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Hydrated nickel (II) halides mediated ring opening reaction with *N*-tosylaziridines

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Abstract

An efficient and water tolerant method for the synthesis of β-haloamines is described utilizing hydrated nickel (II) halides ($NiX_2{\cdot}nH_2O$ X = Cl, Br, I) and aziridines as starting materials. *N*-Tosylaziridines reacted with $NiCl_2{\cdot}6H_2O$ or $NiI_2{\cdot}6H_2O$ giving β-chloro- or β-iodoamines in high yields (73–99%) within a short time, but 10 mol% of *n*-Bu_4NBr should be added in the reactions of *N*-tosylaziridines with $NiBr_2{\cdot}3H_2O$ in order to obtain the high yields of corresponding β-bromoamines. Solvent played an important role in the reactions. The proper solvent for the reaction of $NiCl_2{\cdot}6H_2O$ was DMF, while $NiBr_2{\cdot}3H_2O$ or $NiI_2{\cdot}6H_2O$ proceeded well in 1,4-dioxane.

Keywords: *N*-Tosylaziridines; Hydrated nickel (II) halides; Ring opening reaction; β-Haloamines

Aziridines are important intermediates in organic synthesis because they can react with various nucleophiles leading to highly regio- and stereoselective ring opened products. Methods have been documented for the cleavage of aziridines with heteroatoms such as O, N, S, Se, and halogen [1–4]. Nucleophilic halogen addition to aziridines leads to the formation of β-haloamines, which serve as important precursors for the synthesis of medicinally important compounds [5,6]. Therefore, there is significant current interest in the halogen ring opening reactions of aziridines.

Reagents employed in the reaction of nucleophilic halogen ring opening to aziridines are mainly halides such as hydrogen halides, metal halides, quaternary ammonium halides [1,2,7–9]. Almost all the halides reacted with aziridines under strongly acidic condition; this limits their application in the reactions of aziridines bearing acid sensitive functional groups. $CeCl_3{\cdot}7H_2O$ could react with aziridines or catalyze the reaction of aziridines with NaI affording β-chloro- or β-iodoamines under nearly neutral condition, but β-bromoamines was not obtained by the protocol [10]. On the other hand, the reactions using some non-ionic compounds, such as Me_3SiX (X = Cl, I) and Ph_3P/X_2 (X = Cl, Br, I), as substrates suffered from harsh reaction conditions or high toxicity of halogen (X_2) [11]. So the development of a mild, convenient and general method is desired for the synthesis of β-haloamines. We here describe a new approach using hydrated nickel (II) halides ($NiX_2{\cdot}nH_2O$, X = Cl, Br, I), an inexpensive, non-toxic and

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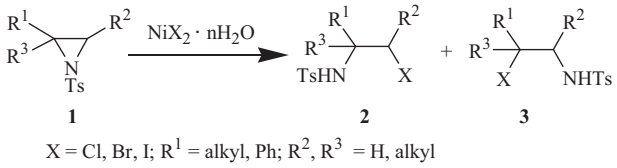


Scheme 1. The ring opening reaction of aziridines with hydrated nickel (II) halides.

ready available salts as halogen sources for the reactions. The reactions smoothly proceeded under convenient condition (Scheme 1).

The reactions were performed by heating the mixture of aziridine **1** and $NiX_2{\cdot}nH_2O$ (60 mol%) in a proper solvent, but 10 mol% of *n*-Bu_4NBr (TBAB) should be added as a catalyst in the reactions of $NiBr_2{\cdot}3H_2O$. Control experiments were carried out for the discussion of reaction conditions.

The best yield of **2a** [12] (99%; R^1, $R^2 = -(CH_2)_4-$; R^3 = H, X = Cl) was obtained by heating the mixture of 7-(toluene-4-sulfonyl)-7-azabicyclo[4.1.0]heptane **1a** and $NiCl_2{\cdot}6H_2O$ (60 mol%) at 70 °C within 15 min in DMF. However, when 1,4-dioxane was used as a solvent in stead of DMF under above conditions, the reaction could not occur. In the case of $NiI_2{\cdot}6H_2O$ (60 mol%), the high yield of **2a** (98%, X = I) was obtained in 1,4-dioxane (reflux, 3 h).

