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Ring Opening of a Trisubstituted Aziridine With Amines: Regio- and Stereoselective Formation of Substituted 1,2-Diamines

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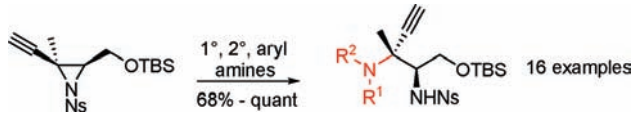
ABSTRACT



The formation of substituted 1,2-diamines via nucleophilic ring opening of a trisubstituted ethynyl aziridine was performed with complete regio- and stereoselective control. Various amines with different levels of nucleophilicity were employed and gave similar results. The ring opening reaction is not limited to ethynyl aziridines, as other alkyl trisubstituted aziridines gave the same results. This method allows for the formation of unique vicinal diamines while providing a fully substituted carbon center in a stereoselective manner under mild conditions.

Aziridines are useful intermediates in organic chemistry due to their highly strained ring systems that allow for a wide range of reactivity. Chiral nonracemic aziridines, in particular, are especially valuable in target syntheses.[1] Nucleophilic ring opening reactions are generally used to exploit this reactivity; however, di-, tri-, and tetrasubstituted aziridines exhibit diminished reactivity due to increased steric hindrance, and they also may suffer from poor regioselectivity since both carbons on an aziridine are electrophilic. However, acceptable levels of regio- and stereoselectivity can often be achieved by varying the substituents or through the use of Lewis acids.[2] Very few non-Lewis acid-catalyzed intermolecular nucleophilic ring opening reactions exist to induce preferential attack at the more substituted carbon of the aziridine.[3] Through the use of a Lewis acid, these reactions benefit from quaternization of the nitrogen, but under basic conditions there can be regioselective preference for attack at the more substituted carbon. The use of phenol nucleophiles under mildly basic conditions has been thoroughly investigated to generate tertiary alkyl-aryl ethers.[4] However, few investigations report the generation of a fully substituted carbon through an aziridine ring opening reaction.[5]

Nucleophilic ring opening of aziridines with nitrogen nucleophiles has attracted significant attention in the organic community due to increasing interest of 1,2-diamine compounds in synthetic and medicinal chemistry. (+)-CP-99,994[6] is a potent and selective human neurokinin-1-P receptor

(1) (a) Hale, K. J.; Domostoj, M. M.; Tookes, D. A.; Irving, E.; Scheinmann, F. *Org. Lett.* **2003**, *5*, 2927. (b) Smith, A. B., III; Kim, D.-S. *Org. Lett.* **2004**, *6*, 1493. (c) Crawley, S. L.; Funk, R. L. *Org. Lett.* **2006**, *8*, 3995. (d) Liu, H.; Pattabiraman, V. R. *Org. Lett.* **2007**, *9*, 4211. (e) Collins, J.; Drouin, M.; Sun, X.; Rinner, U.; Hudlicky, T. *Org. Lett.* **2008**, *10*, 361. (f) Yoshimitsu, T.; Ino, T.; Tanaka, T. *Org. Lett.* **2008**, *10*, 3169. (g) Wehn, P. M.; Du Bois, J. *Angew. Chem., Int. Ed.* **2009**, *48*, 3802. (h) Trost, B. M.; Dong, G. *Chem.—Eur. J.* **2009**, *15*, 6910.

(2) (a) Hu, X., E. *Tetrahedron* **2004**, *60*, 2701. (b) Yudin, A. K., Ed.; *Aziridines and Epoxides in Organic Synthesis*; WILEY-VCH: Weinheim, Germany, 2006.

(3) (a) Lin, P.-y.; Bellos, K.; Stamm, H.; Onistschenko, A. *Tetrahedron* **1992**, *48*, 2359. (b) Maligres, P. E.; See, M. M.; Askin, D.; Reider, P. J. *Tetrahedron Lett.* **1997**, *38*, 5253. (c) Sureshkumar, D.; Gunasundari, T.; Ganesh, V.; Chandrasekaran, S. *J. Org. Chem.* **2007**, *72*, 2106.

