Tetrahedron Letters 49 (2008) 4601–4603

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

Aziridine synthesis in the presence of catalytic amounts of pyridiniums or viologens

Zheng Xue, Arindam Mazumdar, Louisa J. Hope-Weeks †, Michael F. Mayer *

Department of Chemistry and Biochemistry, Texas Tech University, Lubbock, TX 79409-1061, USA

ARTICLE INFO

Article history:
Received 22 April 2008
Revised 17 May 2008
Accepted 19 May 2008
Available online 29 May 2008

ABSTRACT

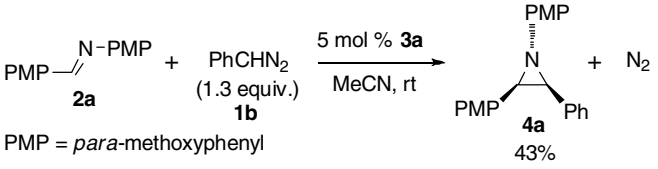
Pyridinium and viologen species were found to induce an aziridine-forming reaction from various imines and phenyldiazomethane. The reactions were generally high yielding and demonstrated *cis*-aziridine selectivity.

Aziridines are versatile precursors to an array of nitrogen-containing functionalities by way of ring-opening reactions.[1] The majority of these reactions generally feature quantitative conversion and high regioselectivity. As such, they have been additionally recognized as members of one of the three main classes of reactions that meet the criteria of click chemistry.[2]

Of modern catalytic methods for aziridine synthesis,[3] the catalytic synthesis of aziridines from diazo compounds (**1**) and imines (**2**) has been investigated extensively.[4,5] The vast majority of these reactions are reported to occur via one of two common mechanisms, that is, via addition of a carbenoid to an imine or via direct attack of a diazo compound onto a Lewis acid-activated imine.

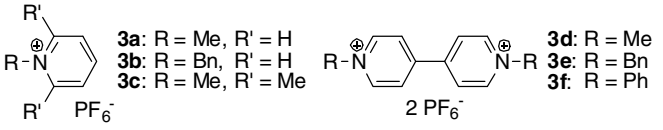
A recent Letter, however, disclosed the unique finding that aziridine-formation occurs from various imines and ethyl diazoacetate (EDA, **1a**) in room temperature ionic liquids without any catalysts or additives.[6] A patent from the same group further described high yielding syntheses of aziridines from EDA **1a** and various imines both in 1-butyl-3-methylimidazolium hexafluorophosphate (bmimPF_6) and in *N*-butylpyridinium hexafluorophosphate again without any additives or catalysts.[7] Given our interest in these reactions along with our motivation to develop new catalyst platforms, we were intrigued by the mode of action of these ionic liquids as well as the possibility of finding more potent analogs that could be used in catalytic quantities.

We initially examined the possible reaction of EDA **1a** with several imines (**2**) in the presence of catalytic quantities of *N*-methylpyridinium hexafluorophosphate **3a** but we observed only trace amounts of aziridine products (**4**).[8] When the more reactive phenyldiazomethane **1b** was used in place of EDA **1a**, we found a notable increase in the amount of aziridine formed. However, the percent conversion of **2a** and the isolated yield of **4a** was quite modest, Eq. 1.



(1)

In a search for more efficient pyridinium additives, a series of compounds (**3b–f**) that are structurally related to **3a** were synthesized and applied to the aziridine-forming reaction (Fig. 1).



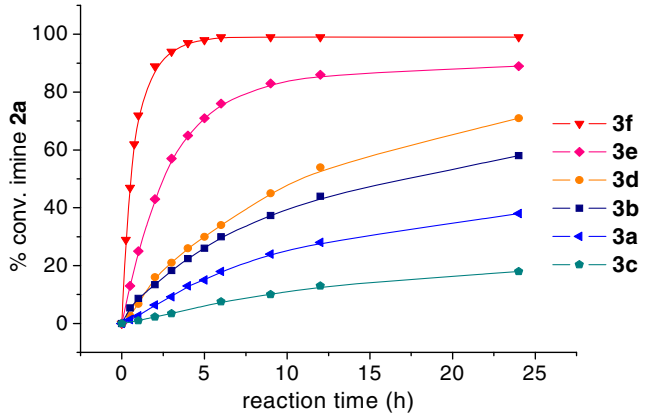


Figure 1. Consumption of imine **2a**, measured by ^{1}H NMR spectroscopy, in reactions performed as in Eq. 1 with additives **3a–f** at a fixed ionic strength (2.5 mM PF_6^-; 4 mol % **3a–c**; and 2 mol % **3d–f**).

