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A New and Efficient Procedure for $Bi(OTf)_3$-Promoted [3+2] Cycloaddition of *N*-Tosylaziridines to Yield Imidazolines

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[3+2] Cycloaddition of a series of substituted *N*-tosylaziridines with various nitriles promoted by $Bi(OTf)_3$ is described for the synthesis of substituted imidazolines under mild reaction conditions. The procedure works well over a range of substrates to give the corresponding products in good to excellent yields (up to 99%).

Introduction

Imidazolines are useful intermediates for the preparation of drugs, natural products, and relevant compounds, such as midaglizole, deriglidole, and efaroxan, which have been found to exhibit anti-inflammatory, antinociceptive, immunomodulating, antioxidative, antitumor, and anticancer activity.[1] Because of their synthetic value and pharmacological properties,[2] interest and considerable effort have focused on the construction of imidazolines and their derivatives. In recent years, some attractive methods for their synthesis have been developed.[3] Among these methods, the [3+2] cycloaddition of *N*-tosylaziridines with nitriles, as a more efficient method, provides direct access to them and tremendous efforts have been devoted to devising catalytic versions of this transformation. Several Lewis acids including $BF_3{\cdot}Et_2O$,[4,7] $Cu(OTf)_2$,[5] ZnX_2 (X = Cl, Br, I),[6] $Zn(OTf)_2$,[7] and $Sc(OTf)_3$[8] have been employed as catalysts and identified for this transformation. Despite these creative efforts and significant progress, the design of new catalysts that are cheaper and more efficient and the development of new methods that are more effective remain a considerable challenge and are a long-standing problem. The use of Lewis acids in organic synthesis, especially in catalysis, has been one of the most rapidly developing fields in synthetic organic chemistry. Among these Lewis acids, bismuth(III) trifluoromethanesulfonate, $[Bi(OTf)_3]$, has attracted much attention and has also been used in numerous reactions[9] in the last decade due to its strong activity and low cost relative to those of most other known catalysts, easy removal by filtration, versatility, and water-stability.[10] Herein, we will describe another new application of $Bi(OTf)_3$ as Lewis acid catalyst, which promotes the [3+2] cycloaddition reaction of *N*-tosylaziridines with nitriles to afford excellent yields (up to 99%) under mild conditions.

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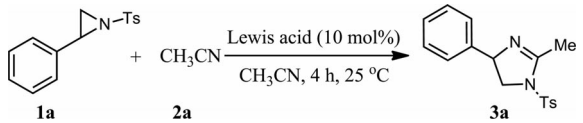
Results and Discussion

Optimization of the Reaction Conditions

Initially, with *N*-tosyl-2-phenylaziridine (**1a**) and acetonitrile (**2a**) as the model reaction, our aim was to identify the best catalyst for this reaction. Consequently, a series of Lewis acids were screened under an atmosphere of air at room temperature. As summarized in Table 1, the significant effect of the central metal on the yield was observed. When $Ti(OiPr)_4$ was tried, the reaction did not take place (Table 1, entry 1). Other Lewis acids such as $ZnCl_2$, $FeCl_3$, $ZrCl_4$, $Sm(OTf)_3$, $La(OTf)_3$, $In(OTf)_3$, and $BF_3{\cdot}Et_2O$ afforded weaker effects (Table 1, entries 2–8). To our delight, this initial attempt revealed that $Bi(OTf)_3$ possessed the best activity and afforded the highest yield (38%) (Table 1, entry 9).