(4) (a) Li, P.; Evans, C. D.; Joullié, M. M. *Org. Lett.* **2005**, *7*, 5325. (b) Li, P.; Forbeck, E. M.; Evans, C. D.; Joullié, M. M. *Org. Lett.* **2006**, *8*, 5105. (c) Forbeck, E. M.; Evans, C. D.; Gilleran, J. A.; Li, P.; Joullié, M. M. *J. Am. Chem. Soc.* **2007**, *129*, 11463. (d) Grimley, J. S.; Sawayama, A. M.; Tanaka, H.; Stohlmeywe, M. M.; Woiwode, T. F.; Wandless, T. J. *Angew. Chem., Int. Ed.* **2007**, *46*, 8157. (e) Li, P.; Evans, C. D.; Wu, Y.; Cao, B.; Hamel, E.; Joullié, M. M. *J. Am. Chem. Soc.* **2008**, *130*, 2351.

(5) (a) Chakraborty, T. K.; Ghosh, A.; Raja, T. V. *Chem. Lett.* **2003**, 32. (b) Voronkov, M. V.; Kanamarlapudi, R. C.; Richardson, P. *Tetrahedron Lett.* **2005**, *46*, 6907. (c) He, Z.; Yudin, A. K. *Angew. Chem., Int. Ed.* **2010**, *49*, 1607.

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antagonist. (+)-Zanamiriv, or Relenza, and (−)-Oseltamivir phosphate, commonly known as Tamiflu, are both antiviral drugs (Figure 1).[7] (+)-Zanamiriv was the first neuraminidase

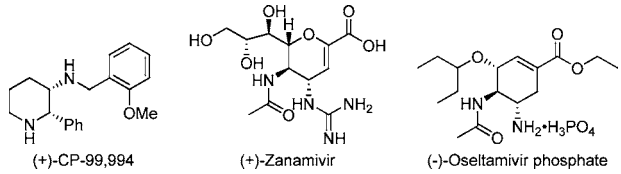
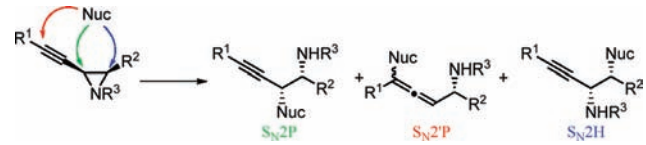


Figure 1. Select biologically active 1,2-diamines.

inhibitor developed commercially and is used in the treatment and prophylaxis of both Influenza A and B viruses. (−)-Oseltamiriv phosphate, a prodrug, behaves in a similar manner.

The use of an aziridine is one of the most straightforward methods to make vicinal diamines because upon nucleophilic ring opening with a nitrogen nucleophile a 1,2-diamine is generated. However, this reaction can sometimes require the use of a Lewis acid. There are numerous reports in the literature where metal triflates,[8] silica gel,[9] metal halides,[10] β-CD,[11] and organoboranes[12] are used to catalyze nucleophilic ring opening with simple amine nucleophiles. Also, when disubstituted aziridines were used, the regioselectivity was diminished. There are very few examples in the literature where a trisubstituted aziridine has been employed, and the conditions required to effect opening were harsh with nucleophilic attack occurring at the less substituted carbon.[5a] To solve the issue of regioselectivity and the use of a Lewis acid, a trisubstituted ethynyl aziridine was employed. Ring opening of alkynyl aziridines can occur in three ways: S_N2P, $S_N2'P$, S_N2H (Scheme 1).[13] The most common attack occurs

Scheme 1. Nucleophilic Addition of Alkynyl Aziridines

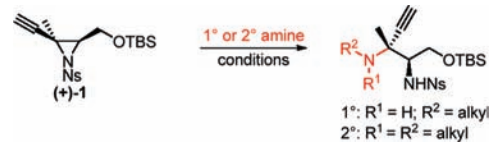


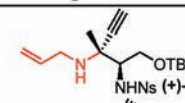
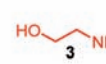
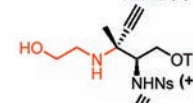
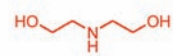
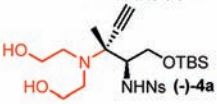
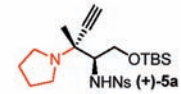
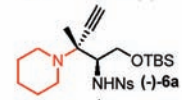
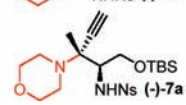
at the propargylic position (S_N2P) due to activation from the alkyne, but a mixture of regioisomeric products can be obtained with $S_N2'P$ attack on the alkyne to give an allene or attack occurring at the homopropargylic carbon (S_N2H). However, when a trisubstituted ethynyl aziridine is employed, ring opening occurs at the more substituted carbon. Thus, fully substituted carbons can be obtained in a stereoselective manner.

The ethynyl trisubstituted aziridine that we have used in this study was the known aziridine **1**[4c] for its relative ease of synthesis. In addition, this aziridine possesses two functional group handles: the silyl ether and the alkyne, which can be further manipulated.

