ChemComm

Cite this: Chem. Commun., 2011, 47, 2967-2969

COMMUNICATION

A facile noncatalytic pathway for the nitrene transfer process: expeditious access to aziridines[†]

Indranirekha Saikia, Bishwapran Kashyap and Prodeep Phukan*

Received 6th December 2010, Accepted 5th January 2011 DOI: 10.1039/c0cc05387b

A fast and efficient method has been developed for generation of sulfonyl nitrene from N,N-dibromo-p-toluenesulfonamide (TsNBr₂) in the presence of a base without any catalyst. This method was applied to produce aziridines from different kinds of olefins within a short time in high yields.

Nitrenes are among the most fundamental reactive intermediates in organic synthesis.¹ Nitrene transfer reaction provides an effective route for the construction of biologically important molecules such as drugs and natural products.² Consequently, development of new synthetic methods for this reactive intermediate is considered as the frontiers of organic synthesis. Classical methods for generation of nitrenes are: thermal or photochemical decomposition of hydrazoic acid, alkyl and aryl azides, sulfonyl azides, azidoformates and cyanogen azide.^{1,3} In the recent past, several nitrene sources were reported. The most commonly employed nitrene source is PhI=NR that can also be formed in situ by oxidizing sulfonamides or other amines with PhI(OAc)₂ or PhIO.² However, due to some limitations in the use of these iminoiodinanes, alternative nitrogen sources such as chloramine-T (TsN(Cl)Na), bromamine-T (TsN(Br)Na) and organic azides (RN_3) were more recently investigated.²

A very common and widely utilized nitrene insertion reaction as a synthetic tool for achieving nitrogeneous molecules is the synthesis of aziridines.^{2,4} Aziridines exhibit highly regioand stereoselective ring opening reactions which provide a convenient entry to the stereoselective preparation of functionalized amino compounds, heterocycles, and alkaloids.⁵ Among several approaches, metal-catalyzed aziridination of alkenes with proper nitrene sources is the most widely utilized method for the synthesis of the three-membered ring structure.² Iminoiodinane derivatives such as [N-(p-tolylsulfonyl)imino]phenyliodinane (PhI=NTs)⁶ and its variants have been extensively used as the nitrene source in the presence of several transition metal catalysts including those based on Cu,⁷ Mn,⁸ Fe,⁹ Rh,¹⁰ Ru,¹¹ Ag,¹² and Au.¹³ Alternative nitrene sources such as N-halo-sulfonamides,¹⁴ organic azides,¹⁵ etc. were also used in the presence of a catalyst. Recently, we have found that TsNBr₂ is a very reactive and efficient reagent for various



organic transformations.¹⁶ In this communication, we wish to report an expeditious, noncatalytic route for the synthesis of aziridines directly from olefins using TsNBr₂ as a nitrene source (Scheme 1).

During the course of our investigation, we found that TsNBr₂ is a strong source of the bromonium ion and liberation of the bromonium ion from TsNBr₂ is very facile. It is well known that carbene can be generated by α-dehalogenation of gem-dihalo compounds.¹⁷ We presumed that, analogous to carbene formation, it should be possible to generate nitrene from N,N-dibromo-p-toluenesulfonamide by debromination in the presence of a base. With this view in mind, we have carried out a reaction by adding a solution of TsNBr₂ (1.2 equiv.) in dichloromethane to a mixture of K_2CO_3 (2.5 equiv.) and styrene (1 equiv.) in dichloromethane at room temperature. The process was carried out under inert atmosphere and the progress of the reaction was monitored by TLC. We observed that the reaction is very fast and the corresponding aziridine was isolated in 63% yield after 10 minutes of reaction. In order to find out the best reaction condition, we have investigated the effect of various solvents on the product yield (Table 1).

When acetonitrile was used as a solvent the reaction did not produce the expected product after 10 minutes of reaction. Further investigation on the reaction using ethyl acetate as a solvent gave the best result of 84% isolated yield of the corresponding aziridine. The reaction was also studied with

Table 1 Influence of solvent and K_2CO_3 amount on the synthesis of aziridine from styrene^{*a*}

Entry	Solvent	$K_2CO_3/mmol$	Yield ^b (%)	
1	DCM	2.5	63	
2	CH ₃ CN	2.5	Trace	
3	EtOAc	2.5	84	
4.	EtOAc	1	25	
5	EtOAc	1.5	40	
6	EtOAc	3.5	84	

 a Reaction conditions: styrene (1 mmol), TsNBr₂ (1.2 mmol), solvent (10 mL), rt, 10 min. b Isolated yield.

