Tetrahedron Letters 50 (2009) 363–365

Contents lists available at ScienceDirect

Tetrahedron Letters

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

PPh_3/halogenating agent-mediated highly efficient ring opening of activated and non-activated aziridines

Manoj Kumar [a,b], Sanjay K. Pandey [a], Shikha Gandhi [a], Vinod K. Singh [a,*]

[a] Department of Chemistry, Indian Institute of Technology Kanpur, Kanpur 208 016, India
[b] Department of Chemistry, D.A.V. College, Kanpur 208 001, India

ARTICLE INFO

Article history:
Received 20 September 2008
Revised 30 October 2008
Accepted 5 November 2008
Available online 7 November 2008

Keywords:
Aziridines
β-Haloamines
PPh_3/halogenating agents

ABSTRACT

We report here the use of PPh_3/halogenating agents as highly efficient reagents for the ring opening of aziridines with halides. The method works effectively for both activated and non-activated aziridines, and furnishes the products in excellent yields within a short period of time.

Aziridines, small ring heterocycles, are attractive building blocks for the synthesis of a variety of nitrogen containing biologically active compounds.[1,2] The high ring strain energy endows them with high reactivity and enables easy ring cleavage with various nucleophiles.[3,4] The use of halides as nucleophiles leads to the formation of β-haloamines, which serve as important precursors for the synthesis of medicinally important compounds.[5] However, the reactivity of the ring is dependent on the substituent on the nitrogen atom. The presence of electron withdrawing substituents activates the ring, which then reacts easily with nucleophiles to form ring-opened products. Several reports on ring opening of activated aziridines with halides have appeared in the literature.[4b,6] Most suffer from several disadvantages such as long reaction times, tedious work-up procedures and harsh reaction conditions. In contrast to activated aziridines, non-activated aziridines are relatively inert towards nucleophiles and require prior activation. Therefore, reports on ring opening of non-activated aziridines with halides are relatively scarce. A strong protic acid such as HCl has been employed in some cases.[7] Bu_4NX and NH_4X have been used for the ring opening of sugar aziridines, but the reaction requires refluxing conditions and works only when bromide is used as the halide.[8] For the last one decade, we have been actively involved in the study of ring cleavage reactions of activated and non-activated aziridines with various nucleophiles.[4]

We had reported earlier the ring opening of activated aziridines with halides using activated DMF complexes.[4b] Ph_3PCl_2 and Ph_3PBr_2 activated DMF complexes worked well for the reaction. We envisaged that the reaction would proceed well even in the absence of DMF. To our delight, excellent results were obtained when the same reaction was carried out in acetonitrile. Gratifyingly, the same reaction system has worked efficiently when non-activated aziridines were used as the substrates. In this Letter, we report a convenient and highly efficient procedure for the ring opening of both activated and non-activated aziridines with halides.

Initially, the reaction of *N*-tosylcyclohexyl aziridine was studied in the presence of PPh_3 and a variety of halogenating agents (Table 1).[9,10] Almost all the halogenating agents gave good to excellent yields of the ring-opened product. Among the chlorinating agents used, cyanogen chloride gave a moderate yield of product (Table 1, entry 10). Carbon tetrachloride, hexachloroethane, hexachloroacetone and triphosgene afforded the corresponding product in good yield (Table 1, entries 4–6 and 8). Excellent yields were obtained with all the other reagents (Table 1, entries 1–3, 7 and 9). PPh_3Br_2 and NBS/PPh_3 furnished excellent yields of bromide ring-opened adducts (Table 1, entries 12 and 13). Similarly, both I_2/PPh_3 and NIS/PPh_3 gave excellent yields of iodinated products (Table 1, entries 14 and 15). Being slightly superior to other reagents, PPh_3Cl_2, PPh_3Br_2 and I_2/PPh_3 were used for further studies.

The ring cleavage reaction was then extended to a variety of cyclic and acyclic *N*-tosylaziridines. The results are summarized in Table 2. Acyclic aziridines (Table 2, entries 1–9) gave only one regioisomer of the product obtained via the nucleophilic attack at the less hindered position. All the cyclic aziridines gave the trans product. The reaction was also extended to cyclic aziridines containing a double bond in the ring and satisfactory results were obtained in all the cases (Table 2, entries 18–23).