Cyclic and aliphatic amines (Table 1) are not reported to participate in ring opening reactions with activated aziridines

Table 1. Nucleophile Ring Opening with Cyclic and Aliphatic Amines[a]



entry	amine	product	yield[b]
1	 2	 NHNs (+)-2a	81%[c]
2	 3	 NHNs (+)-3a	93%
3	 4	 NHNs (-)-4a	70%[d,e]
4	 5	 NHNs (+)-5a	quant
5	 6	 NHNs (-)-6a	quant
6	 7	 NHNs (-)-7a	99%

[a] Reaction condtions: aziridine (1 equiv), amine (2 equiv), $PhCH_3$ (0.1 M). [b] Isolated yield. [c] Same reaction conditions as footnote *a* with the following exception: amine (6 equiv). [d] Same reaction conditions as footnote *a* with the following exception: CH_2Cl_2/MeCN (1:1); (0.1 M). [e] Same reaction conditions as footnote *a* with the following exception: amine (4 equiv).

(6) (a) Desai, M. C.; Lefkowitz, S. L.; Thadeio, P. F.; Longo, K. P.; Snider, R. M. *J. Med. Chem.* **1992**, *35*, 4913. (b) Rosen, T.; Seeger, T. F.; McLean, S.; Desai, M. C.; GuarinoK., J.; Bryce, D.; Pratt, K.; Heym, J.; Chalabi, P. M. *J. Med. Chem.* **1993**, *36*, 3197. (c) Desai, M. C.; Thadeio, P. F.; Lefkowitz, S. L. *Tetrahedron Lett.* **1993**, *34*, 5831. (d) Chandrasekhar, S.; Mohanty, P. K. *Tetrahedron Lett.* **1999**, *40*, 5071. (e) Yamakazi, N.; Atobe, M.; Kibayashi, C. *Tetrahedron Lett.* **2002**, *43*, 7979. (f) Tsuritani, N.; Yamada, K. I.; Yoshikawa, N.; Shibasaki, M. *Chem. Lett.* **2002**, 276. (g) Huang, P. Q.; Liu, L. X.; Wei, B. G.; Ruan, Y. P. *Org. Lett.* **2003**, *5*, 1927. (h) Oshitari, T.; Mandai, T. *Synlett* **2006**, 3395. (i) Davis, F. A.; Zhang, Y.; Li, D. *Tetrahedron Lett.* **2007**, *48*, 7838.

(7) (a) Smith, P. W.; Sollis, S. L.; Howes, P. D.; Cherry, P. C.; Starkey, I. D.; Cobley, K. N.; Weston, H.; Scicinski, J.; Merritt, A.; Whittington, A.; Wyatt, P.; Taylor, N.; Green, D.; Bethell, R.; Madar, S.; Fenton, R. J.; Morley, P. J.; Pateman, T.; Beresford, A. *J. Med. Chem.* **1998**, *41*, 787. (b) Smith, P. W.; Robinson, J. E.; Evans, D. N.; Sollis, S. L.; Howes, P. D.; Trivedi, N.; Bethell, R. C. *Bioorg. Med. Chem. Lett.* **1999**, *9*, 601.

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(9) Anand, R. V.; Pandey, G.; Singh, V. K. *Tetrahedron Lett.* **2002**, *43*, 3975.

(10) (a) Anaya de Parrodi, C.; Vazques, V.; Quintero, L.; Juarista, E. *Synth. Commun.* **2001**, *31*, 3295. (b) Yadav, J. S.; Reddy, B. V. S.; Rao, K. V.; Raj, K. S.; Prasad, A. R. *Synthesis* **2002**, *2002*, 1061. (c) Yadav, J. S.; Reddy, B. S. V.; Jyothirmai, B. *Synlett* **2002**, *2002*, 53. (d) Swamy, N. R.; Venkateswarlu, Y. *Synth. Commun.* **2003**, *33*, 547.

(11) Reddy, M. A.; Reddy, L. R.; Bhanumathi, N.; Rao, K. R. *Chem. Lett.* **2001**, 246.