Having identified $Bi(OTf)_3$ as a viable activator, an optimization of other reaction conditions was undertaken to lead to further improvements in the reaction, and the results are presented in Table 2. Solvent screening revealed that no products could be obtained with toluene and THF. CH_2Cl_2 provided the product in 34% yield (Table 2, entry 3). However, CH_3CN showed the best potential, and a 38% yield was achieved (Table 2, entry 4). The reaction temperature evidently affected the yield (Table 2, entries 4–8). There was a tendency for higher temperature to result in higher yields. The yield of the reaction reached the highest value (67%) at 65 °C (Table 2, entry 8). Subsequently, the reaction time was investigated. Interestingly, the product was obtained with 75% yield in 1 h (Table 2, entry 10). Either reducing or prolonging the reaction time failed to increase the yield (Table 2, entries 8, 9, 11). The amount of CH_3CN had little or no effect on the reaction (Table 2, entries 10,

Table 1. The [3+2] cycloaddition reaction of *N*-tosyl-2-phenylaziridine with acetonitrile promoted by various Lewis acids.[a]



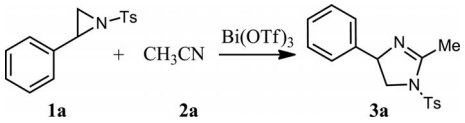
1a 2a 3a

Entry	Lewis acid	Yield [%][b]
1	$Ti(OiPr)_4$	ND[c]
2	$ZnCl_2$	14
3	$FeCl_3$	11
4	$ZrCl_4$	18
5	$Sm(OTf)_3$	22
6	$La(OTf)_3$	7
7	$In(OTf)_3$	17
8	$BF_3{\cdot}Et_2O$	10
9	$Bi(OTf)_3$	38

[a] All reactions were performed with *N*-tosyl-2-phenylaziridine (0.2 mmol) and Lewis acid (10 mol-%) in acetonitrile (1.0 mL) at 25 °C for 4 h. [b] Isolated yield. [c] Not detected.

12–13). Considering its operational stability and convenience, CH_3CN (0.5 mL) was chosen. On the contrary, the catalyst loading had an effect on the reactivity of the reaction. With increased catalyst loading, the reactivity was improved gradually and the yield rose steadily (Table 2, entries 13–16). Up to 99% yield was obtained when 30 mol-% $Bi(OTf)_3$ was used (Table 2, entry 16). In order to achieve milder reaction conditions, the reaction temperature was reduced and the catalyst loading was accordingly increased

Table 2. Effects of other conditions on the reaction.[a]



1a 2a 3a

Entry	Solvent	*T* [°C]	*t* [h]	Solvent dosage [mL]	Catalyst loading [mol-%]	Yield [%][b]
1	toluene	25	4	1	10	ND[c]
2	THF	25	4	1	10	ND
3	CH_2Cl_2	25	4	1	10	34
4	CH_3CN	25	4	1	10	38
5	CH_3CN	0	4	1	10	32
6	CH_3CN	45	4	1	10	50
7	CH_3CN	55	4	1	10	61
8	CH_3CN	65	4	1	10	67
9	CH_3CN	65	0.5	1	10	56
10	CH_3CN	65	1	1	10	75
11	CH_3CN	65	2	1	10	68
12	CH_3CN	65	1	0.25	10	73
13	CH_3CN	65	1	0.5	10	75
14	CH_3CN	65	1	0.5	5	53
15	CH_3CN	65	1	0.5	20	87
16	CH_3CN	65	1	0.5	30	99
17	CH_3CN	25	1	0.5	30	94
18	CH_3CN	25	1	0.5	40	98
19	CH_3CN	25	4	0.5	40	>99

[a] Unless otherwise indicated, all the reactions were carried out with the specified conditions according to the given procedure (see the Experimental Section). [b] Isolated yield. [c] Not detected.

to obtain better yields (Table 2, entries 17–19). In summary, extensive screening showed that the optimized reaction conditions were 0.2 mmol *N*-tosyl-2-phenylaziridine and 40 mol-% $Bi(OTf)_3$ in 0.5 mL CH_3CN in air at room temperature and a reaction time of 4 h (Table 2, entry 19).