* Corresponding author. Tel.: +91 512 2597291; fax: +91 512 2597436.
E-mail address: vinodks@iitk.ac.in (V. K. Singh).

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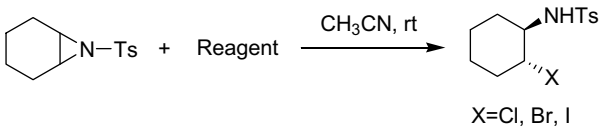
doi:10.1016/j.tetlet.2008.11.009

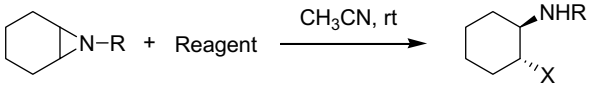
Table 1
Screening of reagents for the ring opening of an aziridine



Entry	Reagent[a]	X	Time (h)	Yield (%)[b]
1	Cl_3CCN/PPh_3	Cl	1	91
2[c]	PPh_3Cl_2	Cl	1	99
3	Cl_3CCONH_2/PPh_3	Cl	1	92
4	CCl_4/PPh_3	Cl	1	80
5	Cl_3CCCl_3/PPh_3	Cl	1	80
6	$Cl_3CCOCCl_3/PPh_3$	Cl	1	87
7	CCl_3COOH/PPh_3	Cl	1	97
8	Triphosgene/PPh_3	Cl	1.5	85
9	NCS/PPh_3	Cl	2	99
10	Cyanogen chloride/PPh_3	Cl	1	70
11	CBr_4/PPh_3	Br	1	83
12[c]	PPh_3Br_2	Br	1	99
13	NBS/PPh_3	Br	1	95
14	I_2/PPh_3	I	1	93
15	NIS/PPh_3	I	1	90

[a] Ratio of aziridine:halogenating agent:PPh_3 was 1.0:2.1:2.0.
[b] Isolated yield.
[c] Ratio of aziridine:reagent was 1.0:2.1.

Table 3
Reaction of non-activated aziridines with halogenating agents



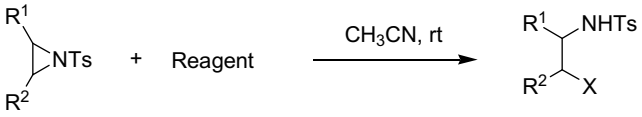
Entry	R	Reagent	X	Product	Time	Yield (%)[a]
1	C_6H_5	PPh_3Cl_2	Cl	**4a**	5 min	96
2	C_6H_5	PPh_3Br_2	Br	**5a**	5 min	63
3	C_6H_5	PPh_3/I_2	I	**6a**	10 min	66
4	4-$MeOC_6H_4$	PPh_3Cl_2	Cl	**4b**	5 min	98
5	4-$MeOC_6H_4$	PPh_3Br_2	Br	**5b**	5 min	70
6	4-$MeOC_6H_4$	PPh_3/I_2	I	**6b**	5 min	97
7	4-ClC_6H_4	PPh_3Cl_2	Cl	**4c**	30 min	99
8	4-ClC_6H_4	PPh_3Br_2	Br	**5c**	30 min	99
9	4-ClC_6H_4	PPh_3/I_2	I	**6c**	30 min	98
10	3,4-(OCH_2O)–C_6H_3	PPh_3Cl_2	Cl	**4d**	15 min	85
11	3,4-(OCH_2O)–C_6H_3	PPh_3Br_2	Br	**5d**	30 min	67
12	3,4-(OCH_2O)–C_6H_3	PPh_3/I_2	I	**6d**	10 min	90
13	2-Naphthyl	PPh_3Cl_2	Cl	**4e**	2 h	97
14	2-Naphthyl	PPh_3Br_2	Br	**5e**	30 min	71
15	2-Naphthyl	PPh_3/I_2	I	**6e**	30 min	99
16	$CH_2C_6H_5$	PPh_3Cl_2	Cl	**4f**	10 min	80

[a] Isolated yield.

