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Tetrahedron Letters 45 (2004) 9661–9663
Tetrahedron Letters

Regioselective ring opening of aziridines with activated DMF complexes: a facile synthesis of β-haloamines

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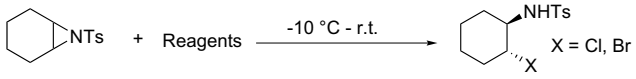
Received 26 January 2004; revised 20 October 2004; accepted 28 October 2004

Abstract—A wide variety of aziridines were converted to the corresponding β-haloamines using activated DMF complexes in good to excellent yields with high regioselectivity.

Aziridines are versatile intermediates for the synthesis of nitrogen-containing biologically active compounds.[1–3] Extensive studies have been carried out on opening of aziridines with a variety of nucleophiles such as amines,[4] alcohols,[5] azides,[6] Wittig reagents,[7] and organometallic reagents.[8] Very few reports are known for the synthesis of β-haloamines, which are versatile building blocks in the field of organic and medicinal chemistry. In the literature, these have been synthesized via the amino halogenation of olefins[9] and aziridine ring opening using halides as nucleophiles.[10] In continuation of our studies in this area,[5,11] we were interested in the synthesis of β-haloamines from aziridines. At the outset, we envisaged that an activated DMF complex should work well for the proposed reaction based on mechanistic concepts (vide infra). Various reagents such as $POCl_3$, $(COCl)_2$, triphosgene, $N_3P_3Cl_6$, $SOCl_2$, SO_2Cl_2, cyanuric chloride, $(PhO)_2POCl$, Ph_3PCl_2, Ph_3PBr_2, PBr_3 are known to activate DMF and all of them should give the required β-haloamine compound. Although activated DMF complexes are known for formylation, haloformylation, halogenation and ring annulation reactions,[12] they have not been used for the synthesis of β-haloamines. In this letter, we describe our work on the synthesis of β-haloamines from aziridines using activated DMF complexes.

A solution of *N*-tosylcyclohexyl aziridine (1 mmol) was added to the freshly prepared activated DMF complex (2 mmol) at −10 °C. The reaction mixture was gradually warmed to room temperature. After completion of the reaction (time indicated in Table 1), the reaction mixture was added to ice-cold water and extracted with ethyl acetate. Work-up and purification by silica gel column chromatography gave the desired β-haloamines in good to excellent yields (Table 1). All the activated DMF complexes gave ring-opened products in high yields. The same experimental procedure was followed for all other activated aziridines.

Table 1.



Entry	Reagents	Products	Time (h)	Isolated yield (%)
1	$POCl_3$/DMF	X = Cl	6	91
2	$(COCl)_2$/DMF	X = Cl	3	98
3	Triphosgene/DMF	X = Cl	2	99
4	$N_3P_3Cl_6$/DMF	X = Cl	12	95
5	$SOCl_2$/DMF	X = Cl	6	89
6	SO_2Cl_2/DMF	X = Cl	6	84
7	Cyanuric chloride/DMF	X = Cl	12	77
8	$(PhO)_2POCl$/DMF	X = Cl	6	99
9	Ph_3PCl_2/DMF	X = Cl	6	85
10	Ph_3PBr_2/DMF	X = Br	12	88
11	PBr_3/DMF	X = Br	12	93

The ring cleavage reaction was extended to a variety of cyclic and acyclic *N*-tosylaziridines using oxalyl chloride, triphosgene and phosphorous tribromide as the activating agents in combination with DMF. The results are summarized in Table 2. Cyclic *N*-tosylaziridines gave quantitative yields of products (entries 1, 2 and 3). In the