* Corresponding author. Tel.: +1 806 742 0019; fax: +1 806 742 1289.
E-mail addresses: Louisa.Hope-Weeks@ttu.edu (L. J. Hope-Weeks), mf.mayer@ttu.edu (M. F. Mayer).
† For crystallographic analysis. Tel.: +1 806 742 4487; fax: +1 806 742 1289.

0040-4039/$ - see front matter © 2008 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2008.05.085

Table 1
Substrate Scope[a]

Entry	Imine[b]	R^1	R^2	Loading (mol %) **3f**	Time (h)[c]	Cis:trans[d]	Yield[e] (%) cis, trans
1	**2a**	*p*-MeO–C_6H_4	*p*-MeO–C_6H_4	2	8	>50:1	88, —
2	**2b**	Ph	*p*-MeO–C_6H_4	2	12	20:1	86, 4
3	**2c**	*p*-MeO–C_6H_4	Ph	2	10	10:1	79, 7
4	**2d**	Ph	Ph	2	12	8:1	91[f]
5	**2e**	Ph	*p*-NO_2–C_6H_4	5	24 (94%)	6.5:1	81[f]
6	**2f**	*p*-NO_2–C_6H_4	Ph	5	12	9:1	84, 8
7	**2g**	Ph	*p*-Br–C_6H_4	5	8	10:1	91[f]
8	**2h**	Ph	*o*-Br–C_6H_4	10	12	6.6:1	91[f]
9	**2i**	Ph	*n*-Bu	10	24 (95%)	>50:1	54, —
10	**2j**	CO_2Et	*p*-MeO–C_6H_4	10	12	3.5:1	73, 16
11	**2k**	CO_2Et	Ph_2CH	10	24 (97%)	2.3:1	50, 20
12	**2l**	*t*-Bu	Ph	10	12 (95%)	1:50	—, 93

[a] Reactions performed at room temperature in MeCN with 1.3 equiv **1b**.
[b] Imine **2** substitution is R^1–CH=NR^2.
[c] Time required for complete consumption of the imine, unless otherwise noted by % conversion in parentheses.
[d] Determined from the ^{1}H NMR spectrum of the crude product.
[e] Isolated yields of aziridines **4**.
[f] Aziridines isolated as a mixture of cis and trans isomers.

When *N*-benzylpyridinium hexafluorophosphate **3b** was employed, a further enhancement in the conversion of **2a** was observed along with an increase in the yield of **4a**. However, when additive **3c** was tested, the conversion of **2a** was considerably reduced. We figured this rate trend paralleled the relative electrophilicity of these pyridinium species. With that in mind, we prepared the more electron-deficient viologens (**3d–f**) and tested their capacity to induce the aziridine-forming reaction from **1b** and **2a**. Indeed, both 2 mol % methyl viologen **3d** (−450 mV vs SCE)[9] and 2 mol % benzyl viologen **3e** (−370 mV vs SCE)[9] were more effective than 4 mol % of the top-performing pyridinium **3b**. Lastly, 2 mol % phenylviologen **3f** (−247 mV vs SCE)[9] induced a fairly clean *cis*-aziridine-forming reaction with consumption of the imine within 8 h.

Since phenylviologen **3f** was reasonably efficient at inducing the aziridine-forming reaction, we used **3f** in a study of the steric and electronic limitations of the imine in this reaction, Table 1. We found that the reaction was general and satisfactory for all imines tested. The most obvious trend observed was that electron-rich imines generally underwent the quickest reaction with the least amount of **3f**.

The unsubstituted *N*-benzylideneaniline **2d** underwent reaction to give a 91% isolated yield of aziridine **4d** as an 8:1 mixture of diastereomers, entry 4. The configuration of the major isomer of **4d** was confirmed to be the cis-isomer by single crystal X-ray analysis, Figure 2.[10] This result is consistent with the ^3J coupling constants found for the major, non-symmetrically-substituted aziridine isomers (**4**) in entries 1–11 of Table 1.

Importantly, satisfactory reactions were not restricted to electron-rich aromatic imines. Electron-deficient imines, however, did require longer reaction periods and higher loadings of **3f** to achieve nearly complete consumption of the imine. For example, the *p*-nitrophenyl-substituted imines **2e** and **2f** required 5 mol % **3f** and at least 50% more time (vs **2a**) to consume the imine. Additionally, the *N*-butyl imine **2i** underwent reaction with excellent stereoselectivity, comparable to imine **2a**.

