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Silylmethyl-Substituted Aziridine and Azetidine as Masked 1,3- and 1,4-Dipoles for Formal [3 + 2] and [4 + 2] Cycloaddition Reactions

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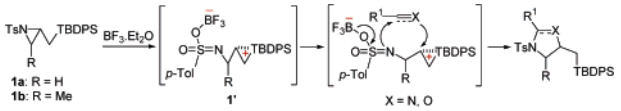
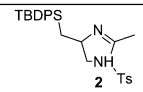
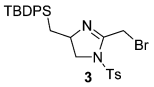
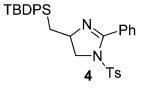
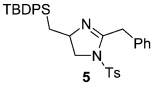
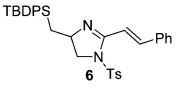
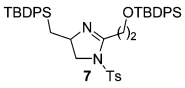
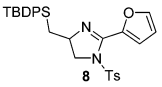
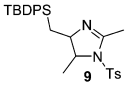
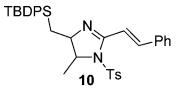
Small polyfunctional heterocycles play an important role in the drug discovery process.[1] Aziridine is a versatile building block for the syntheses of many nitrogen-containing biologically active molecules. It reacts with various nucleophiles, and its ability to undergo regioselective ring-opening contributes largely to its high synthetic value.[2,3] The cycloaddition reaction of aziridine with dipolarophiles, in particular, is a useful method for the syntheses of nitrogen-containing five- and six-ring molecules.[4] We report herein on the generation of 1,3- and 1,4-dipoles from aziridine and azetidine, respectively, wherein the negative charge is stabilized on the nitrogen by a sulfone function and the positive charge is stabilized on a carbon by *tert*-butyldiphenylsilylmethyl substituent through the β-effect of silicon[5,6] (Scheme 1), and their applications for formal [3 + 2] and [4 + 2] cycloadditions with nitrile and carbonyl substrates to generate five- and six-ring heterocycles in a single step. The cycloaddition chemistry of aziridine has thus far been limited to the stabilization of the above cation by an aryl substituent that has limited further usage. Since *tert*-butyldiphenylsilylmethyl is latent to CH_2OH function,[7] the present methodology widens the scope of the aziridine chemistry enormously.

Scheme 1



The reaction outlined in Scheme 1 entails initial nucleophilic attack of nitrile or cabonyl function at the positive end of the dipole **1′**. The subsequent intramolecular nucleophilic capture of the nitrilium or oxonium ion by the negatively charged nitrogen results in the formation of 2-imidazolines or oxazolidines, respectively. 2-Imidazolines are useful intermediates for the syntheses of molecules with pharmacological activities, such as anticancer, anti-inflammatory, and antidiabetic.[8] The reactions with nitriles, leading to 2-imidazolines, are collected in Table 1. $BF_3{\cdot}Et_2O$ offered the best results among the several Lewis acids attempted to promote the reaction. Both aromatic and aliphatic nitriles reacted with **1a** to furnish the products **2**−**8** in excellent yields (entries 1−7). TBDPS-protected 3-hydroxy propionitrile reacted without event while retaining the protecting group (entry 6). The reaction is stereospecific. The *cis*-**1b** reacted with acetonitrile to form the *cis* product exclusively (entry 8), and the *trans*-**1b** gave mainly the *trans* product at low temperature. However, the *trans*-**1b** exhibited increased tendency with increased temperature for the formation of the *cis* product (entry 9). The *cis* and *trans* relationships of the $TBDPSCH_2$ and CH_3 substituents in the adducts were ascertained by nOe measurements.

Table 1. Formal [3 + 2] Additions of Aziridines **1a**−**b** with Nitriles[a]

Entry	Aziridine	Nitrile	Product	Yield[b] % (*cis*:*trans*)
1	**1a**	CH_3CN	 **2**	90
2	**1a**	Br–CN	 **3**	85
3	**1a**	PhCN	 **4**	87
4	**1a**	Ph–CN	 **5**	90
5	**1a**	Ph–CN	 **6**	84
6	**1a**	TBDPSO–$(CH_2)_2$–CN	 **7**	82
7	**1a**		 **8**	87
8	**1b** (*cis*)	CH_3CN	 **9**	92 (95:5)[c] 92 (90:10)
9	**1b** (*trans*)	CH_3CN	**9**	92 (25:75)[c] 92 (56:44)
10	**1b** (*cis*/*trans*)	Ph–CN	 **10**	86 (67:33)

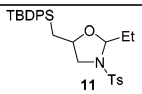
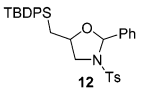
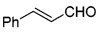
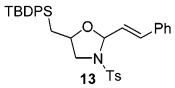
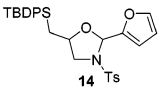
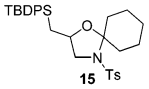
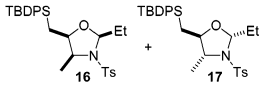
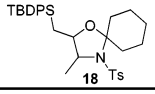
[a] Unless noted otherwise, all the reactions were carried out in CH_2Cl_2 for 5 min using 1 equiv each of the nitrile and $BF_3{\cdot}Et_2O$ at 25 °C. [b] Isolated yields. [c] Reaction was conducted at −78 °C.