If DMF and 1,4-dioxane were used as solvents respectively in the reaction of $NiBr_2{\cdot}3H_2O$ (60 mol%) with **1b** (R^1 = Ph; R^2 = H) in the absence of TBAB, the low total yields of **2b** and **3b** (DMF, 70 °C, 46%; 1,4-dioxane, reflux, 40%) were obtained, and two undetermined side-products were formed. However when 10 mol% of TBAB was added to the reaction of **1b** with $NiBr_2{\cdot}3H_2O$ in 1,4-dioxane, a high yield (97%) of bromides **2b** and **3b** (R^1 = Ph; R^2, R^3 = H, X = Br) was obtained within 4 h. These results indicated that the proper reaction conditions were different depending on various nickel (II) halides (Table 1).

Results for the reactions of aziridines (**1a**–**1e**) with nickel (II) halides under specified conditions as shown in Table 1 are summarized in Table 2. The aziridines (**1a**–**1e**) gave moderate to excellent yields (66–99%) of corresponding *β*-haloamines. The regioselectivities of the reactions depended on the structure of aziridines and the type of halogen anions. Cyclic aziridines **1a** afforded *trans*-*β*-haloamines in high yields (96–99%; entries 1–3 in Table 2). Phenyl aziridine **1b** or trimethyl aziridine **1c** reacted with these three nickel (II) halides ($NiX_2{\cdot}nH_2O$, X = Cl, Br, I) respectively leading to two isomers **2b** (or **2c**) and **3b** (or **3c**) (entries 4–9 in Table 2), while the isomer with a halogen atom at secondary or tertiary carbon was the main product, as expected for a charge-controlled ring-opening process. The reactions of terminal *n*-butyl aziridine **1d** afforded two products **2d** and **3d** in the ratios of 93/7 (X = Cl), 75/25 (X = Br) and 90/10 (X = I) (entries 10–12 in Table 2); however, for the terminal *n*-hexadecyl aziridine **1e**, one regioisomer **2e** incorporating the halogen atom at the less substituted carbon were obtained due to the increased steric hindrance (entries 13–15 in Table 2).

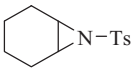
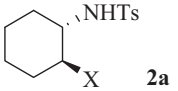
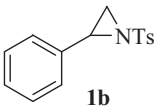
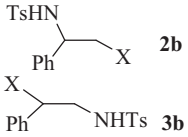
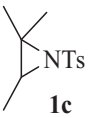
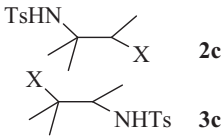
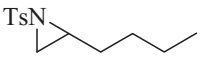
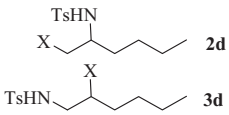
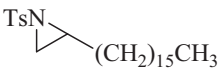
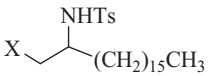
In the eye of the nickel (II) halide, $NiBr_2{\cdot}3H_2O$/TBAB led to relatively low regioselectivities (entries 5, 8 and 11 in Table 2) and took the longest time (4–12 h) among these three nickel (II) halides when they reacted with a same aziridine respectively (entries 2, 5, 8, 11 and 14 in Table 2). The lowest yield (66%) also provided by the reaction of $NiBr_2{\cdot}3H_2O$/TBAB with **1c**, giving **2c** and **3c** (entry 8, Table 2), while 26% of 3-methyl-*N*-tosylbut-3-en-2-amine **4** (Fig. 1) was isolated as a side-product. It was indicated that the carbon cation such as **5** (Fig. 1) might be involved in the reaction of **1c** with $NiBr_2{\cdot}3H_2O$ catalyzed by TBAB. These results reflect the differences between $NiBr_2{\cdot}3H_2O$ and $NiCl_2{\cdot}6H_2O$ or $NiI_2{\cdot}6H_2O$.

In conclusion, aziridines could react with hydrated nickel (II) halides ($NiX_2{\cdot}nH_2O$ X = Cl, Br, I) leading to corresponding *β*-haloamines in moderate to excellent yields and regioselectivities, which provided a new convenient

Table 1
The optimized reaction conditions of aziridines **1** with different nickel (II) halides.

Entry	Nickel (II) halide	Ratio of **1**/$NiX_2{\cdot}nH_2O$	Solvent	*T* (°C)	Catalyst
1	$NiCl_2{\cdot}6H_2O$	1:0.6	DMF	70	–
2	$NiBr_2{\cdot}3H_2O$	1:0.6	1,4-dioxane	Reflux	10 mol% TBAB
3	$NiI_2{\cdot}6H_2O$	1:0.6	1,4-dioxane	Reflux	–

Table 2
The results of the reactions of aziridines with hydrated nickel (II) halides.

