Structural Revision of the Ring-Opened Product in the $ZnCl_2$-Catalyzed Reactions of 1-Benzyl-2-phenylaziridine with Thiols

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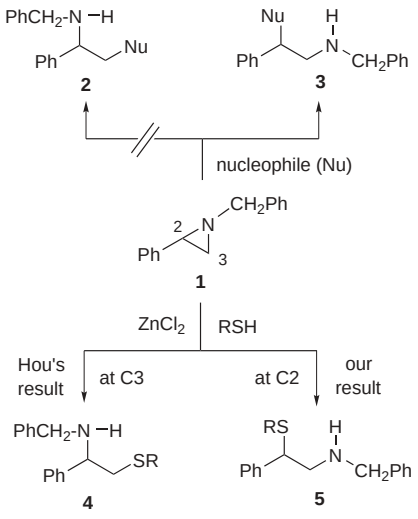
Abstract: The reported β-amino sulfide structures for the products in the $ZnCl_2$-catalyzed ring-opening reactions of 1-benzyl-2-phenylaziridine with thiols should be revised to 2-amino-1-phenylethyl sulfides from 2-amino-2-phenylethyl sulfides.

Key words: structural revision, β-amino sulfide, ring-opening, 1-benzyl-2-phenylaziridine, thiol, $ZnCl_2$

Aziridines are very versatile synthetic intermediates for the synthesis of biologically active *N*-containing compounds. Their reactivity is dependent upon highly strained three-member ring structures and thus, a nucleophilic ring-opening reaction is one of major reaction paths.[1] During the course of our studies on aziridine chemistry[2] we tried to prepare 2-substituted 1-phenylethylamines **2** from 1-benzyl-2-phenylaziridine (**1**) by ring-opening reaction with organometallics including higher-ordered organocupurates or halides as nucleophiles. However, the ring-opened products that were obtained were only isomeric 2-phenylethylamines **3** resulting from the attack of nucleophiles at the benzylic (C2) position.

In 2001, Hou et al.[3] reported the effective cleavage of aziridines including **1** with various thiols in the presence of $ZnCl_2$, in which thiols exclusively attacked at the non-benzylic (C3) position to give 2-amino-2-phenylethyl sulfides **4** when **1** was used as a substrate. However, our trials for the ring-opening reaction of **1** with thiols under their conditions resulted in the exclusive formation of isomeric 2-amino-1-phenylethyl sulfides **5**, contrary to the reported results (Scheme 1). In this paper we present the structural revision of the β-amino sulfides obtained in the $ZnCl_2$-catalyzed ring-opening reaction of 1-benzyl-2-phenylaziridine (**1**) with thiols.



Scheme 1 Nucleophilic ring-opening reaction of 1-benzyl-2-phenylaziridine (**1**)

According to the Hou's conditions,[3] we at first tried the ring-opening reaction of **1** with 2-bromothiophenol in order to prepare 2-benzylamino-2-phenylethyl 2-bromophenyl sulfide (**6**) for our synthetic utility. Treatment of **1** with 2-bromothiophenol in the presence of a catalytic amount of $ZnCl_2$ in CH_2Cl_2 at room temperature for 10 minutes afforded a ring-opened product in 63% yield. At a glance, the ring-opened product could be assigned to be an intended product **6** by comparison of its ^1H NMR data with those of the so-called Hou's product, 2-benzylamino-2-phenylethyl phenyl sulfide (**4**: R = phenyl) [CH: δ_H 4.40 (t, J = 7.3 Hz, 1 H), CH_2: δ_H 3.10 (d, J = 7.3 Hz, 2 H), PhCH_2N: δ_H 3.80 (s, 2 H)], obtained in the reaction using thiophenol as a nucleophile. The 2-bromothiophenol-derived product showed signals assignable to the sequence of PhC(NCH_2Ph)HCH_2SAr [CH: δ_H 4.52 (t, J = 7.0 Hz, 1 H) and δ_C 52.1; CH_2: δ_H 3.11, 3.15 (dd, J = 12.4, 7.0 Hz, each 1 H,) and δ_C 53.7] in **6**, in addition to *N*-benzyl methylene group [δ_H 3.78, 3.82 (d, J = 13.5 Hz, each 1 H) and δ_C 53.3] and an aromatic quaternary carbon (δ_C 136.1) bonded to sulfur function in the ^1H- and ^{13}C NMR spectra. However, possibility of the alternative sequence of PhC(SAr)HCH_2NCH_2Ph in an isomeric 2-benzylamino-1-phenylethyl 2-bromophenyl sulfide (**7**) could not be excluded by the above NMR data.