The ethyl carboxylate-substituted imines **2j** and **2k** underwent reactions with the lowest observed diastereoselectivities. As expected though, the aziridines **4j** and **4k** were not accompanied by formation of isomeric β-amino-α,β-unsaturated esters as is the case when the same aziridines are synthesized via Lewis acid-catalyzed reactions of *N*-benzylidene imines and ethyl diazoacetate.[5m] This is presumably due to the reversed positioning of the phenyl and ethylcarboxylate moieties, which would otherwise

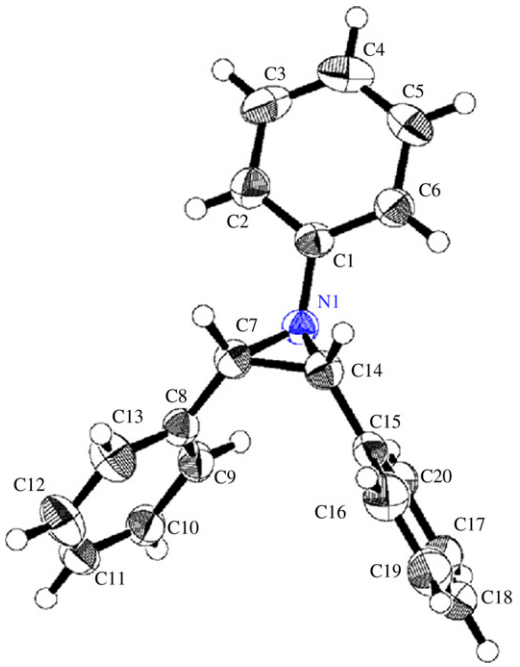
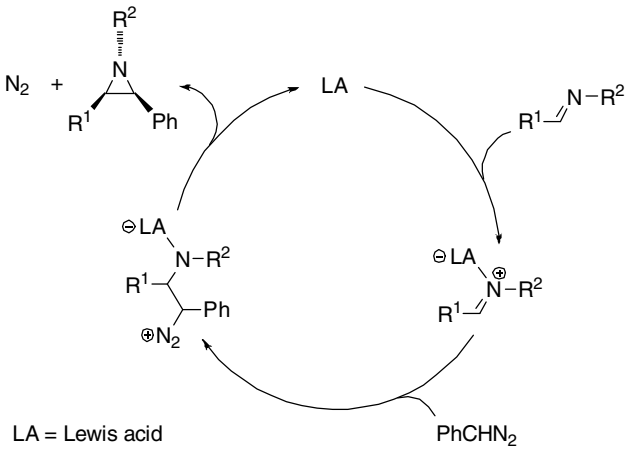


Figure 2. X-ray crystal structure of **4d**.



Scheme 1.

facilitate migration of the phenyl group.[4a] Lastly, in contrast to all other imines tested, as shown in Table 1, imine **2l** reacted stereoselectively to provide the *trans*-aziridine isomer **4l**.

Mechanistically, while adventitious proton catalysis has not been ruled out,[11] the predominant *cis*-aziridine selectivity observed here is consistent with that found in most Lewis acid-catalyzed aziridine-forming reactions from imines and diazo compounds. This result may be indicative of a similar mechanism of imine activation and aziridine synthesis, Scheme 1, as noted by Xia and co-workers.[6]

In summary, through observation of the correlation of rate of consumption of the imine with standard reduction potentials of the pyridinium and viologen additives, we have optimized the viologen additive such that a reasonably efficient *cis*-aziridine-forming reaction can be induced by catalytic amounts of viologens from phenyldiazomethane and various imines.

Acknowledgment

We thank the Robert A. Welch Foundation for financial support of this research project (Grant No. D-1635).

Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2008.05.085.