Entry	Aziridine	$NiX_2{\cdot}nH_2O$	Product		Time	Yield (%) [b]	Ref. [c]
1	 **1a**	$NiCl_2{\cdot}6H_2O$	 **2a**	X = Cl	35 min	99	[12]
2		$NiBr_2{\cdot}3H_2O$ [a]		X = Br	4 h	96	[13]
3		$NiI_2{\cdot}6H_2O$		X = I	3 h	98	[10]
4	 **1b**	$NiCl_2{\cdot}6H_2O$	 **2b** **3b**	X = Cl	1.5 h	90(**2b**/**3b** = 23/77)	[13]
5		$NiBr_2{\cdot}3H_2O$ [a]		X = Br	4 h	97(**2b**/**3b** = 32/68)	[13,14]
6		$NiI_2{\cdot}6H_2O$		X = I	3 h	96(**2b**/**3b** $\leq$ 5/95)	[14]
7	 **1c**	$NiCl_2{\cdot}6H_2O$	 **2c** **3c**	X = Cl	2 h	85(**2c**/**3c** = 8/92)	[16]
8		$NiBr_2{\cdot}3H_2O$ [a]		X = Br	12 h	66(**2c**/**3c** = 31/67)	[16]
9		$NiI_2{\cdot}6H_2O$		X = I	1 h	73(**2c**/**3c** = 5/95)	[16]
10	 **1d**	$NiCl_2{\cdot}6H_2O$	 **2d** **3d**	X = Cl	1 h	97(**2d**/**3d** = 93/7)	[15]
11		$NiBr_2{\cdot}3H_2O$ [a]		X = Br	4.5 h	96(**2d**/**3d** = 75/25)	[12,13]
12		$NiI_2{\cdot}6H_2O$		X = I	1.5 h	94(**2d**/**3d** = 90/10)	[14]
13	 **1e**	$NiCl_2{\cdot}6H_2O$	 **2e**	X = Cl	1.5 h	99	[16]
14		$NiBr_2{\cdot}3H_2O$ [a]		X = Br	9.5 h	99	[16]
15		$NiI_2{\cdot}6H_2O$		X = I	7 h	84	[16]

[a] 10 mol% of TBAB was added as catalyst.
[b] Isolated yield. Ratios of the two regioisomers **2** and **3** were determined by 600 MHz ^{1}H NMR.
[c] The products were identified by comparison with the authentic sample or spectra.

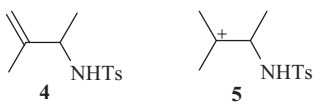


Fig. 1. The structures of compound **4** and cation **5**.

way to synthesize β-haloamines. n-Bu_4NBr (TBAB) should be added as a catalyst in the reaction of aziridines with $NiBr_2{\cdot}3H_2O$ to obtain the high yields of corresponding β-bromoamines, while any catalysts were needless for $NiCl_2{\cdot}6H_2O$ and $NiI_2{\cdot}6H_2O$. The inexpensive, non-toxic, ready available and water tolerant inorganic salts might be used as general reagents for the preparations of β-haloamines.