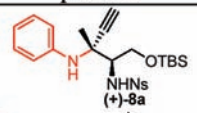
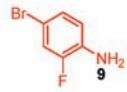
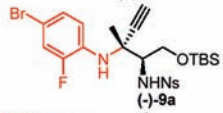
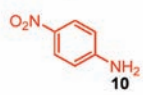
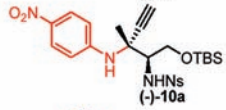
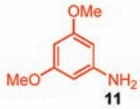
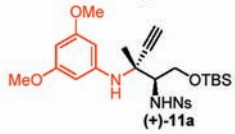
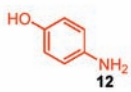
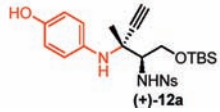
(12) (a) O'Neil, I. A.; Woolley, J. C.; Southern, J. M.; Hobbs, H. *Tetrahedron Lett.* **2001**, *42*, 8243. (b) Watson, I. D. G.; Yudin, A. K. *J. Org. Chem.* **2003**, *68*, 5160.

under Lewis acid catalysis,[10] but the mild non-Lewis acidic conditions described here gave excellent yields (70%−quant) of the ring opened product. Cyclic amines differed in their reaction times (0.5−3 h) with **1**, but all gave the desired product in excellent yields. Both primary and secondary aliphatic amines were slower in their respective reaction times, compared to cyclic amines, so an excess of the amine was used to accelerate the reaction. It is important to note that this had no adverse effects on the outcome of the reaction, and the reaction was also compatible with an alcohol functional group on the nucleophile (entries 2 and 3).

Aromatic amines (Table 2) also gave good yields of the ring opened products. Both electron-deficient (entries 2 and 3) and electron-rich (entry 5) aryl amines were sufficiently nucleophilic to participate. Electron-deficient aromatic amines did require mild heating, as a result of their poor nucleophilicity, but even upon heating, the regioselectivity was maintained. This is of interest because non-nucleophilic N-containing compounds are known to need a catalyst for conjugate addition to electron-poor olefins,[14] but, in our hands, a catalyst was not necessary. 4-Hydroxyaniline, under neutral conditions, reacted solely at the nitrogen atom to give product **12a** in 89% yield. Protection of the phenol was not necessary.

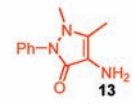
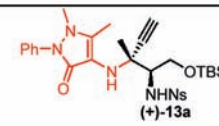
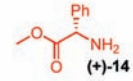
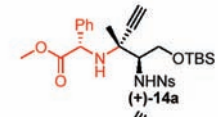
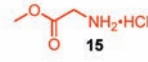
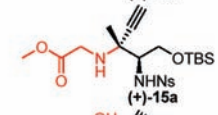
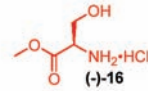
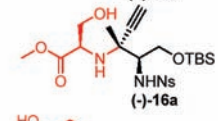
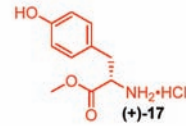
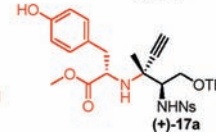
Amino pyrazolone **13** and amino acid derivatives, either as the free base or the hydrochloride salt, were also able to act as nucleophiles toward the aziridine (Table 3). An equimolar amount of triethylamine was used to neutralize the hydrochloride salt, and the amino acids that had two other groups that displayed no reactivity (entries 4 and 5), gave the 1,2-amine as the only product.

Table 2. Nucleophilic Ring Opening with Aromatic Amines[a]

entry	aryl amine	product	yield[b]
1	 8	 (+)-8a	69%
2	 9	 (-)-9a	86%[c]
3	 10	 (-)-10a	70%[c]
4	 11	 (+)-11a	98%
5[b]	 12	 (+)-12a	89%[d]

[a] Reaction conditions: aziridine (1 equiv), aromatic amine (2 equiv), $PhCH_3$ (0.1 M). [b] Isolated yield. [c] Same reaction conditions as footnote *a* with the following exception: reaction heated to 55 °C. [d] Same reaction conditions as footnote *a* with the following exception: DMF (0.1 M).

Table 3. Nucleophilic Ring Opening with Amino Pyrazolone and Amino Acids[a]

entry	amine	product	yield[b]
1	 13	 (+)-13a	87%
2	 (+)-14	 (+)-14a	94%[c]
3	 15	 (+)-15a	82%[d]
4	 (-)-16	 (-)-16a	74%[d,e]
5	 (+)-17	 (+)-17a	68%[d,f]

[a] Reaction conditions: aziridine (1 equiv), amine (2 equiv), CH_2Cl_2 (0.1 M). [b] Isolated yield. [c] Reaction conditions: amine (6 equiv), $PhCH_3$ (0.1 M). [d] Salt was neutralized with equal molar amount of TEA and amine salt. [e] Reaction conditions: amine (4 equiv), CH_2Cl_2/MeCN (1:1), at 55 °C. [f] Same reaction conditions as footnote *e* with the following exception: amine (6 equiv).