Thus, we applied 2 D NMR techniques for the structural determination of the ring-opened product. The HMBC experiments showed diagnostic cross peaks between the methine proton (δ_H 4.52) and the sulfur-substituted aromatic quaternary carbon (δ_C 136.1) and between the *N*-benzyl methylene protons (δ_H 3.78 and 3.82) and the methylene carbon (δ_C 53.7) derived from the aziridine ring. However, it was difficult to explain the presence of the former sequence of PhC(NCH_2Ph)HCH_2SAr in the molecule because these cross peaks must be coming from unusual four-bond connection. Instead, the latter sequence of PhC(SAr)HCH_2NCH_2Ph can be reasonably deduced because of the commonly acceptable three-bond connection,

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as shown Figure 1. Therefore, the product in the $ZnCl_2$-catalyzed ring-opening reaction of 1-benzyl-2-phenylaziridine (**1**) with 2-bromothiophenol should be 2-benzylamino-1-phenyethyl 2-bromophenyl sulfide (**7**), but not 2-benzylamino-2-phenylethyl 2-bromophenyl sulfide (**6**) as expected from the Hou's paper.[3]

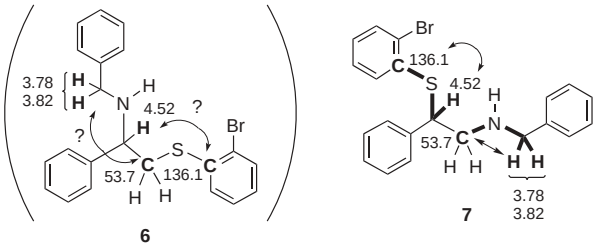
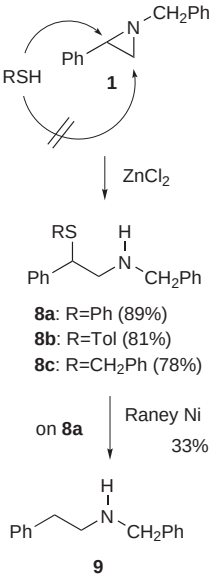


Figure 1 Selected H-C correlations in the HMBC experiments in the ring-opened product of **1** with 2-bromothiophenol

These situations made us re-examine Hou's experiments using the same nucleophiles used by them. The $ZnCl_2$-catalyzed ring-opening reactions of **1** using thiophenol, 4-methylthiophenol, and phenylmethylthiol were carried out under the reported conditions and smooth reaction was observed in each case, to afford the product **8** in good yields, the spectral data of which were identical with those in the literature[3] (see Scheme 2). Thus, the general efficiency of the $ZnCl_2$-catalyzed ring-opening reaction of 1-benzyl-2-phenylaziridine (**1**) with thiols was confirmed, but the correct structure of the product remained unclear.



Scheme 2 The $ZnCl_2$-promoted ring-opening reactions of 1-benzyl-2-phenylaziridine (**1**) with thiols followed by reductive desulfurization of the thiophenol-derived sulfide **8a** with Raney Ni

Next, we tried the chemical conversion of the product **8a** (R = Ph) obtained in the reaction using thiophenol to a known phenylethylamine derivative in order to unambiguously determine whether the ring-opened product was 2-benzylamino-2-phenyethyl sulfide like **4**, a non-benzylic position (C3) attacked product, or 2-benzylamino-1-phenylethyl sulfide like **5**, a benzylic position (C2) attacked one. Treatment of **8a** with Raney Ni in EtOH under reflux afforded the known *N*-benzyl-*N*-(2-phenylethyl)amine (**9**)[4] in 33% yield as the sole reduction product. These facts indicated that the starting sulfide should be 2-benzylamino-1-phenylethyl phenyl sulfide resulting from the attack on the benzylic (C2) position of the 2-phenylaziridine **1** (Scheme 2).