Acknowledgments

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[16] Spectral data of new compounds: [**3c**] (X = Cl, entry 7 in Table 2): ^{1}H NMR (600 MHz, $CDCl_3$): δ 1.08 (d, 3H, J = 6.6 Hz), 1.52 (s, 3H), 1.53 (s, 3H), 2.43 (s, 3H), 3.35 (m, 1H), 4.62 (d, 1H, J = 9.0 Hz), 7.31 (d, 2H, J = 7.8 Hz), 7.76 (d, 2H, J = 7.8 Hz). Anal. Calcd. for $C_{12}H_{18}ClNO_2S$: C 52.26, H 6.58, N 5.08. Found: C 52.23, H 6.55, N 5.07. **2c/3c** (X = Br, entry 8 in Table 2): ^{1}H NMR (600 MHz, $CDCl_3$): δ 1.10 (d, 3H, J = 6.6 Hz, **3c**), 1.29 (s, 3H, **2c**), 1.32 (s, 3H, **2c**), 1.66 (d, 3H, J = 6.6 Hz, **2c**), 1.69 (s, 3H, **3d**), 1.69 (s, 3H, **3c**), 1.72 (s, 3H, **3c**), 2.43 (s, 3H, **3c**), 2.43 (s, 3H, **2c**), 3.10 (m, 1H, **3c**), 4.28 (m, 1H, **2c**), 4.60 (d, 1H, J = 8.4 Hz, **3c**), 4.92 (brs, 1H, **2c**), 7.30 (d, 2H, J = 8.4 Hz, **2c**), 7.31 (d, 2H, J = 8.4 Hz, **3c**), 7.76 (d, 2H, J = 8.4 Hz, **3c**), 7.78 (d, 2H, J = 8.4 Hz, **3c**); EI-MS m/z 319(M^+, 1), 240(4), 198(100), 155(96), 91(95). Anal. Calcd. for $C_{12}H_{18}BrNO_2S$: C 45.01, H 5.67, N 4.37. Found: C 45.03, H 5.70, N 4.35. **3c** (X = I, entry 9 in Table 2): ^{1}H NMR (600 MHz, $CDCl_3$): δ 1.10 (d, 3H, J = 6.6 Hz), 1.85 (s, 3H), 1.92 (s, 3H), 2.25 (m, 1H), 2.43 (s, 3H), 4.60 (d, 1H, J = 9.6 Hz), 7.31 (d, 2H, J = 7.8 Hz), 7.76 (d, 2H, J = 7.8 Hz). Anal. Calcd. for $C_{12}H_{18}INO_2S$: C 39.25, H 4.94, N 3.81. Found: C 39. 26, H 4.96, N 3.83. **2e** (X = Cl, entry 13 in Table 2): ^{1}H NMR (600 MHz, $CDCl_3$): δ 0.88 (t, 3H, J = 6.6 Hz), 1.03–1.34 (m, 28H), 1.40–1.56 (m, 2H), 2.43 (s, 3H), 3.42–3.54 (m, 3H), 4.70 (d, 1H, J = 7.8 Hz), 7.31 (t, 2H, J = 7.8 Hz), 7.77 (d, 2H, J = 7.8 Hz). EI-MS m/z 457 (M^+, 1), 408 (58), 232 (37), 155 (100), 91 (88). Anal. Calcd. for $C_{25}H_{44}ClNO_2S$: C 65.54, H 9.68, N 3.06. Found: C 65.57; H, 9.69, N 3.07. **2e** (X = Br, entry 14 in Table 2): ^{1}H NMR (600 MHz, $CDCl_3$): δ 0.88 (t, 3H, J = 6.6 Hz), 1.03–1.32 (m, 28H), 1.41–1.56 (m, 2H), 2.43 (s, 3H), 3.30–3.36 (m, 1H), 3.37–3.43 (m, 2H), 4.69 (d, 1H, J = 8.4 Hz), 7.31 (t, 2H, J = 7.8 Hz), 7.77 (d, 2H, J = 7.8 Hz). Anal. Calcd. for $C_{25}H_{44}BrNO_2S$: C 59.74, H 8.82, N 2.79. Found: C 59.77, H 8.83, N 2.79. **2e** (X = I, entry 15 in Table 2): ^{1}H NMR (600 MHz, $CDCl_3$): δ 0.88 (t, 3H, J = 7.2 Hz), 1.00–1.34 (m, 28H), 1.35–1.48 (m, 2H), 2.43 (s, 3H), 2.93 (m, 1H), 3.14–3.25 (m, 2H), 4.61 (d, 1H, J = 8.4 Hz), 7.31 (t, 2H, J = 7.8 Hz), 7.77 (d, 2H, J = 7.8 Hz). Anal. Calcd. for $C_{25}H_{44}INO_2S$: C 54.63, H 8.07, N 2.55. Found: C 54.61, H 8.05, N 2.54. **4**: ^{1}H NMR (600 MHz, $CDCl_3$): δ 1.17 (d, 3H, J = 7.2 Hz), 1.56 (s, 3H), 2.42 (s, 3H), 3.84 (m, 1H), 4.44 (d, 1H, J = 7.2 Hz), 4.72 (s, 1H), 4.80 (s, 1H), 7.28 (d, 2H, J = 9.0 Hz), 7.74 (d, 2H, J = 8.4 Hz); EI-MS m/z 239 (M^+, 1), 155 (8.1), 91 (21), 84 (100). Anal. Calcd. for $C_{12}H_{17}NO_2S$: C 60.22, H 7.16, N 5.85. Found: C 60.23, H 7.19, N 5.86.