References and notes

1. (a) Hu, X. E. *Tetrahedron* **2004**, *60*, 2701; (b) Sweeney, J. B. *Chem. Soc. Rev.* **2002**, *31*, 247; (c) Zwanenburg, B.; ten Holte, P. *Top. Curr. Chem.* **2001**, *216*, 93; (d) McCoull, W.; Davis, F. A. *Synthesis* **2000**, 1347; (e) Pearson, W. H.; Lian, B. W.; Bergmeier, S. C.. In *Comprehensive Heterocyclic Chemistry II*; Padwa, A., Ed.; Oxford: Pergamon, 1996; Vol. 1A, p 1; (f) Tanner, D. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 599.
2. (a) Fokin, V. V.; Wu, P. In *Aziridines and Epoxides in Organic Synthesis*; Yudin, A. K., Ed.; Wiley-VCH: Weinheim, 2006; Chapter 12; (b) Kolb, H. C.; Finn, M. G.; Sharpless, K. B. *Angew. Chem., Int. Ed.* **2001**, *40*, 2004.
3. (a) Mößner, C.; Bolm, C. In *Transition Metals for Organic Synthesis*; Beller, M., Bolm, C., Eds.; Wiley-VCH: Weinheim, 2004; Vol. 2, p 389; (b) Müller, P.; Fruit, C. *Chem. Rev.* **2003**, *103*, 2905; (c) Jacobsen, E. N. In *Comprehensive Asymmetric Catalysis*; Jacobsen, E. N., Pfaltz, A., Yamamoto, H., Eds.; Springer: New York, 1999; Chapter 17.
4. (a) Mazumdar, A.; Xue, Z.; Mayer, M. F. *Synlett* **2007**, 2025; (b) Wipf, P.; Lyon, M. A. *ARKIVOC* **2007**, *12*, 91; (c) Pellicciari, R.; Amori, L.; Kuznetsova, N.; Zlotsky, S.; Gioiello, A. *Tetrahedron Lett.* **2007**, *48*, 4911; (d) Lu, Z.; Zhang, Y.; Wulff, W. D. *J. Am. Chem. Soc.* **2007**, *129*, 7185; (e) Deng, Y.; Lee, Y. R.; Newman, C. A.; Wulff, W. D. *Eur. J. Org. Chem.* **2007**, 2068; (f) Alonso, C. M. A.; Neves, M. G. P. M. S.; Tomé, A. C.; Silva, A. M. S.; Cavaleiro, J. A. S. *Jordan J. Chem.* **2006**, *1*, 95; (g) Zhu, S.; Liao, Y.; Zhu, S. *Synlett* **2005**, 1429; (h) Lee, S.-H.; Song, I.-W. *Bull. Korean Chem. Soc.* **2005**, *26*, 223; (i) Vanderhoydonck, B.; Stevens, C. V. *Synthesis* **2004**, 722; (j) Li, Y.; Chan, P. W. H.; Zhu, N.-Y.; Che, C.-M.; Kwong, H.-L. *Organometallics* **2004**, *23*, 54; (k) Redlich, M.; Hossain, M. M. *Tetrahedron Lett.* **2004**, *45*, 8987; (l) Williams, A. L.; Johnston, J. N. *J. Am. Chem. Soc.* **2004**, *126*, 1612; (m) Krumper, J. R.; Gerisch, M.; Suh, J. M.; Bergman, R. G.; Tilley, T. D. *J. Org. Chem.* **2003**, *68*, 9705; (n) Yadav, J. S.; Reddy, B. V. S.; Rao, M. S.; Reddy, P. N. *Tetrahedron Lett.* **2003**, *44*, 5275; (o) Morales, D.; Pérez, J.; Riera, L.; Riera, V.; Corzo-Suárez, R.; García-Granda, S.; Miguel, D. *Organometallics* **2002**, *21*, 1540; (p) Spanedda, M. V.; Crousse, B.; Narizuka, S.; Bonnet-Delpon, D.; Bégué, J.-P. *Collect. Czech. Chem. Commun.* **2002**, *67*, 1359; (q) Mayer, M. F.; Wang, Q.; Hossain, M. M. *J. Organomet. Chem.* **2001**, *630*, 78; (r) Loncaric, C.; Wulff, W. D. *Org. Lett.* **2001**, *3*, 3675; (s) Aggarwal, V. K.; Ferrara, M.; O'Brien, C. J.; Thompson, A.; Jones, R. V. H.; Fieldhouse, R. *J. Chem. Soc., Perkin Trans. 1* **2001**, 1635; (t) Doyle, M. P.; Hu, W.; Timmons, D. J. *Org. Lett.* **2001**, *3*, 933; (u) Lee, S.-H.; Han, T.-D.; Yu, K.; Ahn, K.-H. *Bull. Korean Chem. Soc.* **2001**, *22*, 449; (v) Crousse, B.; Narizuka, S.; Bonnet-Delpon, D.; Bégué, J.-P. *Synlett* **2001**, 679; (w) Antilla, J. C.; Wulff, W. D. *Angew. Chem., Int. Ed.* **2000**, *39*, 4518; (x) Sengupta, S.; Mondal, S. *Tetrahedron Lett.* **2000**, *41*, 6245; (y) Redlich, M.; Mahmood, S. J.; Mayer, M. F.; Hossain, M. M. *Synth. Commun.* **2000**, *30*, 1401; (z) Kubo, T.; Sakaguchi, S.; Ishii, Y. *Chem. Commun.* **2000**, 625.
