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$BiCl_3$ promoted aza-Prins type cyclization: a rapid and efficient synthesis of 2,4-disubstituted piperidines

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Abstract

Several N-protected homoallyl amines and epoxides were subjected to an aza-Prins cyclization. A rapid and efficient $BiCl_3$ promoted stereoselective synthesis of *trans*-2,4-disubstituted piperidine derivatives was achieved.

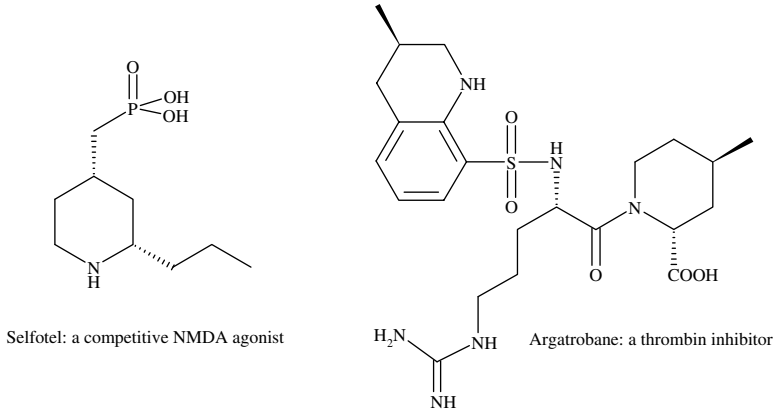
Keywords: Homoallyl amines; Aza-Prins-cyclization; $BiCl_3$; Piperidines

1. Introduction

Substituted piperidines are important heterocycles, which appear in many drugs and drug candidates (Fig. 1).[1,2] Compounds with the piperidine sub-structure exhibit anti-hypertensive,[3] antibacterial,[4] anticonvulsant,[5] anti-inflammatory and anti-proliferative activities. Many natural products having a piperidine moiety have been isolated[6] and thus this moiety is an important building block for various biologically significant compounds.[7,8]

Epoxides are extensively used as starting materials and intermediates in organic synthesis because of their ease of formation and versatile reactivity towards nucleophiles.

Bismuth salts have attracted attention due to their low toxicity, low cost and good stability.[9] They have been reported as environmentally benign Lewis acid



Selfotel: a competitive NMDA agonist

Argatrobane: a thrombin inhibitor

Fig. 1.

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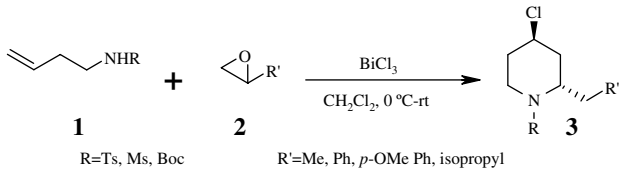


Scheme 1.

catalysts for Friedel-Craft reactions,[10] opening of epoxides,[11] allylation reactions[12] and intramolecular Sakurai cyclizations.[13]

Due to the importance of bismuth compounds in organic synthesis, we undertook a study on the utility of bismuth(III) chloride as a catalyst for the opening of epoxides with N-protected homoallyl amines. In this Letter, we

Table 1
Synthesis of 2,4-disubstituted piperidines

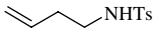
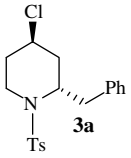
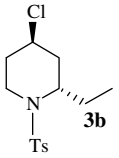
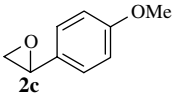
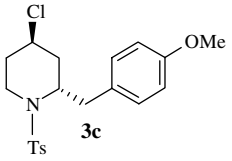
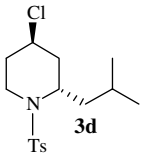
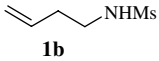
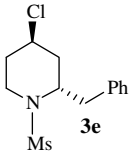
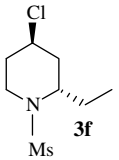
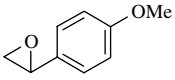
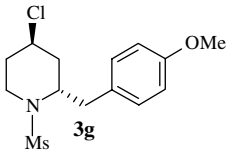
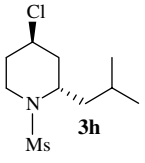
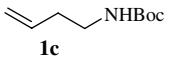
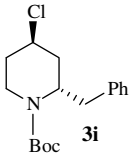
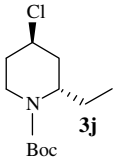
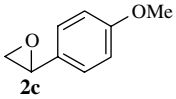
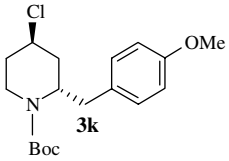
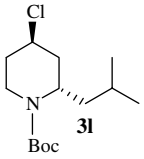
Entry	Homoallyl amine	Epoxide	Piperidine[a]	Yield[b]
1	 **1a**	 **2a**	 **3a**	93
2		 **2b**	 **3b**	80
3		 **2c**	 **3c**	90
4		 **2d**	 **3d**	88
5	 **1b**	 **2a**	 **3e**	92
6		 **2b**	 **3f**	83
7		 **2c**	 **3g**	94
8		 **2d**	 **3h**	87