Substrate Generality

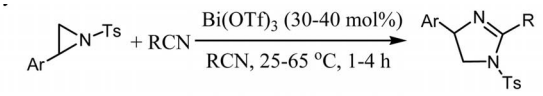
The [3+2] cyclization reaction was then extended to a variety of *N*-tosylaziridines derived from various substituted styrenes with acetonitrile (**2a**) (aliphatic nitrile) and benzonitrile (**2b**) (aromatic nitrile). The reaction worked with either acetonitrile or benzonitrile equally well, and the corresponding products were obtained in good to excellent yields (Table 3). With regard to acetonitrile, the electronic properties of the substituents on the aromatic ring of *N*-tosylaziridines had an obvious influence on the yield. Aziridines bearing electron-withdrawing groups supplied better results than those with electron-donating groups (Table 3, entries 2–5 vs. 6–10). It was noteworthy that steric hindrance had no evident effect on the yield, and the *ortho*-, *meta*-, and *para*-substituted aziridines afforded equable yields (Table 3, entries 3–10). In addition, aromatic aziridines with condensed rings were also found to be suitable substrates (Table 3, entries 11–12). As for benzonitrile, equally good results were attained (up to 95% yield). Both electronic and steric properties of the substituents on the phenyl rings of the aziridines played an important role on the yield. Somewhat lower yield was obtained with aziridines possessing electron-donating groups (Table 3, entry 8 vs. 5), and 2- and 4-chlorostyrene-derived aziridines gave higher yields than 3-chlorostyrene-derived aziridine (Table 3, entries 3, 5 vs. 4). Because of the effect of steric hindrance, 4-chlorostyrene-directed aziridine afforded better yield than 2-chlorostyrene-directed aziridine (Table 3, entry 5 vs. 3).

Furthermore, we explored the [3+2] cycloaddition of *N*-tosyl-2-phenylaziridine with other nitriles for a better understanding of the generality of this method in the presence of $Bi(OTf)_3$ under the optimum reaction conditions (Table 4). With substituted benzonitriles, the electronic properties of the substituents on the aromatic ring of the aziridines played an important role on the yield. Accordingly, the electron-richness of the substituent showed a positive effect on the yield (Table 4, entry 1 vs. 2). Aliphatic nitriles such as phenylacetonitrile could also afford 77% yield, which was lower than that with acetonitrile; this might be attributed to the steric effect (Table 4, entry 3).

Mechanistic Considerations

According to these experimental results and previous studies, we assume that $Bi(OTf)_3$ would be the active species that activated aziridine **1**, and a possible catalytic cycle that would explain the origin of the reactivity is proposed (Scheme 1). At the first stage, aziridinium salt **8** is formed through a combination of the N-atom of aziridines and the

Table 3. Substrate scope for the $Bi(OTf)_3$ promoted [3+2] cycloaddition of *N*-tosylaziridine **1** with nitrile **2**.

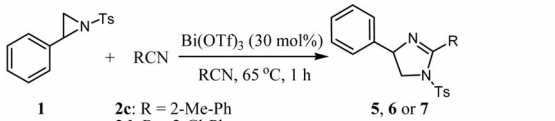


1 **2a**: R = Me; **2b**: R = Ph **3** or **4**

Entry	Aziridine	Product	Yield [%][a] R=Me[b]	Yield [%][a] R=Ph[c]
1	**1a**		99(**3a**)	95(**4a**)
2	**1b**		99(**3b**)	95(**4b**)
3	**1c**		99(**3c**)	84(**4c**)
4	**1d**		99(**3d**)	75(**4d**)
5	**1e**		99(**3e**)	95(**4e**)
6	**1f**		83(**3f**)	-
7	**1g**		84(**3g**)	-
8	**1h**		88(**3h**)	84(**4h**)
9	**1i**		90(**3i**)	-
10	**1j**		91(**3j**)	-
11	**1k**		94(**3k**)	-
12	**1l**		99(**3l**)	90(**4l**)

[a] Isolated yield. Satisfactory spectroscopic data were obtained for these compounds (see Supporting Information). [b] These reactions were performed with aziridine **1** (0.2 mmol) and $Bi(OTf)_3$ (40 mol-%) in acetonitrile (0.5 mL) at 25 °C under an atmosphere of air for 4 h. [c] These reactions were performed with aziridine **1** (0.2 mmol) and $Bi(OTf)_3$ (30 mol-%) in benzonitrile (0.5 mL) at 65 °C in air for 1 h.