After successful application of the methodology to activated aziridines, a variety of non-activated aziridines with different substituents at the *N*-atom were then explored using PPh_3Cl_2, PPh_3Br_2 and PPh_3/I_2 as reagents (Table 3). The reaction was smooth with all the aziridines and the products were formed in moderate to excellent yields. Variously substituted *N*-aryl aziridines were studied and the products were obtained in short reaction times (Table 3, entries 1–12). Even in the case of *N*-benzyl aziridine, the product was obtained in 10 min and in good yield (Table 3, entry 16).

In conclusion, we have developed a novel and a very efficient method for the ring cleavage of aziridines with halides. The method provides a convenient procedure for the synthesis of β-haloamines. Excellent results have been obtained with both activated and non-activated aziridines and thus, the method can be generalized to a large variety of substrates.

Table 2
Reaction of activated aziridines with halogenating agents



Entry	R^1	R^2	Reagent	X	Product	Time	Yield (%)[a]
1	*n*-C_4H_9	H	PPh_3Cl_2	Cl	**1a**	30 min	75
2	*n*-C_4H_9	H	PPh_3Br_2	Br	**2a**	15 min	84
3	*n*-C_4H_9	H	PPh_3/I_2	I	**3a**	15 min	83
4	*n*-C_6H_{13}	H	PPh_3Cl_2	Cl	**1b**	30 min	75
5	*n*-C_6H_{13}	H	PPh_3Br_2	Br	**2b**	15 min	82
6	*n*-C_6H_{13}	H	PPh_3/I_2	I	**3b**	15 min	76
7	$C_6H_5CH_2$	H	PPh_3Cl_2	Cl	**1c**	1 h	91
8	$C_6H_5CH_2$	H	PPh_3Br_2	Br	**2c**	1 h	97
9	$C_6H_5CH_2$	H	PPh_3/I_2	I	**3c**	1 h	96
10	–$(CH_2)_3$–		PPh_3Cl_2	Cl	**1d**	1 h	76
11	–$(CH_2)_3$–		PPh_3Br_2	Br	**2d**	30 min	92
12	–$(CH_2)_3$–		PPh_3/I_2	I	**3d**	30 min	96
13	–$(CH_2)_4$–		PPh_3Cl_2	Cl	**1e**	1 h	99
14	–$(CH_2)_4$–		PPh_3Br_2	Br	**2e**	1 h	99
15	–$(CH_2)_4$–		PPh_3/I_2	I	**3e**	1 h	93
16	–$(CH_2)_6$–		PPh_3Br_2	Br	**2f**	1 h	94
17	–$(CH_2)_6$–		PPh_3/I_2	I	**3f**	30 min	83
18	–CH_2CH=$CHCH_2$–		PPh_3Cl_2	Cl	**1g**	5 h	70
19	–CH_2CH=$CHCH_2$–		PPh_3Br_2	Br	**2g**	30 min	91
20	–CH_2CH=$CHCH_2$–		PPh_3/I_2	I	**3g**	30 min	79
21	–CH_2CH_2CH=$CHCH_2CH_2$–		PPh_3Cl_2	Cl	**1h**	24 h	51
22	–CH_2CH_2CH=$CHCH_2CH_2$–		PPh_3Br_2	Br	**2h**	1 h	71
23	–CH_2CH_2CH=$CHCH_2CH_2$–		PPh_3/I_2	I	**3h**	1 h	47

[a] Isolated yield.

Acknowledgements

V.K.S. thanks the DRDO, Government of India for a research grant. S.G. thanks the Council of Scientific and Industrial Research, New Delhi, for a senior research fellowship.