Department of Chemistry, Gauhati University, Guwahati-781014, Assam, India. E-mail: pphukan@yahoo.com

[†] Electronic supplementary information (ESI) available: NMR spectral data. See DOI: 10.1039/c0cc05387b

varying amount of K_2CO_3 (Table 1). Yields of the corresponding aziridine were found to be lower when the amount of the base was reduced, while increase of base amount could not improve the yield. Finally, the use of 2.5 equiv. of K_2CO_3 was found to be optimum for the best result.

After optimizing the reaction conditions, the process was extended to a variety of olefins.[‡] Results are summarized in Table 2. Initially, we examined the reaction for different styrenes. It can be seen from Table 2 that various styrenes bearing functional groups reacted successfully to give the corresponding aziridine in high yields within a short time. After being successful in the case of styrenes, we extended the procedure to various kinds of olefins such as indene, β -methyl

Table 2 Aziridination of various alkenes with $TsNBr_2^a$



^{*a*} Reaction conditions: olefin (1 mmol), K_2CO_3 (2.5 mmol), $TsNBr_2$ (1.2 mmol), EtOAc (10 mL), rt. ^{*b*} Isolated yield. ^{*c*} trans : cis = 6 : 1 ^{*d*} cis : trans = 5 : 1. ^{*e*} trans : cis = 4 : 1.



Scheme 2 Plausible mechanism of formation of aziridine.

styrene, cyclohexene, 1-octene, ethyl acrylate, cyclohexenone, ethyl cinnamate, *etc.*, which produced the corresponding aziridine in high yields (Table 2). However, cyclohexenone and ethyl cinnamate took longer time for completion of the reaction. It is well known that nitrene π -insertion reaction is a concerted process which imposes stereochemical consequences in the product. We observed that when *trans*- β -methyl styrene was subjected to aziridination reaction, the resultant product exhibited *trans*-selectivity (Table 2, entry 5), while *cis*- β -methyl styrene produced the product having *cis*-selectivity (Table 2, entry 6). Similar trend of *trans*-selectivity was observed for *trans*-3-hexene also (Table 2, entry 8).

Mechanistically, it is likely that analogous to carbene formation reaction,¹⁷ there is a strong possibility of generation of sulfonyl nitrene from *N*,*N*-dibromo-*p*-toluene sulfonamide in the presence of K_2CO_3 . Initial step of the reaction is the abstraction of the Br⁺ ion by the base which subsequently loses KBr to form the nitrene (Scheme 2). We observed that the solution becomes very turbid at the end of the reaction which is due to the precipitation of KBr. Formation of KBr during the reaction was confirmed by a positive silver nitrate test.

To confirm the formation of the nitrene intermediate, we have carried out an experiment to trap the nitrene intermediate with benzene.¹⁸ When a mixture of *N*,*N*-dibromo-*p*-toluene sulfonamide (1 equiv.) and K₂CO₃ (2 equiv.) was heated in dry benzene at 150 °C for 6 h, corresponding 1-[(4-methylphenyl)-sulfonyl]-1*H*-azepine (**15**) was formed in 22% yield along with *p*-toluene sulfonamide (Scheme 3).

To further confirm the formation of the nitrene intermediate, we treated $TsNBr_2$ with a phosphorous compound under the same reaction conditions.¹⁹ When triphenyl phosphine was reacted with $TsNBr_2$, iminophosphorane **16b** was formed in 80% yield (Table 3, entry 1) after 30 min of reaction. Similarly, triethyl phosphite also produced the corresponding product **17b** in high yield (Table 3, entry 2).

One interesting observation we made during our investigation is that, when a mixture of $TsNBr_2$ and K_2CO_3 was stirred in DMF at room temperature, the corresponding amidine, *N*-[(dimethylamino)methylene]-4-methylbenzene-sulfonamide (**18**), was obtained in quantitative yield. Similar to the Vilsmeier– Haack reaction, this process might involve an iminium intermediate species at the initial stage of the reaction due to the interaction of $TsNBr_2$ with DMF (Scheme 4). Since,



Scheme 3 Formation of azepine.

Table 3	Reaction	of pho	osphorous	compounds	with	TsNBr ₂
---------	----------	--------	-----------	-----------	------	--------------------

	Dup TeNBr.	K ₂ CO ₃ (2.5 equiv)		
	R*P + 13002 1.2 eq	EtOAc, rt, 30 min	r p-nis	
Sl. No	Substrate (a)	Product (b)	T/min	Yield ^a (%)
16	PPh ₃	TsN=PPh ₃	30	80
17	P(OEt) ₃	TsN=P(OEt) ₃	30	76
^a Isolate	d vield			



Scheme 4 Formation of amidine from DMF.

 $TsNBr_2$ is an excellent source of Br^+ species, formation of the iminium ion is very likely. The presence of base facilitates subsequent abstraction of the second Br^+ ion to yield the sulfonyl amidine derivative.