In conclusion, we have demonstrated the exclusive attack at the benzylic (C2) position of 1-benzyl-2-phenylaziridine (**1**) with thiols in the $ZnCl_2$-catalyzed ring-opening reaction, in which 2-benzylamino-1-phenylethyl sulfides were formed, contrary to the Hou's report.[3] Recently Yudin et al.[5] studied the tris(pentafluorophenyl)borane-caytalyzed ring-opening reaction of aziridines with nitrogen or sulfur nucleophiles and reported the exclusive production of the so-called Hou's product, 2-benzylamino-2-phenyl phenyl sulfide, when **1** was treated with thiophenol. The same structure that was given in Hou's report was also given as the reaction product in their case because of identical spectral data. However, as mentioned above, the structure of the ring-opened product obtained by Yudin et al.[5] should be revised from 2-benzylamino-2-phenylethyl phenyl sulfide to 2-benzylamino-1-phenylethyl phenyl sulfide.

IR spectra were recorded on a JASCO FT/IR-300E spectrophotometer. ^{1}H- (400 MHz) and ^{13}C NMR (100 MHz) spectra were recorded in $CDCl_3$ on a JEOL JNM-LA400, and TMS (0.00 ppm) and the middle resonance of $CDCl_3$ (77.0 ppm) were used as an internal standard, respectively. EIMS were recorded on JEOL JMS-GCMATE. FABMS were recorded on JEOL JMS-HX110 with *m*-nitrobenzyl alcohol as a matrix. Reactions were monitored by TLC on Kieselgel 60 F_{254} (Merck, 5715). Raney Ni in water was purchased from Aldrich Co. Ltd. Column chromatography was performed on silica gel (Fuji Silysia, FL100D).

The $ZnCl_2$-Catalyzed Ring-Opened Reaction of 1-Benzyl-2-phenylaziridine (1) with Thiols

According to the reported method,[3] a thiol was added to a mixture of **1** and $ZnCl_2$ (0.05 mol equiv) in anhyd CH_2Cl_2 and the resulting mixture was stirred at r.t. under Ar. After addition of Et_2O the mixture was partitioned with sat. NH_4Cl and 1% aq KOH, and H_2O. The organic solution was dried over $MgSO_4$ and evaporated. The residual oil was purified by column chromatography (hexane–EtOAc, 10:1) to give a ring-opened product **8**.

With 2-Bromophenylthiol: *N*-Benzyl-*N*-[2-(2-bromophenylthio)-2-phenylethyl)amine (7)

p-Bromothiophenol (45 mg, 0.24 mM), **1** (50 mg, 0.24 mM), and $ZnCl_2$ (3 mg, 0.019 mM) in anhyd CH_2Cl_2 (0.3 mL) were treated for 10 min to give a colorless oil (60 mg, 63%). IR (neat): 3325 (NH) cm^{-1}. ^{1}H NMR: δ = 3.11, 3.15 (dd, *J* = 12.4, 7.0 Hz, each 1 H, C_1-H_2), 3.78, 3.82 (d, *J* = 13.5 Hz, each 1 H, NCH_2Ph), 4.52 (t, *J* = 7.0 Hz, 1 H, C_2-H), 7.00 (ddd, *J* = 7.9, 7.3, 1.6 Hz, 1 H, ArH), 7.10 (td, *J* = 7.9, 1.5 Hz, 1 H, ArH), 7.18 (dd, *J* = 7.9, 1.5 Hz, 1 H, ArH), 7.21–7.36 (m, 10 H, ArH), 7.52 (dd, *J* = 7.9, 1.5 Hz, 1 H, ArH). ^{13}C NMR: δ = 52.1, 53.3, 53.7, 126.0, 127.0, 127.7, 127.8, 128.0, 128.4, 128.7, 131.9, 132.0, 133.0, 136.1, 139.6, 139.8. FABMS: *m/z* = 400, 398 [MH^+].