Table 4. [3+2] Cycloaddition of *N*-tosyl-2-phenylaziridine with a variety of nitriles (RCN) in the presence of $Bi(OTf)_3$.[a]

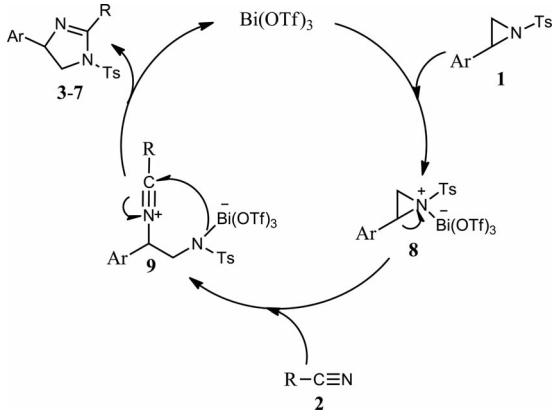


1 **2c**: R = 2-Me-Ph; **2d**: R = 2-Cl-Ph; **2e**: R = Bn **5**, **6** or **7**

Entry	Aziridine	Nitrile	Product	Yield [%][b]
1		**2c**	**(5)**	95
2	**1a**	**2d**	**(6)**	70[c]
3		**2e**	**(7)**	77

[a] These reactions were performed with *N*-tosyl-2-phenylaziridine (**1a**) (0.2 mmol) and $Bi(OTf)_3$ (30 mol-%) in nitrile (0.5 mL) at 65 °C in air for 1 h. [b] Isolated yield. [c] In this case, CH_2Cl_2 served as the solvent, and 10 equiv. of nitrile was used.

Bi center of $Bi(OTf)_3$, which enhances the electrophilicity of the C-atom of the aziridines. At the second stage, the nitrile attacks the substituted C-atom of the nitrogen-containing heterocycle of salt **8** activated to form key intermediate **9**. At the third stage, the C-atom of the nitrile is attacked by the activated N-atom to generate the product, which is more stable in view of stereostructure, and $Bi(OTf)_3$ is regenerated.



Scheme 1. The proposed catalytic cycle.

Conclusions

We have described $Bi(OTf)_3$ as a novel and efficient catalyst in the [3+2] cycloaddition of aziridines with nitriles and developed a new and direct strategy for the synthesis of imidazolines under mild reaction conditions. More importantly, good to excellent yields have been obtained for a wide variety of substrates. The attractive advantages of this pres-

ent method include employing easily available, relatively inexpensive, water-stable $Bi(OTf)_3$ as catalyst, experimental ease of operation, extremely mild conditions – room temperature with the tolerance of moisture and air, with almost no side reaction.

Experimental Section

Typical Procedure for the Synthesis of Imidazolines: Nitrile **2** (0.5 mL) was added to a mixture of aziridine **1** (0.2 mmol) and $Bi(OTf)_3$. The reaction mixture was stirred at the specified temperature for a period of time under an atmosphere of air. After completion of the reaction, as indicated by TLC, the mixture was quenched with water and extracted with ethyl acetate (2 × 5 mL). The combined organic layers were dried with anhydrous Na_2SO_4 and concentrated under vacuum. The residue was purified by column chromatography on silica gel with petroleum ether/ethyl acetate to afford imidazoline.

Supporting Information (see footnote on the first page of this article): General methods, experimental procedure for the synthesis of imidazolines and characterization data.