In conclusion, an efficient protocol has been developed for direct generation of sulfonyl nitrene from N,N-dibromo-p-toluenesulfonamide which was further reacted with olefin to form the corresponding aziridine. The aziridination process is very facile in ethylacetate at room temperature without a catalyst. The procedure is fast, easy to perform at room temperature and applicable to various olefins to give corresponding aziridines in high yield.

Financial support from DST, India (Grant No. SR/S1/ RFPC-07/2006), is gratefully acknowledged. IS thanks to CSIR and BK thanks to UGC for research fellowship. We thank IIT-Guwahati and NEHU, Shillong, for analytical data and reviewers for their valuable suggestions.

Notes and references

‡ General procedure: to a solution of olefin (1 mmol) and K_2CO_3 (2.5 mmol), in dry ethyl acetate (5 mL), a solution of $TsNBr_2$ (1.2 mmol) in dry ethyl acetate (5 mL) was added dropwise under nitrogen atmosphere at room temperature. After completion of the reaction, an aqueous solution of 10% sodium thiosulfate (5 mL) was added and the organic layer separated. After usual workup, the crude product was purified by flash chromatography on silica gel (230–400 mesh) with petroleum ether/ethyl acetate as eluent.

- (a) C. J. Moody and G. H. Whitham, *Reactive Intermediates*, New York, Oxford UP, 1992; (b) *Nitrenes*, ed. W. Lwowski, Interscience, New York, 1970; (c) R. Belloli, J. Chem. Educ., 1971, 48, 422.
- 2 (a) S. Fantauzzi, A. Caselli and E. Gallo, *Dalton Trans.*, 2009, 5434; (b) H. M. L. Davies and J. R. Manning, *Nature*, 2008, 451, 417; (c) M. M. Diaz-Requejo and P. J. Perez, *Chem. Rev.*, 2008, 108, 3379; (d) I. D. G. Watson, L. Yu and A. K. Yudin, *Acc. Chem. Res.*, 2006, 39, 194; (e) Z. Li and C. He, *Eur. J. Org. Chem.*, 2006, 4313; (f) J. A. Halfen, *Curr. Org. Chem.*, 2005, 9, 657; (g) P. Müller and C. Fruit, *Chem. Rev.*, 2003, 103, 2905; (h) P. Dauban and R. H. Dodd, *Synlett*, 2003, 1571.
- 3 (a) D. W. Cornell, R. S. Berry and W. Lwowski, J. Am. Chem. Soc., 1966, 88, 544; (b) L. Horner and A. Christmann, Chem. Ber., 1963, 96, 388; (c) W. Lwowski, Angew. Chem., Int. Ed. Engl., 1967, 6, 897; (d) A. G. Anastassiou and H. E. Simmons, J. Am. Chem. Soc., 1967, 89, 3177.