Table 1 (*continued*)

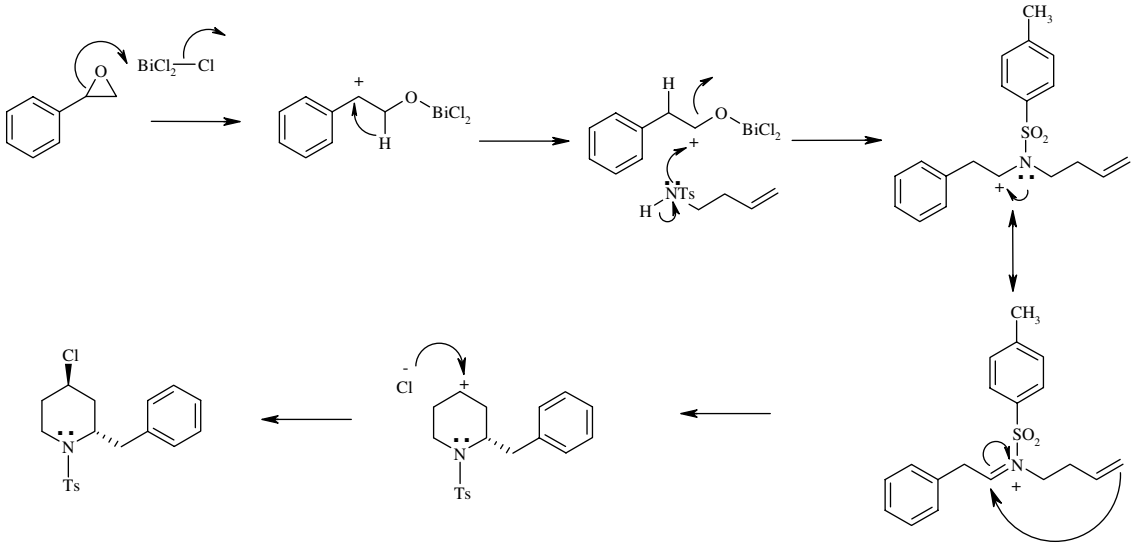
Entry	Homoallyl amine	Epoxide	Piperidine[a]	Yield[b]
9	 **1c**	 **2a**	 **3i**	93
10		 **2b**	 **3j**	84
11		 **2c**	 **3k**	92
12		 **2d**	 **3l**	90

[a] All the products were characterized by ^{1}H NMR and IR spectroscopy.
[b] Isolated and optimized overall yields.

Table 2
Comparison of yields and reaction times for the formation of **3a** using various Lewis acids

Lewis acid	Yield (%)	Reaction time (h)
$BiCl_3$	93	0.5
$InCl_3$	70	8
$ZrCl_4$	80	2
$FeCl_3$	68	6

describe the stereoselective synthesis of *trans*-4-chloro-2-substituted piperidines by the reaction of epoxides and N-protected homoallyl amines using $BiCl_3$ as a Lewis acid catalyst under mild reaction conditions (Scheme 1). Various mono-N-protected homoallyl amines were treated with structurally diverse epoxides in the presence of $BiCl_3$ in dichloromethane at 0 °C to room temperature for a period of 30–60 min (Table 1). Products **3** were obtained in good



Scheme 2.

to high yields. In all the cases the *trans*-2,4-diastereomer was the major product, the trans stereochemistry of the products being confirmed by comparison of the ^{1}H NMR data of **3a** with those reported.[14] With *N*-benzyl and *N*-allyl homoallyl amines the reaction was not successful. The reaction was carried out in various solvents and the best results were obtained in dichloromethane. We also used other Lewis acids to observe their effect on reaction time, yields and diastereoselectivity (Table 2). In all the cases diastereoselectivity remained the same (9:1) but shorter reaction times and higher yields were obtained with $BiCl_3$. Epoxides were always attacked on the less hindered carbon. The probable mechanism for this reaction is shown in Scheme 2. The reaction is expected to proceed through iminium ion formation stabilized by adjacent sulfonyl or carbonyl functionalities.