The regio- and stereochemistry of the products were confirmed by X-ray analysis. From the ORTEP drawings of **2a** and **7a** (Figure 2) it is clear that the nitrogen of the amine is bonded to the more substituted carbon of the former aziridine and that the reaction proceeded with inversion.

The ring opening reaction with amines can be applied to various types of trisubstituted aziridines (Table 4). Aziridine **18**, which is diastereomeric at the C2 position, proceeded well, yielding only one regioisomer. This result shows that the reaction is stereospecific with the ring opening occurring with inversion. The reaction is ame-

(13) Chemla, F.; Ferreira, F. *Curr. Org. Chem.* **2002**, *6*, 539.
(14) Gimbert, C.; Moreno-Mañas, M.; Pérez, E.; Vallribera, A. *Tetrahedron* **2007**, *63*, 8305.

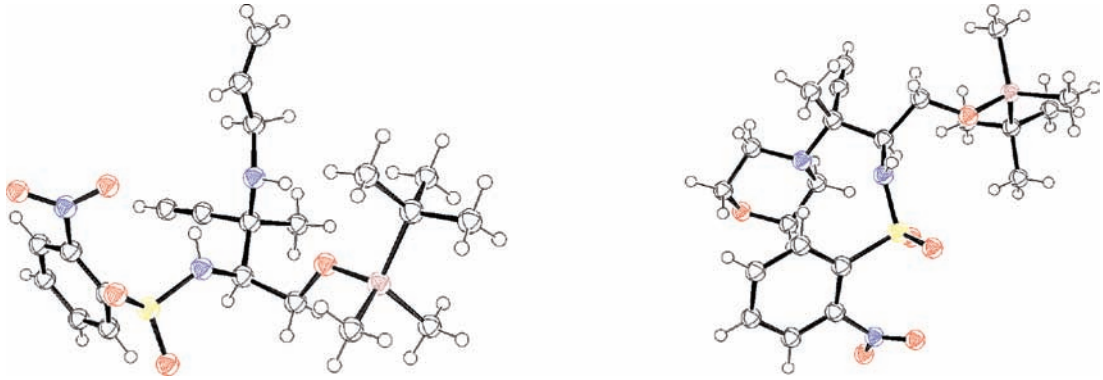
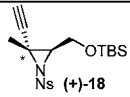
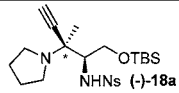
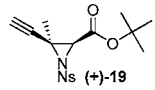
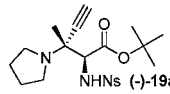
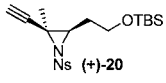
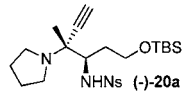
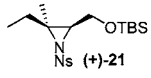
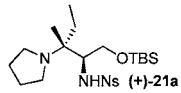
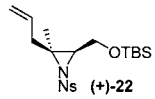
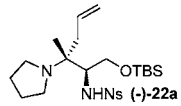


Figure 2. ORTEP drawings of compounds **2a** and **7a**.

nable to other functional groups at C3, as aziridine **19** has a *tert*-butyl ester[4c] and **20** has the silyl ether homologated by one carbon from the aziridine ring. The regioselective ring opening of the homologated aziridine (**20**) indicates that the functional group at C3 does not play a role in directing the regioselectivity as the electronic properties of the aziridine should change, but the same regioselectivity is observed. The trisubstituted ethyl (**21**) and allyl (**22**) aziridines also underwent ring opening, albeit with a longer reaction time (3 days), thus showing that the alkyne is not needed to direct the ring opening.

In conclusion, we have developed a method to make substituted 1,2-diamines via nucleophilic ring opening of an aziridine. The ring opening occurs exclusively at the more hindered and electronically activated C2-carbon with inversion of configuration.

Table 4. Nucleophilic Ring Opening of Various Trisubstituted Aziridines with Pyrrolidine[a]

entry	aziridine	product	yield[b]
1			96%
2			90%
3			87%
4			81%
5			91%

[a] Reaction conditions: aziridine (1 equiv), pyrrolidine (2 equiv), $PhCH_3$ (0.1 M). [b] Isolated yield.

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Supporting Information Available: Spectroscopic data and procedures for aziridines **20** and **22** and ring opened products **2a**−**22a**. The crystallographic data for aziridine **20** and ring opened products **2a** and **7a**. This material is available free of charge via the Internet at http://pubs.acs.org.

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