>16</sub>H<sub>15</sub>ClN<sub>2</sub>O<sub>4</sub>S: C, 52.39; H, 4.12; N, 7.64. Found: C, 52.77; H, 4.33; N, 7.36. Compound **3** (Table 2, entry 13, Ar = 4-ClC<sub>6</sub>H<sub>4</sub>, R = Et) Z-isomer: Yellowish solid, yield 81%, mp 172–174 °C. IR (KBr)  $\nu_{\max}$  3045, 2833, 1607, 1555, 1520, 1463, 1333, 1162, 810, 860 cm<sup>-1</sup>. <sup>1</sup>H NMR (400 MHz; CDCl<sub>3</sub>/TMS)  $\delta$ : 0.92 (t, 3H, *J* = 7.8 Hz, CH<sub>3</sub>), 1.78 (q, 2H, *J* = 7.8 Hz, CH<sub>2</sub>), 2.35 (s, 3H, TsCH<sub>3</sub>), 4.97 (s, 1H, 3-H), 7.00–7.21 (m, 4H, 4-ClC<sub>6</sub>H<sub>4</sub>), 7.32 (d, 2H, *J* = 8.1 Hz, Ts), 7.79 (d, 2H, *J* = 8.1 Hz, Ts) <sup>13</sup>C NMR (100 MHz; CDCl<sub>3</sub>/TMS)  $\delta$ : 10.8, 24.6, 33.1, 48.9, 82.0, 127.1, 128.0, 129.0, 130.2, 132.1, 134.0, 136.7, 144.7. EIMS

- (*m/z*): 380 ( $M^+$ ). Anal. Calcd for  $C_{17}H_{17}ClN_2O_4S$ : C, 53.61; H, 4.50; N, 7.36.  
Found: C, 53.84; H, 4.24; N, 7.71.
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