In conclusion, we report a novel and facile synthesis of piperidine derivatives using $BiCl_3$ as a catalyst for epoxide opening using N-protected homoallyl amines. The catalyst is insensitive to air moisture and the products were formed in high yields with high stereoselectivity.

2. General procedure

To a stirred solution of styrene oxide (240 mg, 2 mmol) and 1-(*N*-tosyl) amino-3-butene (450 mg, 2 mmol) in dry dichloromethane (15 mL) was added bismuth(III) chloride (630 mg, 2 mmol) at 0 °C under a nitrogen atmosphere. The mixture was allowed to attain room temperature and was stirred for 30 min. After work-up, the solution was concentrated and the crude mixture was purified by column chromatography over silica gel to give the 2,4-disubstituted piperidine.

3. Spectral analysis of selected compounds

3.1. *trans*-2-Benzyl-4-chloro-1-tosylpiperidine (**3a**)

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.54 (2H, d, $J = 8.3$ Hz), 7.24 (5H, m), 7.10 (2H, d, $J = 6.0$ Hz), 4.36 (1H, m), 4.15 (1H, m), 3.83 (1H, dd, $J = 11.3$, 3.0 Hz), 3.11 (1H, td, $J = 11.3$, 3.0 Hz), 2.79 (2H, m), 2.41 (3H, s), 2.11 (1H, m), 2.00 (1H, m), 1.66 (2H, m). IR (KBr, cm^{-1}): 3029, 2931, 1597, 1455, 1156. Anal. Calcd for $C_{19}H_{22}ClNO_2S$: C, 62.71; H, 6.09; N, 3.85. Found: C, 62.68; H, 6.12; N, 3.90.

3.2. *trans*-4-Chloro-2-ethyl-1-tosylpiperidine (**3b**)

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.69 (2H, d, $J = 8.4$ Hz), 7.29 (2H, d, $J = 8.4$ Hz), 4.00 (2H, m), 3.85 (1H, dd, $J = 12.8$, 2.3 Hz), 3.00 (1H, td, $J = 12.8$, 2.3 Hz), 2.45 (3H, s), 1.99 (2H, m), 1.62 (1H, m), 1.47 (1H, m), 1.25 (2H, m), 0.90 (3H, t, $J = 7.6$ Hz). IR (KBr, cm^{-1}): 2924, 2858, 1596, 1453, 1334, 1155. Anal. Calcd for $C_{14}H_{20}ClNO_2S$: C, 55.71; H, 6.68; N, 4.64. Found: C, 55.76; H, 6.72; N, 4.67.

3.3. *trans*-2-Benzyl-4-chloro-1-mesylpiperidine (**3e**)

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.24 (5H, m), 4.37 (1H, m), 4.21 (1H, m), 3.84 (1H, dd, $J = 14.6$, 2.3 Hz), 3.13 (1H, td, $J = 12.8$, 2.3 Hz), 2.88 (2H, m), 2.22 (3H, s), 1.92 (2H, m), 1.41 (2H, m). IR (KBr, cm^{-1}): 3040, 2957, 1492, 1458, 1339, 1163. Anal. Calcd for $C_{13}H_{18}ClNO_2S$: C, 54.25; H, 6.30; N, 4.87. Found: C, 54.28; H, 6.32; N, 4.86.

3.4. *trans*-4-Chloro-2-ethyl-1-mesylpiperidine (**3f**)

^{1}H NMR (300 MHz, $CDCl_3$): δ 4.00 (2H, m), 3.81 (1H, dd, $J = 12.8$, 2.3 Hz), 3.03 (1H, td, $J = 12.8$, 2.6 Hz), 2.87 (3H, s), 2.16 (2H, m), 1.25 (2H, m), 1.13 (2H, m), 0.97 (3H, t, $J = 7.6$ Hz). IR (KBr, cm^{-1}): 2942, 1598, 1447, 1352, 1152. Anal. Calcd for $C_8H_{16}ClNO_2S$: C, 42.57; H, 7.14; N, 6.20. Found: C, 42.61; H, 7.12; N, 6.24.