- 4 Aziridines and Epoxides in Organic Synthesis, ed. A. K. Yudin, Wiley-VCH, Weinheim, 2006.
- 5 (a) W. H. Pearson, B. W. Lian and S. C. Bergmeier, in Comprehensive Heterocyclic Chemistry II, ed. A. Padwa, Pergamon Press, New York, 1996, vol. IA, pp. 1–6; (b) D. Tanner, Angew. Chem., Int. Ed. Engl., 1994, 33, 599; (c) X. E. Hu, Tetrahedron, 2004, 60, 2701; (d) F. A. Davis and S. M. Coull, Synthesis, 2000, 1347; (e) H. Stamm, Journal für praktische Chemie, 1999, 341, 319; (f) D. Sureshkumar, S. M. Koutha and S. Chandrasekaran, J. Am. Chem. Soc., 2005, 127, 12760.
- 6 (a) Y. Yamada, T. Yamamoto and M. Okawara, *Chem. Lett.*, 1975, 361; (b) D. A. Evans, M. M. Faul and M. T. Bilodeau, *J. Org. Chem.*, 1991, **56**, 6744.
- 7 (a) Z. Conser, K. R. Li and E. N. Jacobsen, J. Am. Chem. Soc., 1993, 115, 5326; (b) D. A. Evans, M. M. Faul, M. T. Bilodeau, B. A. Anderson and D. M. Barnes, J. Am. Chem. Soc., 1993, 115, 5328; (c) D. A. Evans, M. T. Bilodeau and M. M. Faul, J. Am. Chem. Soc., 1994, 116, 2742; (d) Z. Li, R. W. Quan and E. N. Jacobsen, J. Am. Chem. Soc., 1995, 117, 5889; (e) P. Dauban and R. H. Dodd, J. Org. Chem., 1999, 64, 5304.
- 8 (a) J.-L. Liang, J.-S. Huang, X.-Q. Yu, N.-Y. Zhu and C.-M. Che, *Chem.-Eur. J.*, 2002, **8**, 1563; (b) D. Mansuy, J. P. Mahy, A. Dureault, G. Bedi and P. Battioni, *J. Chem. Soc., Chem. Commun.*, 1984, 1161.
- 9 (a) J. P. Mahy, P. Battioni and D. Mansuy, J. Am. Chem. Soc., 1986, **108**, 1079; (b) A. C. Mayer, A.-F. Salit and C. Bolm, Chem. Commun., 2008, 5975.
- 10 (a) P. Müller, C. Baud, Y. Jacquier, M. Moran and I. Naegeli, J. Phys. Org. Chem., 1996, 9, 341; (b) J.-L. Liang, S.-X. Yuan, P. W. H. Chan and C.-M. Che, Org. Lett., 2002, 4, 4507.
- 11 (a) S.-M. Au, J.-S. Huang, W.-Y. Yu, W.-H. Fung and C.-M. Che, J. Am. Chem. Soc., 1999, **121**, 9120; (b) W.-I. Man, W. W. Y. Lam, S.-M. Yiu, T.-C. Lau and S.-M. Peng, J. Am. Chem. Soc., 2004, **126**, 15336.
- 12 Y. Cui and C. He, J. Am. Chem. Soc., 2003, 125, 16202.
- 13 Z. Li, X. Ding and C. He, J. Org. Chem., 2006, 71, 5876.
- 14 (a) T. Ando, S. Minakata, I. Ryu and M. Komatsu, Tetrahedron Lett., 1998, 39, 309; (b) J. U. Jeong, B. Tao, I. Sagasser, H. Henniges and K. B. Sharpless, J. Am. Chem. Soc., 1998, 120, 6844; (c) D. P. Albone, P. S. Aujla, P. C. Taylor, S. Challenger and A. M. Derrick, J. Org. Chem., 1998, 63, 9569; (d) S. I. Ali, M. D. Nikalje and A. Sudalai, Org. Lett., 1999, 1, 705; (e) L. Simkhovich and Z. Gross, Tetrahedron Lett., 2001, 42, 8089; (f) B. M. Chanda, R. Vyas and A. V. Bedekar, J. Org. Chem., 2001, 66, 30; (g) A. M. M. Antunes, S. J. M. Marto, P. S. Branco, S. Prabhakar and A. M. Lobo, Chem. Commun., 2001, 405; (h) V. V. Thakur and A. Sudalai, Tetrahedron Lett., 2003, 44, 989; (i) R. Vyas, G.-Y. Gao, J. D. Harden and X. P. Zhang, Org. Lett., 2004, 6, 1907; (j) A. J. Catino, J. M. Nichols, R. E. Forslund and M. P. Doyle, Org. Lett., 2005, 7, 2787; (k) G.-Y. Gao, J. D. Harden and X. P. Zhang, Org. Lett., 2005, 7, 3191; (l) J. Han, Y. Li, S. Zhi, Y. Pan, C. Timonsc and G. Li, Tetrahedron Lett., 2006, 47, 7225
- (a) G.-Y. Gao, J. E. Jones, R. Vyas, J. D. Harden and X. P. Zhang, J. Org. Chem., 2006, 71, 6655; (b) V. Subbarayan, J. V. Ruppel, S. Zhu, J. A. Perman and X. P. Zhang, Chem. Commun., 2009, 4266; (c) K. Omura, M. Murakami, T. Uchida, R. Irie and T. Katsuki, Chem. Lett., 2003, 354; (d) K. Omura, T. Uchida, R. Irie and T. Katsuki, Chem. Commun., 2004, 2060.
- 16 (a) P. Phukan, P. Chakraborty and D. Kataki, J. Org. Chem., 2006, **71**, 7533; (b) I. Saikia and P. Phukan, *Tetrahedron Lett.*, 2009, **50**, 5083; (c) I. Saikia, P. Chakraborty and P. Phukan, *ARKIVOC*, 2009, (xiii), 281; (d) I. Saikia, B. Kashyap and P. Phukan, *Synth. Commun.*, 2010, **40**, 2647.
- 17 O. M. Nefedov, M. P. Egorov, A. I. Ioffe, L. G. Menchikov, P. S. Zuev, V. I. Minkin, Ya. B. Simkin and M. N. Glukhovtsev, *Pure Appl. Chem.*, 1992, 64, 265.
- 18 N. R. Ayyangar, R. B. . Bambal and A. B. Lugade, J. Chem. Soc., Chem. Commun., 1981, 790.
- 19 H. Morita, A. Tatami, T. Maeda, B. J. Kim, W. Kawashima, T. Yoshimura, H. Abe and T. Akasaka, J. Org. Chem., 2008, 73, 7159.