

## Heteropoly Acid as Efficient, Cost-effective, and Recyclable Solid Acid for the Rapid Synthesis of Substituted Imidazolines

J. S. Yadav,\* B. V. Subba Reddy, T. Pandurangam, and U. V. Subba Reddy

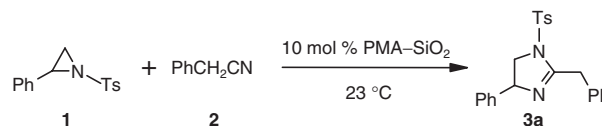
Division of Organic Chemistry, Indian Institute of Chemical Technology, Hyderabad-500 007, India

(Received May 19, 2008; CL-080505; E-mail: yadavpub@iict.res.in)

Aziridines undergo smooth ring opening with a range of nitriles in the presence of 10 mol % of phosphomolybdic acid supported on silica gel (PMA-SiO<sub>2</sub>) under mild reaction conditions to afford the corresponding imidazolines in good yields and with high regioselectivity. The use of silica gel as solid support facilitates an easy recovery and reuse of the catalyst thereby making the process quite simple, more convenient, and cost-effective.

Aziridines are well-known carbon electrophiles capable of reacting with various nucleophiles and their ability to undergo regioselective ring-opening reactions contributes largely to their synthetic value.<sup>1</sup> They are useful intermediates for the synthesis of many biologically interesting molecules such as amino acids,<sup>2</sup> heterocycles,<sup>3</sup> and alkaloids.<sup>4</sup> Aziridines can also undergo a formal [3 + 2] cycloaddition with a range of dipolarophiles leading to five-membered nitrogen-containing heterocycles.<sup>5,6</sup> In particular, the cycloaddition of aziridines with nitriles has special interest because the resultant imidazolines are known to exhibit a wide range of pharmacological activities.<sup>7</sup> Consequently, there have been some reports on the regioselective ring opening of aziridines with nitriles using acid catalysis such as boron trifluoride, zinc(II) bromide, scandium(III) triflate, and copper(II) triflate.<sup>8,9</sup> However, many of these procedures involve the use of stoichiometric amount of catalysts and require anhydrous conditions and also involve the formation of side products resulting in low conversion. Since, imidazolines are very useful targets in medicinal chemistry, the development of simple, convenient, cost-effective, and efficient approaches are highly desirable. Moreover, no attempt has been made to recycle the catalyst, thereby making the process more economic and environmentally friendly.

The use of heteropoly acids, HPAs, as environmentally friendly and economically viable solid acids, is increasing continuously owing to their ease of handling, high catalytic activities, and reactivities. They possess unique properties such as well-defined structure, Brønsted acidity, possibility to modify their acid-base and redox properties by changing their chemical composition (substituted HPAs), ability to accept and release electrons and high proton mobility, etc.<sup>10</sup> HPAs are very strong acids, approaching the super acid region, with a Brønsted acidity greatly exceeding that of ordinary mineral acids and solid acids. This makes it possible to carry out a catalytic process at low concentrations and at lower temperatures. In view of green chemistry, the substitution of harmful liquid acids by reusable solid HPAs as catalysts in organic synthesis is the most promising application of these acids.<sup>11</sup> Among them, phosphomolybdic acid (PMA, H<sub>3</sub>PMo<sub>12</sub>O<sub>40</sub>) is one of the less expensive and commercially available catalysts.<sup>12</sup> Supported HPAs are more active than unsupported HPAs. PMA-SiO<sub>2</sub> is a stable, non-hy-



Scheme 1.

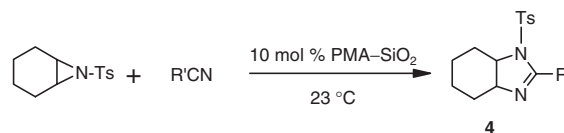
groscopic, and highly active catalytic system than unsupported PMA.<sup>13</sup>

In continuation of our efforts to explore the synthetic utility of phosphomolybdic acid supported on silica gel (PMA-SiO<sub>2</sub>),<sup>14</sup> we herein report a simple and convenient method for the synthesis of imidazolines from aziridines and nitriles. Initially, we attempted 1,3-dipolar cycloaddition of styrene *N*-tosylaziridine (1) with benzyl cyanide (2) in the presence of 10 mol % phosphomolybdic acid supported on silica gel. The reaction went to completion in 2.0 h at room temperature and the product was obtained 3a in 80% yield (Scheme 1).