We ascertained next the efficacy of the above aziridine-derived 1,3-dipole for reaction with carbonyl species to construct oxazolidines. $BF_3{\cdot}Et_2O$ was discovered again to be the most effective Lewis acid as several other Lewis acids were found to be either much less effective or not effective at all. The reactions proceeded smoothly to generate the desired products in excellent yields (Table 2). Both aromatic and aliphatic carbonyl compounds reacted with **1a** to furnish the products **11**−**15** (entries 1−5). The reaction is stereospecific. The *cis*-**1b** reacted with propanal to form predominantly the *cis* product **16** (entry 6), and the *trans*-**1b** gave mainly the *trans* product (entry 7) at low temperature. However, *trans*-**1b** exhibited increased tendency with increasing temperature for the formation of the *cis* product. Thus, three stereocenters had been generated in the product with high control by taking advantage of aziridine's methyl substituent. The relative stereochemistries of the substituents in the adducts were ascertained by nOe measurements.

We have extended the above chemistry to the silylmethyl-substituted azetidine **19** to generate the 1,4-dipole **19′** and then employed the same for [4 + 2] cycloaddition (Scheme 2). The cycloaddition of azetidine with dipolarophiles constitutes a powerful protocol for the formation of nitrogen-containing six-ring hetero-

10.1021/ja055664t CCC: $30.25

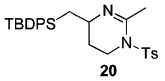
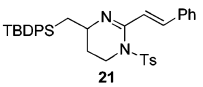
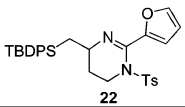
Table 2. [3 + 2] Cycloadditions of **1a**−**b** with Carbonyl Substrates[a]

Entry	Aziridine	Carbonyl	Product	Yield[b] % (*cis*:*trans*)
1	**1a**	EtCHO	 **11**	90 (67:33) 90 (50:50)[c]
2	**1a**	PhCHO	 **12**	87 (57:43)
3	**1a**		 **13**	95 (57:43)
4	**1a**		 **14**	93 (52:48)
5	**1a**		 **15**	80
6	**1b** (*cis*)	EtCHO	 **16** + **17**	92 (95:5)[c] 92 (90:10)
7	**1b** (*trans*)	EtCHO	**16** + **17**	92 (20:80)[c] 92 (47:53)
8	**1b** (cis/*trans*)		 **18**	82 (57:43)

[a] Unless noted otherwise, all the reactions were carried out in CH_2Cl_2 for 5 min using 1 equiv each of the carbonyl substrate and $BF_3{\cdot}Et_2O$ at 25 °C. [b] Isolated yields. [c] Reaction was conducted at −78 °C.

Scheme 2

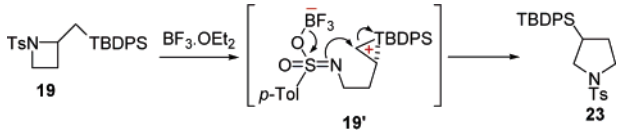
Table 3. [4 + 2] Cycloadditions of Azetidine **19** with Nitriles[a]

Entry	Nitrile	Product	Yield[b] %
1	CH_3CN	 **20**	65
2		 **21**	60
3		 **22**	62

[a] All the reactions were carried out in CH_2Cl_2 for 1 h using 1 equiv each of the nitrile substrate and $BF_3{\cdot}Et_2O$ at 25 °C. [b] Isolated yield.

cycles.[9] The azetidine **19** reacted smoothly with several nitriles under $BF_3{\cdot}Et_2O$ conditions at 25 °C to generate the tetrahydropyrimidine derivatives **20**−**22**. The results are collected in Table 3. Tetrahydropyrimidines are reported to exhibit a wide range of pharmacological activities.[10] The azetidine **19** was also employed to prepare a pyrrolidine derivative. Under $BF_3{\cdot}Et_2O$ conditions, **19** rearranged via silicon migration to form **23** in 92% isolated yield (Scheme 3). The pyrrolidine derivatives are ubiquitous among natural products as they are materials of much pharmacological interest.[11]

Scheme 3



The TBDPS function in **11** was transformed into a hydroxy group under basic conditions following a literature protocol[7] in 60% isolated yield with the sulfonamide function fully intact.

In summary, 2-*tert*-butyldiphenylsilylmethyl-substituted aziridines and the corresponding azetidine reacted efficiently with nitriles and carbonyl substrates to form imidazoline, oxazolidine, and tetrahydropyrimidine products. The azetidine rearranged to the pyrrolidine skeleton efficiently under $BF_3{\cdot}Et_2O$ conditions. These protocols will find application in synthesis, in general, and in drug design, in particular. The development of the enantioselective versions of these ring-forming methodologies and their applications to the syntheses of selected drug candidates are currently being explored.