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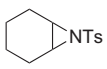
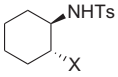
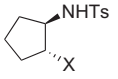
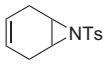
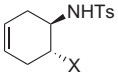
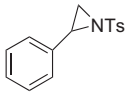
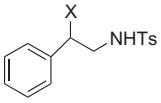
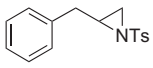
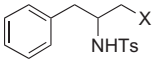
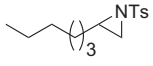
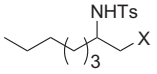
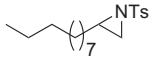
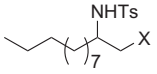
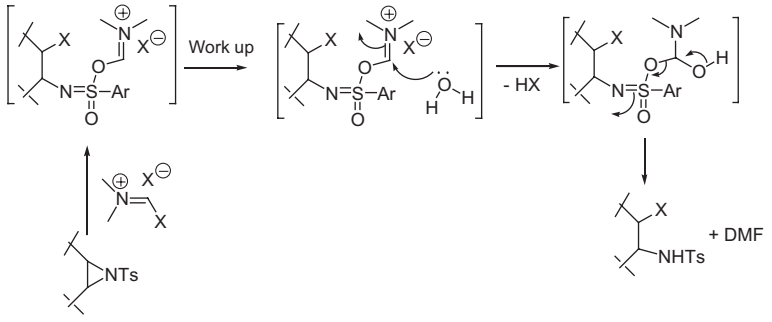
doi:10.1016/j.tetlet.2004.10.161

Table 2.

Entry	Substrate	Products	Isolated yield, % (time, h)		
			$(COCl)_2$/DMF (X = Cl)	$CO(OCCl_3)_2$/DMF (X = Cl)	PBr_3/DMF (X = Br)
1			**1a**: 98 (3)	99 (2)	**1b**: 93 (12)
2			**2a**: 91 (12)	95 (12)	**2b**: 93 (12)
3			**3a**: 87 (12)	98 (12)	**3b**: 92 (12)
4			**4a**: 95 (12)	70 (12)	**4b**: 91 (8)
5			**5a**: 84 (20)	96 (20)	**5b**: 87 (12)
6			**6a**: 86 (24)	82 (24)	**6b**: 90 (12)
7			**7a**: 97 (18)	86 (18)	**7b**: 97 (12)



Scheme 1.

case of phenyl substituted *N*-tosylaziridine (entry 4), we obtained a single regioisomer due to internal attack at the benzylic position. Acyclic terminal aziridines (entries 5, 6 and 7) gave the product resulting from terminal attack at the less hindered position. In all cases, the reaction was highly regioselective as only one product was formed and the yields were good to excellent.

In order to ascertain whether the activated DMF complex is activating the aziridines or is only the source of halide, we performed the ring cleavage reaction in the presence of ionic nucleophiles (LiBr and NaCl)[13] in DMF at room temperature, but no trace of the desired β-haloamine was obtained. This indicates that the activated DMF complex facilitates the cleavage reaction by coordination with the aziridine. A possible reaction mechanism is shown in Scheme 1.

In conclusion, we have demonstrated a very simple, efficient and highly regioselective synthesis of β-haloamines via the ring cleavage of *N*-tosylaziridines using various activated DMF complexes in good to excellent yields.[14]

Acknowledgements

V.K.S. thanks DST for a research grant. A.B. thanks CSIR for a junior research fellowship.

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13. For opening of aziridines with NaCl in the presence of Lewis acids, see: Bisai, A.; Pandey, G.; Pandey, M. K.; Singh, V. K. *Tetrahedron Lett.* **2003**, *44*, 5839.
14. General procedure: In an oven dried round bottom flask, the activated DMF complex (2 mmol) was prepared by adding the activating reagent (2 mmol) in DMF (1 mL) at −10 °C. To this solution of *N*-tosylaziridine (1 mmol) in DMF (0.5 mL) was added at the same temperature and the reaction mixture was allowed to warm to room temperature. After completion, the reaction mixture was added to ice-cold water and extracted with ethyl acetate. Work-up and purification by silica gel column chromatography gave the corresponding β-haloamines in good to excellent yields. Spectral data of *N*-(2-chlorocyclohexyl)-4-methylbenzenesulfonamide (Table 2, entry **1a**):[10] ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.25–1.32 (m, 3H), 1.50–1.78 (m, 3H), 2.04–2.26 (m, 2H), 2.43 (s, 3H, CH_3), 3.00–3.17 (m, 1H) 3.68–3.72 (m, 1H), 4.94 (d, 1H, N*H*), 7.31 (d, J = 8.1 Hz, 2H), 7.78 (d, J = 8.1 Hz, 2H); ^{13}C NMR (100 MHz, $CHCl_3$): δ 21.5, 23.4, 24.5, 32.6, 35.0, 58.8, 62.2, 127.3, 129.6, 137.1, 143.5.