References and notes

1. (a) Lowden, P. A. S. In *Aziridines and Epoxides in Organic Synthesis*; Yudin, A. K., Ed.; Wiley-VCH: Weinheim, Germany, 2006; pp 399–442; (b) Padwa, A.; Woolhouse, A. D. In *Comprehensive Heterocyclic Chemistry;* Lwowski, W., Ed.; Pergamon: Oxford, 1984; pp 47–93.
2. (a) Hu, X. E. *Tetrahedron* **2004**, *60*, 2701–2743 and references cited therein; (b) Tanner, D. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 599–619; (c) Osborn, H. M. I.; Sweeney, J. *Tetrahedron: Asymmetry* **1997**, *8*, 1693–1715.
3. (a) Xiaoyu, S.; Sun, W.; Renhua, F.; Jie, W. *Adv. Synth. Catal.* **2007**, *349*, 2151–2155; (b) Rinaudo, G.; Narizuka, S.; Askari, N.; Crousse, B.; Bonnet-Delpon, D. *Tetrahedron Lett.* **2006**, *47*, 2065–2068; (c) Fan, R.-H.; Hou, X.-L. *J. Org. Chem.* **2003**, *68*, 726–730; (d) Watson, I. D. G.; Yudin, A. K. *J. Org. Chem.* **2003**, *68*, 5160–5167; (e) Riego, E.; Concellon, J. M. *J. Org. Chem.* **2003**, *68*, 6407–6410.
4. (a) Kumar, M.; Gandhi, S.; Kalra, S. S.; Singh, V. K. *Synth. Commun.* **2008**, *38*, 1527–1532; (b) Bisai, A.; Pandey, M. K.; Singh, V. K. *Tetrahedron Lett.* **2004**, *45*, 9661–9663; (c) Prasad, B. A. B.; Sanghi, R.; Singh, V. K. *Tetrahedron Lett.* **2002**, *58*, 7355–7363; (d) Anand, R. V.; Pandey, G.; Singh, V. K. *Tetrahedron Lett.* **2002**, *43*, 3975–3976; (e) Prasad, B. A. B.; Sekar, G.; Singh, V. K. *Tetrahedron Lett.* **2000**, *41*, 4677–4679.
5. (a) Medda, R.; Padiglia, A.; Pedersen, J. Z.; Agro, A. F.; Rotilio, G.; Floris, G. *Biochemistry* **1997**, *36*, 2595–2602; (b) Righi, G.; Franchini, T.; Bonini, C. *Tetrahedron Lett.* **1998**, *39*, 2385–2388; (c) Bonini, C.; Righi, G.; D' Achille, R. *Tetrahedron Lett.* **1996**, *37*, 6893–6896.
6. (a) Das, B.; Krishnaiah, M.; Venkateswarlu, K. *Chem. Lett.* **2007**, *36*, 82–83; (b) Kim, Y.; Ha, H.-J.; Yun, H.; Lee, B. K.; Lee, W. K. *Tetrahedron* **2006**, *62*, 8844–8849; (c) Wu, J.; Sun, X.; Ye, S.; Sun, W. *Tetrahedron Lett.* **2006**, *47*, 4813–4816; (d) Narender, M.; Surendra, K.; Krishnaveni, N. S.; Reddy, M. S.; Rao, K. R. *Tetrahedron Lett.* **2004**, *45*, 7995–7997; (e) Sabitha, G.; Babu, R. S.; Rajkumar, M.; Reddy, Ch. S.; Yadav, J. S. *Tetrahedron Lett.* **2001**, *42*, 3955–3958.
7. (a) Guo, Z.; Schultz, A. Z. *Tetrahedron Lett.* **2004**, *45*, 919–921; (b) Antolini, L.; Bucciarelli, M.; Caselli, E.; Davoli, P.; Forni, A.; Moretti, I.; Prati, F.; Torre, G. *J. Org. Chem.* **1997**, *62*, 8784–8789.
8. Kroutil, J.; Trnka, T.; Budesinsky, M.; Cerny, M. *Eur. J. Org. Chem.* **2002**, 2449–2459.
9. *General procedure*: Halogenating agent (0.53 mmol) and PPh_3 (0.50 mmol) were stirred in acetonitrile (3 mL) for 10 min at rt. Aziridine (0.25 mmol) was then added and the reaction mixture was stirred till the completion of the reaction as monitored by TLC. The evaporation of solvent under reduced pressure and subsequent purification by column chromatography over silica gel gave the pure product.
10. *Procedure for ring opening of aziridine with PPh_3Cl_2 and PPh_3Br_2*: PPh_3Cl_2 or PPh_3Br_2 (0.53 mmol) was added to a stirred solution of aziridine (0.25 mmol) in acetonitrile (3 mL) at rt. After the completion of reaction as monitored by TLC, the solvent was evaporated under reduced pressure and subsequent purification by column chromatography over silica gel gave the pure product.