5. (a) Xie, W.; Fang, J.; Li, J.; Wang, P. G. *Tetrahedron* **1999**, *55*, 12929; (b) Antilla, J. C.; Wulff, W. D. *J. Am. Chem. Soc.* **1999**, *121*, 5099; (c) Juhl, K.; Hazell, R. G.; Jørgensen, K. A. *J. Chem. Soc., Perkin Trans. 1* **1999**, 2293; (d) Wright, D. L.; McMills, M. C. *Org. Lett.* **1999**, *1*, 667; (e) Mayer, M. F.; Hossain, M. M. *J. Org. Chem.* **1998**, *63*, 6839; (f) Nagayama, S.; Kobayashi, S. *Chem. Lett.* **1998**, 685; (g) Rasmussen, K. G.; Juhl, K.; Hazell, R. G.; Jørgensen, K. A. *J. Chem. Soc., Perkin Trans. 2* **1998**, 1347; (h) Mohan, J. M.; Uphade, B. S.; Choudhary, V. R.; Ravindranathan, T.; Sudalai, A. *Chem. Commun.* **1997**, 1429; (i) Rasmussen, K. G.; Jørgensen, K. A. *J. Chem. Soc., Perkin Trans. 1* **1997**, 1287; (j) Gunnoe, T. B.; White, P. S.; Templeton, J. L.; Casarrubios, L. *J. Am. Chem. Soc.* **1997**, *119*, 3171; (k) Aggarwal, V. K.; Thompson, A.; Jones, R. V. H.; Standen, M. C. H. *J. Org. Chem.* **1996**, *61*, 8368; (l) McMills, M. C.; Wright, D. L.; Zubkowski, J. D.; Valente, E. J. *Tetrahedron Lett.* **1996**, *37*, 7205; (m) Casarrubios, L.; Pérez, J. A.; Brookhart, M.; Templeton, J. L. *J. Org. Chem.* **1996**, *61*, 8358; (n) Rasmussen, K. G.; Jørgensen, K. A. *Chem. Commun.* **1995**, 1401; (o) Zhu, Z.; Espenson, J. H. *J. Org. Chem.* **1995**, *60*, 7090; (p) Hansen, K. B.; Finney, N. S.; Jacobsen, E. N. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 676; (q) Moran, M.; Bernardinelli, G.; Müller, P. *Helv. Chim. Acta* **1995**, *78*, 2048; (r) Jephcote, V. J.; John, D. I.; Williams, D. J. *J. Chem. Soc., Perkin Trans. 1* **1986**, 2195; (s) Bartnik, R.; Mlostoń, G. *Tetrahedron* **1984**, *40*, 2569; (t) Bartnik, R.; Mlostoń, G. *Synthesis* **1983**, 924; (u) Baret, P.; Buffet, H.; Pierre, J.-L. *Bull. Soc. Chim. Fr.* **1972**, 2493.
6. Sun, W.; Xia, C.-G.; Wang, H.-W. *Tetrahedron Lett.* **2003**, *44*, 2409; However, another group reported a similar aziridine-forming reaction from EDA **1a** and in situ-generated imines in $bmimPF_6$ with the Lewis acid $Bi(OTf)_3$: Yadav, J. S.; Reddy, B. V. S.; Reddy, P. N.; Rao, M. S. *Synthesis* **2003**, 1387. In this case, the Lewis acid presumably both aided formation of the imine and decreased the time required for the aziridine-forming reaction.
7. Xia, C.; Sun, W.; Wang, H. Process for Preparation of Aziridine Derivatives. CN 1412179, 2003.
8. These results are in accordance with observations by Xia and co-workers who observed no aziridines when catalytic amounts of $bmimPF_6$ were used, see Ref. 6.
9. Monk, P. M. S. *The Viologens*; Wiley: New York, 1998.
10. Single crystals of the major isomer of **4d** that were suitable for X-ray crystallographic analysis were grown from a CH_2Cl_2/MeOH (1:1) solution. Crystallographic data (excluding structure factors) for the structure of *cis*-1,2,3-triphenylaziridine **4d** in this Letter have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication number CCDC 685188. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK, (fax: +44 1223 336033 or e-mail: deposit@ccdc.cam.ac.uk.).
11. Selective *cis*-aziridine-forming reactions from imines and diazo compounds are also known to be catalyzed by Brønsted acids, see Ref. 4l.