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Supporting Information Available: Experimental details and characterization data (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

References

(1) (a) Bemis, G. W.; Murcko, M. A. *J. Med. Chem.* **1996**, *39*, 2887. (b) Schreiber, S. L. *Science* **2000**, *287*, 1964. (c) De Laet, A.; Hehenkamp, J. J.; Wife, R. L. *J. Heterocycl. Chem.* **2000**, *37*, 669. (d) Janvier, P.; Sun, X.; Bienayme, H.; Zhu, J. *J. Am. Chem. Soc.* **2002**, *124*, 2560.

(2) For reviews on reactions of aziridines, see: (a) Ibuka, T. *Chem. Soc. Rev.* **1991**, *27*, 145. (b) Tanner, D. *Angew. Chem., Int. Ed. Engl.* **1994**, *106*, 625. (c) Rayner, C. M. *Synlett* **1997**, 11. (d) McCoull, W.; Davis, F. A. *Syntheis* **2000**, 1347. (e) Sweeney, J. B. *Chem. Soc. Rev.* **2002**, *31*, 247. (f) Dhanukar, V. H.; Zavialov, L. A. *Curr. Opin. Drug Discovery Dev.* **2002**, *5*, 918.

(3) (a) Dahl, R. S.; Finney, N. S. *J. Am. Chem. Soc.* **2004**, *126*, 8356. (b) Bussolo, V. D.; Romano, M. R.; Pineschi, M.; Crotti, P. *Org. Lett.* **2005**, *7*, 1299.

(4) (a) Tufariello, J. J. In *1,3-Dipolar Cycloaddition Chemistry*; Padwa, A., Ed.; Wiley: Chichester, UK, 1984; Vol. 2, p 89. (b) Ungureanu, I.; Klotz, P.; Mann, A. *Angew. Chem., Int. Ed.* **2000**, *39*, 4615. (c) Pohlhaus, P. D.; Bowman, R. K.; Johnson, J. S. *J. Am. Chem. Soc.* **2004**, *126*, 2294.

(5) For discussions on silicon-stabilized β-carbocations, see: (a) Fleming, I. *Frontier Orbitals and Organic Chemical Reactions*; Wiley: London, 1976; p 81. (b) Lambert, J. B.; Zhao, Y.; Emblidge, R. W.; Salvador, L. A.; Liu, X.; So, J.-H.; Chelius, E. C. *Acc. Chem. Res.* **1999**, *32*, 183.

(6) For recent applications of β-effect of silicon to assist the cleavage of cyclopropane ring, see: (a) Yadav, V. K.; Balamurugan, R. *Org. Lett.* **2001**, *3*, 2717. (b) Yadav, V. K.; Balamurugan, R. *Chem. Commun.* **2002**, 514. (c) Yadav, V. K.; Balamurugan, R. *Org. Lett.* **2003**, *5*, 4281. (d) Yadav, V. K.; Sriramurthy, V. *Angew. Chem., Int. Ed.* **2004**, *43*, 2669. (e) Yadav, V. K.; Sriramurthy, V. *Org. Lett.* **2004**, *6*, 4495. (f) Yadav, V. K.; Vijaya Kumar, N. *J. Am. Chem. Soc.* **2004**, *126*, 8652.

(7) (a) Smitrovich, J. H.; Woerpel, K. A. *J. Org. Chem.* **1996**, *61*, 6044. (b) Liu, D.; Kozmin, S. A. *Org. Lett.* **2002**, *4*, 3005.

(8) (a) Ueno, M.; Imaizumi, K.; Sugita, T.; Takata, I.; Takeshita, M. *Int. J. Immunopharm.* **1995**, *17*, 597. (b) Rondu, F.; LeBhihan, G.; Wang, X.; Lamouri, A.; Touboul, E.; Dive, G.; Bellahsene, B.; Renard, P.; Guardiola-Lemaitre, B.; Manechez, D.; Penicaud, L.; Ktorza, A.; Godfroid, J.-J. *J. Med. Chem.* **1997**, *40*, 3793. (c) Bousquet, P.; Feldman, J. *Drugs* **1999**, *58*, 799. (d) Gust, R.; Keilitz, R.; Schmidt, K.; von Rauch, M. *J. Med. Chem.* **2002**, *45*, 3356.

(9) (a) Ungureanu, I.; Klotz, P.; Schoenfelder, A.; Mann, A. *Chem. Commun.* **2001**, 958. (b) Prasad, B. A. B.; Bisai, A.; Singh, V. K. *Org. Lett.* **2004**, *6*, 4829.

(10) (a) Gennady, M.; Robert, L.; Aviva, L. *J. Biol. Chem.* **1999**, *274*, 6920. (b) Messer, W. S., Jr.; Abuh, Y. F.; Ryan, K.; Shephered, M. A.; Schroeder, M.; Abunada, S.; Sehgal, R.; El-Assadi, A. A. *Drug Dev. Res.* **1997**, *40*, 171.

(11) (a) O'Hagan, D. *Nat. Prod. Rep.* **2000**, *17*, 435. (b) Yus, M.; Soler, T.; Foubelo, F. *J. Org. Chem.* **2001**, *66*, 6207 and references therein. (c) Sasaki, M.; Yudin, A. K. *J. Am. Chem. Soc.* **2003**, *125*, 14242.

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