[1] a) F. Rondu, G. Le Bihan, X. Wang, A. Lamouri, E. Touboul, G. Dive, T. Bellahsene, B. Pfeiffer, P. Renard, B. Guardiola-Lemaitre, D. Manechez, L. Penicaud, A. Ktorza, J. J. Godfroid, *J. Med. Chem.* **1997**, *40*, 3793–3803; b) M. Ueno, K. Imaizumi, T. Sugita, I. Takata, M. Takeshita, *Int. J. Immunopharmacol.* **1995**, *17*, 597–603; c) G. Le Bihan, F. Rodu, A. Pelé-Tounian, X. Wang, S. Lidy, E. Touboul, A. Lamouri, G. Dive, J. Huet, B. Pfeiffer, P. Renard, B. Guardiola-Lemaitre, D. Manéchez, L. Pénicaud, A. Ktorza, J. J. Godfroid, *J. Med. Chem.* **1999**, *42*, 1587–1603.

[2] a) Y. Hsiao, L. S. Hegedus, *J. Org. Chem.* **1997**, *62*, 3586–3591; b) A. Viso, R. F. de la Pradilla, C. Guerrero-Strachan, M. Alonso, M. Martínez-Ripoll, I. André, *J. Org. Chem.* **1997**, *62*, 2316–2317; c) I. H. Gilbert, D. C. Rees, A. K. Crockett, R. C. F. Jones, *Tetrahedron* **1995**, *51*, 6315–6336; d) J. C. Jonas, M. J. Garcia-Barrado, I. Angel, J. C. Henquin, *Eur. J. Pharmacol.* **1994**, *264*, 81–84; e) T. L. Berridge, J. C. Doxey, A. G. Roach, *Eur. J. Pharmacol.* **1992**, *213*, 213–218.

[3] a) S. L. You, J. W. Kelly, *Org. Lett.* **2004**, *6*, 1681–1683; b) R. S. Bon, B. van Vliet, N. E. Sprenkels, R. F. Schmitz, F. J. J. de Kanter, C. V. Stevens, M. Swart, F. M. Bickelhaupt, M. B. Groen, R. V. A. Orru, *J. Org. Chem.* **2005**, *70*, 3542–3553; c) M. A. Eissenstat, J. D. Weaver III, *J. Org. Chem.* **1993**, *58*, 3387–3390; d) C. W. Derstine, D. N. Smith, J. A. Katzenellenbogen, *J. Am. Chem. Soc.* **1996**, *118*, 8485–8486; e) X. T. Zhou, Y. R. Lin, L. X. Dai, J. Sun, L. J. Xia, M. H. Tang, *J. Org. Chem.* **1999**, *64*, 1331–1334; f) V. G. Nenajdenko, V. M. Muzalevskiy, A. V. Shastin, E. S. Balenkova, E. V. Kondrashov, I. A. Ushakov, A. Y. Rulev, *J. Org. Chem.* **2010**, *75*, 5679–5688; g) S. Peddibhotla, S. Jayakumar, J. J. Tepe, *Org. Lett.* **2002**, *4*, 3533–3535; h) Q. Zhu, Y. X. Lu, *Org. Lett.* **2010**, *12*, 4156–4159; i) K. Worrall, B. Xu, S. Bontemps, B. A. Arndtsen, *J. Org. Chem.* **2011**, *76*, 170–180.

[4] a) B. A. B. Prasad, G. Pandey, V. K. Singh, *Tetrahedron Lett.* **2004**, *45*, 1137–1141; b) V. K. Yadav, V. Sriramurthy, *J. Am. Chem. Soc.* **2005**, *127*, 16366–16367; c) J. M. Concellón, E. Riego, J. R. Suárez, S. García-Granda, M. R. Díaz, *Org. Lett.* **2004**, *6*, 4499–4501; d) T. Hiyama, H. Koide, S. Fujita, H. Nozaki, *Tetrahedron* **1973**, *29*, 3137–3139.