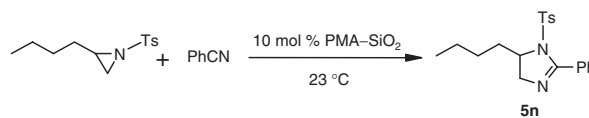
Similarly, benzonitrile and acetonitrile reacted effectively with styrene aziridine to produce the corresponding imidazolines in high yields (Entries b and c, Table 1). Aryl-*N*-tosylaziridines underwent smooth cycloaddition with nitriles by preferential attack at the benzylic position resulting in the formation of product 3a (Entries a-j, Table 1). Because of the stability of the benzylic carbocation, the cycloaddition is highly regioselective.<sup>9</sup> Furthermore; cyclohexene-*N*-tosylaziridine also reacted efficiently with various nitriles such as benzyl cyanide, benzonitrile and acetonitrile to afford the corresponding imidazoline 4 in good yields (Entries k-m, Table 1, Scheme 2).

However, alkyl aziridines such as *n*-hexene- and *n*-octene-*N*-tosylaziridines also participated well in this reaction (Entries n and o, Table 1) under identical conditions. In case of alkyl aziridines, the nucleophile attacks at less hindered terminal position to provide imidazolines 5 in moderate yields. In case of *N*-tosyl-alkyl aziridines (Entries n and o), the corresponding cycloadducts 5n and 5o were isolated as the sole products (Scheme 3).<sup>9</sup>

Thus, this method is highly regioselective affording imidazolines relatively in good yields. The reaction conditions are



Scheme 2.



Scheme 3.

**Table 1.** Cycloaddition of activated aziridines with nitriles catalyzed by PMA-SiO<sub>2</sub>

Entry	Aziridine 1	Nitrile 2	Product <sup>a</sup>	Yield/% <sup>b</sup>	Time/h
a		Ph-CN		80	2.0
b		PhCN		75	2.5
c		MeCN		85	1.5
d		PhCN		72	3.0
e		Ph-CN		78	2.5
f		Me-CN		81	2.5
g		Ph-CN		78	2.0
h		Me-CN		80	2.0
i		MeCN		83	2.0
j		PhCN		78	2.5
k		Ph-CN		70	4.0
l		PhCN		65	4.5
m		MeCN		72	4.0
n		PhCN		60	3.0
o		PhCN		62	3.0

<sup>a</sup>All products were characterized by <sup>1</sup>H NMR, IR, and mass spectrometry. <sup>b</sup>Isolated yield.

mild and no side products or decomposition of the products were observed. However, in the absence of catalyst, the reaction did not give the desired product even at 80 °C after long reaction times (8–12 h). The catalyst was separated from the reaction mixture by simple filtration. The recovered catalyst was washed with dichloromethane and dried in vacuo. Thus, recovered catalyst was reused for further reactions without significant loss of activity. For instance, treatment of styrene aziridine with acetonitrile for 1.5 h gave 85, 83, and 82% yield respectively over three cycles. This observation clearly shows the reusability of the catalyst. In all cases, the reactions were carried out at room

temperature under neat conditions. The scope and generality of this process is illustrated with respect to various aziridines and nitriles, and the results are presented in Table 1.<sup>15</sup>

In summary, we have demonstrated that PMA-SiO<sub>2</sub> is a highly efficient and reusable heterogeneous solid acid catalyst for the cycloaddition of activated aziridines with nitriles. The notable features of this method are high conversions, greater regioselectivity, cleaner reaction profiles, operational simplicity, easy availability, and reusability of the catalyst making it useful and attractive for the preparation of biologically relevant imidazolines.