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References and notes

1. Howard, N.; Abell, C.; Blakemore, W.; Chessari, G.; Congreve, M.; Howard, S.; Jhoti, H.; Murray, C. W.; Seavers, L. C. A.; van Montfort, R. L. M. *J. Med. Chem.* **2006**, *49*, 1346.
2. Wright, J. L.; Gregory, T. F.; Kesten, S. R.; Boxer, P. A.; Serpa, K. A.; Meltzer, L. T.; Wise, L. D. *J. Med. Chem.* **2000**, *43*, 3408.
3. Petit, S.; Nallet, J. P.; Guillard, M.; Dreux, J.; Chermat, R.; Poncelet, M.; Bulach, C.; Simon, P.; Fontaine, C.; Barthelmebs, M.; Imbs, J. L. *Eur. J. Med. Chem.* **1991**, *26*, 19.
4. Zhou, Y.; Gregor, V. E.; Ayida, B. K.; Winters, G. C.; Sun, Z.; Murphy, D.; Haley, G.; Bailey, D.; Froelich, J. M.; Fish, S.; Webber, S. E.; Hermann, T.; Wall, D. *Bioorg. Med. Chem. Lett.* **2007**, *17*, 1206.
5. Bin, H.; Crider, A. M.; Stables, J. P. *Eur. J. Med. Chem.* **2001**, *36*, 265.
6. Bailey, P. D.; Millwood, P. A.; Smith, P. D. *Chem. Commun.* **1998**, *6*, 633.
7. Watson, P. S.; Jiang, B.; Scott, B. *Org. Lett.* **2000**, *2*, 3679.
8. Horton, D. A.; Bourne, G. T.; Smythe, M. L. *Chem. Rev.* **2003**, *103*, 893.
9. (a)*Organobismuth Chemistry*; Suzuki, H., Matano, Y., Eds.; Elsevier: Amsterdam, 2001; (b) Gaspard-Iloughmane, H.; Le Roux, C. *Eur. J. Org. Chem.* **2004**, 2517; (c) Leonard, N. M.; Wieland, L. C.; Mohan, R. S. *Tetrahedron* **2002**, *58*, 8373; (d) Antoniotti, S. *Synlett* **2003**, 1566; (e) Vidal, S. *Synlett* **2001**, 1194.
10. (a) Le Roux, C.; Dubac, J. *Synlett* **2002**, 181; (b) Desmurs, J. R.; Labrouillère, M.; Le Roux, C.; Gaspard, H.; Laporterie, A.; Dubac, J. *Tetrahedron Lett.* **1997**, *38*, 8871; (c) Répichet, S.; Le Roux, C.; Dubac, J.; Desmurs, J. R. *Eur. J. Org. Chem.* **1998**, 2743.
11. (a) Ogawa, C.; Azoulay, S.; Kobayashi, S. *Heterocycles* **2005**, *66*, 201; (b) Ollevier, T.; Lavie-Compin, G. *Tetrahedron Lett.* **2004**, *45*, 49; (c) Ollevier, T.; Lavie-Compin, G. *Tetrahedron Lett.* **2002**, *43*, 7891; (d) Bhatia, K. A.; Eash, K. J.; Leonard, N. M.; Oswald, M. C.; Mohan, R. S. *Tetrahedron Lett.* **2002**, *43*, 8139.
12. Wieland, L. C.; Zerth, H. M.; Mohan, R. S. *Tetrahedron Lett.* **2002**, *43*, 4597.

13. (a) Komatsu, N.; Uda, M.; Suzuki, H.; Takahashi, T.; Domae, T.; Wada, M. *Tetrahedron Lett.* **1997**, *38*, 7215; (b) Wieland, L. C.; Zerth, H. M.; Mohan, R. S. *Tetrahedron Lett.* **2002**, *43*, 4597; (c) Ollevier, T.; Ba, T. *Tetrahedron Lett.* **2003**, *44*, 9003; (d) Leroy, B.; Markó, I. E. *Org. Lett.* **2002**, *4*, 47; (e) Sreekanth, P.; Park, J. K.; Kim, J. W.; Hyeon, T.; Kim, B. M. *Catal. Lett.* **2004**, *96*, 201; (f) Choudary, B. M.; Chidara, S.; Raja Sekhar, C. V. *Synlett* **2002**, 1694; (g) Leroy, B.; Marko, I. E. *Org. Lett.* **2002**, *43*, 47.
14. Carballo, R. M.; Ramirez, M. A.; Rodriguez, M. L.; Martin, V. S.; Padron, J. I. *Org. Lett.* **2006**, *8*, 3837.