[5] M. K. Ghorai, K. Ghosh, K. Das, *Tetrahedron Lett.* **2006**, *47*, 5399–5403.

[6] M. K. Ghorai, K. Das, A. Kumar, K. Ghosh, *Tetrahedron Lett.* **2005**, *46*, 4103–4106.

[7] S. Gandhi, A. Bisai, B. A. B. Prasad, V. K. Singh, *J. Org. Chem.* **2007**, *72*, 2133–2142.

[8] J. Wu, X. Y. Sun, H. G. Xia, *Tetrahedron Lett.* **2006**, *47*, 1509–1512.

[9] a) N. M. Leonard, L. C. Wieland, R. S. Mohan, *Tetrahedron* **2002**, *58*, 8373–8397; b) M. D. Carrigan, D. Sarapa, R. C. Smith, L. C. Wieland, R. S. Mohan, *J. Org. Chem.* **2002**, *67*, 1027–1030; c) J. R. Desmurs, M. Labrouillère, C. Le Roux, H. Gaspard, A. Laporterie, J. Dubac, *Tetrahedron Lett.* **1997**, *38*, 8871–8874; d) C. Le Roux, J. Dubac, *Synlett* **2002**, 181–200; e) S. Répichet, C. Le Roux, J. Dubac, J. R. Desmurs, *Eur. J. Org. Chem.* **1998**, 2743–2746; f) B. Leroy, I. E. Markó, *Tetrahedron Lett.* **2001**, *42*, 8685–8688; g) L. C. Wieland, H. M. Zerth, R. S. Mohan, *Tetrahedron Lett.* **2002**, *43*, 4597–4600; h) C. Le Roux, L. Ciliberti, H. Laurent-Robert, A. Laporterie, J. Dubac, *Synlett* **1998**, 1249–1251; i) A. Orita, C. Tanahashi, A. Kakuda, J. Otera, *Angew. Chem.* **2000**, *112*, 2999–3001; *Angew. Chem. Int. Ed.* **2000**, *39*, 2877–2879; j) M. D. Carrigan, D. A. Freiberg, R. C. Smith, H. M. Zerth, R. S. Mohan, *Synthesis* **2001**, 2091–2094; k) B. Garrigues, F. Gonzaga, H. Robert, J. Dubac, *J. Org. Chem.* **1997**, *62*, 4880–4882; l) H. Laurent-Robert, B. Garrigues, J. Dubac, *Synlett* **2000**, 1160–1162; m) N. M. Leonard, M. C. Oswald, D. A. Freiberg, B. A. Nattier, R. C. Smith, R. S. Mohan, *J. Org. Chem.* **2002**, *67*, 5202–5207; n) M. D. Carrigan, K. J. Eash, M. C. Oswald, R. S. Mohan, *Tetrahedron Lett.* **2001**, *42*, 8133–8135; o) J. Marquié, A. Laporterie, J. Dubac, *J. Org. Chem.* **2001**, *66*, 421–425; p) S. Répichet, C. Le Roux, P. Hernandez, J. Dubac, *J. Org. Chem.* **1999**, *64*, 6479–6482; q) K. A. Bhatia, K. J. Eash, N. M. Leonard, M. C. Oswald, R. S. Mohan, *Tetrahedron Lett.* **2001**, *42*, 8129–8132; r) E. Callens, A. J. Burton, A. G. M. Barremtt, *Tetrahedron Lett.* **2006**, *47*, 8699; s) R. M. A. Pinto, J. A. R. Salvador, C. Le Roux, *Synlett* **2006**, 2047–2050; t) T. Ollevier, Z. Li, *Org. Biomol. Chem.* **2006**, *4*, 4440–4443; u) T. Ollevier, E. Nadeau, V. Desyroy, *e-EROS Encyclopedia of Reagents for Organic Synthesis* **2009**.

[10] S. Vidal, *Synlett* **2001**, 1194–1195.

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