#### References and Notes

- a) A. R. Katritzky, C. W. Rees, *Comprehensive Heterocyclic Chemistry*, Pergamon Press, Oxford, **1984**, Vol. 7, p. 47. b) J. E. G. Kump, in *Comprehensive Organic Synthesis*, ed. by B. M. Trost, I. Fleming, Pergamon Press, Oxford, **1991**, Vol. 7, p. 469.
- a) D. Tanner, *Angew. Chem., Int. Ed. Engl.* **1994**, 33, 599. b) W. McCoull, F. A. Davis, *Synthesis* **2000**, 1347.
- a) A. Dureault, I. Tranchepain, J. C. Depeyaz, *J. Org. Chem.* **1989**, 54, 5324. b) D. Tanner, H. M. He, *Tetrahedron* **1992**, 48, 6079.
- a) T. Hudlicky, H. Luna, J. D. Price, F. Rulin, *J. Org. Chem.* **1990**, 55, 4683. b) I. V. Kozhevnikov, *Chem. Rev.* **1998**, 98, 171.
- a) J. S. Yadav, B. V. S. Reddy, S. K. Pandey, P. Srihari, I. Prathap, *Tetrahedron Lett.* **2001**, 42, 9089. b) C.-H. Ding, L.-X. Die, X.-L. Hou, *Synlett* **2004**, 1691.
- a) J. O. Baeg, H. Alper, *J. Org. Chem.* **1992**, 57, 157. b) H. Maas, C. Bensimon, H. Alper, *J. Org. Chem.* **1998**, 63, 17. c) T. Munegumi, I. Azumaya, T. Kato, H. Masu, S. Saito, *Org. Lett.* **2006**, 8, 379.
- a) M. Ueno, K. Imaizumi, T. Sugita, I. Takata, M. Takeshita, *Int. J. Immunopharmacol.* **1995**, 17, 597. b) P. Bousquet, P. J. Feldman, *Drugs* **1999**, 58, 99.
- a) J. M. Concellon, E. Riego, J. R. Suarez, S. Garcia-Granda, M. R. Diaz, *Org. Lett.* **2004**, 6, 4499. b) M. K. Ghorai, K. Das, A. Kumar, K. Ghosh, *Tetrahedron Lett.* **2005**, 46, 4103. c) T. Hiyama, H. Koide, S. Fujita, H. Nozaki, *Tetrahedron* **1973**, 29, 3137. d) S. Gandhi, A. Bisai, B. A. B. Prasad, V. K. Singh, *J. Org. Chem.* **2007**, 72, 2133.
- a) J. Wu, X. Sun, H.-G. Xia, *Tetrahedron Lett.* **2006**, 47, 1509. b) M. K. Ghorai, K. Ghosh, K. Das, *Tetrahedron Lett.* **2006**, 47, 5399. c) B. A. B. Prasad, G. Pandey, V. K. Singh, *Tetrahedron Lett.* **2004**, 45, 1137. d) V. K. Yadav, V. Sriramamurthy, *J. Am. Chem. Soc.* **2005**, 127, 16366.
- M. Misono, I. Ono, G. Koyano, A. Aoshima, *Pure Appl. Chem.* **2000**, 72, 1305.
- I. V. Kozhevnikov, *Chem. Rev.* **1998**, 98, 171.
- a) N. Azizi, L. Torkiyan, M. R. Saidi, *Org. Lett.* **2006**, 8, 2079. b) G. D. K. Kumar, S. Baskaran, *Chem. Commun.* **2004**, 1026. c) H. Hamamoto, G. Anilkumar, H. Tohma, Y. Kita, *Chem.—Eur. J.* **2002**, 8, 5377. d) E. Rafiee, H. Jafari, *Bioorg. Med. Chem. Lett.* **2006**, 16, 2463.
- a) G. D. K. Kumar, S. Baskaran, *J. Org. Chem.* **2005**, 70, 4520. b) E. F. Kozhevnikova, E. G. Derouane, I. V. Kozhevnikov, *Chem. Commun.* **2002**, 1178. c) H. Firouzabadi, N. Iranpoor, K. Amani, *Synthesis* **2003**, 408.
- a) J. S. Yadav, S. Raghavendra, M. Satyanarayana, E. Balanarsaiah, *Synlett* **2005**, 2461. b) J. S. Yadav, M. Satyanarayana, E. Balanarsaiah, S. Raghavendra, *Tetrahedron Lett.* **2006**, 47, 6095.
- General procedure: A mixture of *N*-tosylaziridine (1 mmol), nitrile (10 mmol), and PMA-SiO<sub>2</sub> (10 mol %) was stirred at ambient temperature for the appropriate time (Table 1). After completion of the reaction as indicated by TLC, the reaction mixture was filtered and washed with dichloromethane (3 × 10 mL). The combined organic layers were dried over anhydrous Na<sub>2</sub>SO<sub>4</sub>, concentrated in vacuo and purified by column chromatography on silica gel (Merck, 100–200 mesh, ethyl acetate–hexane, 2:8) to afford pure imidazoline. The products were characterized by NMR, IR, and mass spectrometry and also by comparison with authentic samples.<sup>8,9</sup> 2-Ethyl-4,5-dihydro-4-(4-methoxyphenyl)-1-tosyl-1*H*-imidazole (3f) Viscous liquid: IR (neat):  $\nu_{\text{max}}$  3283, 2925, 2854, 1646, 1513, 1328, 1158, 1092, 814, 663 cm<sup>-1</sup>. <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>):  $\delta$  7.77–6.76 (m, 8H), 4.93 (dd, *J* = 8.0, 10.2 Hz, 1H), 4.14 (t, *J* = 10.2 Hz, 1H), 3.79 (s, 3H), 3.57 (dd, *J* = 8.0, 10.2 Hz, 1H), 2.77 (q, *J* = 8.0 Hz, 2H), 2.52 (s, 3H), 1.31 (t, *J* = 7.3 Hz, 3H). LC-MS: *m/z*: 359 (*M* + 1). <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>):  $\delta$  21.4, 29.5, 49.1, 55.2, 56.2, 81.2, 113.9, 126.9, 127.8, 129.6, 130.2, 134.3, 137.0, 143.2, 159.6.