With Thiophenol: *N*-Benzyl-*N*-(2-phenyl-2-phenylthioethyl)amine (8a)

Thiophenol (0.09 mL, 0.86 mM), **1** (181 mg, 0.86 mM), and $ZnCl_2$ (6 mg, 0.047 mM) in anhyd CH_2Cl_2 (3 mL) were treated for 15 min to give a colorless oil (246 mg, 89%). IR (neat): 3337 (NH) cm^{-1}. ^1H NMR: δ = 3.09 (d, *J* = 7.3 Hz, 2 H, C_1-H_2), 3.79 (s, 2 H, NCH_2Ph), 4.37 (t, *J* = 7.3 Hz, 1 H, C_2-H), 7.18–7.33 (m, 15 H, ArH). FABMS: *m*/*z* = 320 [MH^+].

With 4-Methylthiophenol: *N*-Benzyl-*N*-[2-phenyl-2-(4-methylphenylthio)ethyl]amine (8b)

4-Methylthiophenol (41 mg, 0.33 mM), **1** (70 mg, 0.33 mM), and $ZnCl_2$ (3 mg, 0.019 mM) in anhyd CH_2Cl_2 (5 mL) were treated for 1 h to give a colorless oil (89 mg, 81%). IR (neat): 3324 (NH) cm^{-1}. ^1H NMR: δ = 2.29 (s, 3 H, PhMe), 3.07 (d, *J* = 7.3 Hz, 2 H, C_1-H_2), 3.77 (s, 2 H, NCH_2Ph), 4.30 (t, *J* = 7.3 Hz, 1 H, C_2-H), 7.00 (d, *J* = 7.9 Hz, 2 H, ArH), 7.14 (d, *J* = 8.1 Hz, 2 H, ArH), 7.20–7.31 (m, 10 H, ArH). FABMS: *m*/*z* = 334 [MH^+].

With Phenylmethylthiol: *N*-Benzyl-*N*-[2-phenyl-2-(phenylmethylthio)ethyl]amine (8c)

Phenylmethylthiol (32 mg, 0.26 mM), **1** (51 mg, 0.24 mM), and $ZnCl_2$ (2 mg, 0.015 mM) in anhyd CH_2Cl_2 (0.7 mL) were treated for 2 h to give a colorless oil (62 mg, 78%). IR (neat): 3315 (NH) cm^{-1}. ^1H NMR: δ = 2.97 (d, *J* = 7.3 Hz, 2 H, C_1-H_2), 3.46, 3.57 (d, *J* = 13.4 Hz, each 1 H, SCH_2Ph), 3.69 (s, 2 H, NCH_2Ph), 3.90 (t, *J* = 7.3 Hz, 1 H, C_2-H), 7.20–7.36 (m, 15 H, ArH). FABMS: *m*/*z* = 334 [MH^+].

***N*-Benzyl-*N*-phenylethylamine (9)**

After the water in 50% slurry of Raney Ni in water was replaced by EtOH, a mixture of the sulfide (50 mg, 0.16 mmol) and the Raney Ni (0.4 mL in EtOH) in EtOH (1.2 mL) was refluxed for 10 h. After dilution with CH_2Cl_2 (ca 3 mL) the mixture was filtered through Celite pad and the filtrate was evaporated. Purification of the residue by preparative TLC ($CHCl_3$–MeOH, 20:1) gave **9** as a colorless oil (11 mg, 33%). IR (neat): 3321 (NH) cm^{-1}. ^1H NMR: δ = 2.82–2.93 (m, 4 H, NCH_2CH_2Ph), 3.80 (s, 2 H, NCH_2Ph), 7.19–7.33 (m, 10 H, ArH). EIMS: *m*/*z* (%) = 211 (0.2) [M^+], 120 (42), 91 (100).

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