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Asymmetric Route to Pyridines Bearing a Highly Functionalized 2-Alkyl Substituent by Aziridine Ring-Opening Reactions

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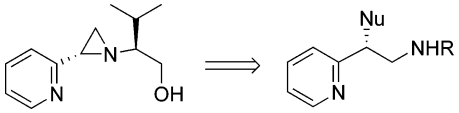

The aziridine prepared from the 2-pyridineimine derived from (*S*)-valinol underwent ring-opening by attack of nitrogen, sulfur, and oxygen nucleophiles. Complete or prevalent regioselectivity was obtained using cerium trichloride heptahydrate as a catalyst. In some cases, the N-substituent could be removed by an oxidative protocol.

Introduction

During the past decade, chiral nonracemic aziridines have assumed a significant role as synthetic tools for organic chemists.[1] Besides the usefulness of aziridines as bases and ligands for organometallic catalysts in enantioselective reactions,[2] these compounds provide the C−C−N fragment for the construction of functionalized acyclic molecules by stereo- and regioselective ring-opening with nucleophiles.[2e,3] An electron-withdrawing N-substituent allows for facile ring-opening reactions. On the other hand, activation by a Lewis acid or an electrophile is required to achieve the ring-opening of *N*-alkyl-substituted aziridines. We have recently reported the synthesis of the 2-(2-pyridyl)-substituted aziridine **1** by the addition of chloromethyllithium to the pyridineimine derived from (*S*)-valinol.[4] Therein, we described a few examples of ring-opening reactions promoted by hydroiodic acid, acetyl chloride,[5] and the combined use of a reactive alkyl halide and carbonyldiimidazole. In all cases, the halide ion regio- and stereoselectively attacked on the substituted, benzylic aziridine carbon.

Stimulated by the plethora of reports describing the ring opening of unactivated aziridines by heteronucleophiles, we applied a few such procedures to the aziridine **1**, aiming to assess the factors controlling the regioselectivity of the nucleophilic attack, providing the polyfunctional compounds **2** or **3** (Scheme 1). In particular, we planned to prepare the compounds **2**, whose structural features are the homobenzylic amine moiety and the benzylic stereocenter. We envisaged that these compounds and those obtained by removal or transformation of the N-substituent can find use as chiral nonracemic polydentate ligands in enantioselective catalytic reactions. Moreover, this skeleton is present in a number of compounds, e.g., **4**[6] and **5**,[7] which have been described in recent patents reporting their herbicide and fungicide properties.

Therefore, we began investigating the reactivity of the pyridyl-substituted aziridine **1** with different N-, S-, and O-nucleophiles

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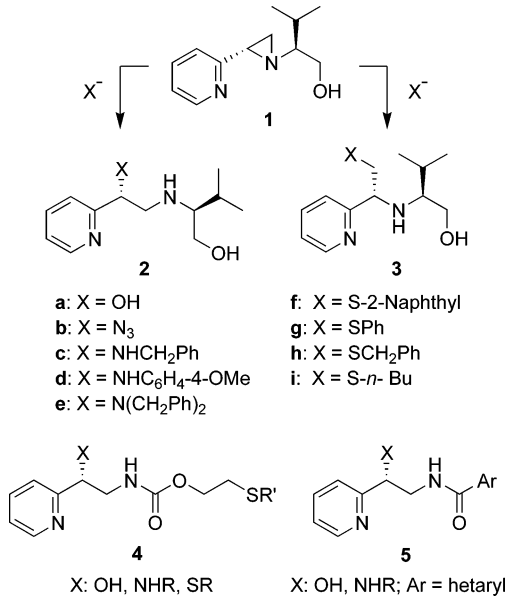
SCHEME 1. Ring-Opening of the Aziridine 1 by Attack of Heteronucleophiles



to define the optimal reaction conditions allowing for a selective ring-opening.

Results and Discussion

The protocols for the Lewis acid promoted nucleophilic ring-opening of analogous substituted aziridines, as described by other groups, were taken into account. A series of reactions with several heteronucleophiles in different experimental conditions demonstrated that it is possible to activate the aziridine ring and control the regioselectivity of the ring-opening process by the proper choice of the reagent, Lewis acid, and solvent. The reactions gave the products **2**, coming from nucleophilic attack at the more substituted aziridine carbon, either exclusively or together with the alternative product **3** (Table 1). Initial attempts involved water as the nucleophile in the presence of a protic[8] or Lewis acid catalyst.[9] Heating a mixture of aziridine **1** and *p*-toluenesulfonic acid (20 mol %) in 9:1 acetonitrile−water at the reflux temperature for 6 h gave a mixture of the regioisomeric ring-opening products **2a** and **3a** (82:18), which were separated by column chromatography. Slightly better results were obtained using cerium trichloride heptahydrate (30 mol %) with other experimental conditions remaining constant; by this manner, an improved regioselectivity (86:14) was obtained.

Then, efforts were devoted to optimizing the reaction with sodium azide, with the aim of preparing the benzylic azide **2b**. By using sodium azide as the nucleophile source, an acetonitrile−water mixture (9:1) was used as the solvent. Having observed no reactivity at the reflux temperature in the absence of a Lewis acid, we evaluated ceric ammonium nitrate (CAN)[9] and cerium trichloride heptahydrate,[10] which were both found to be effective catalysts in the same solvent mixture either at room temperature or at the reflux temperature.

In both cases, we obtained good results. As a matter of fact, the benzylic azide **2b** was formed exclusively and isolated in high yield. A slightly lower yield of **2b** was obtained using sodium azide (2 equiv) and aluminum trichloride[11] (10 mol %) in 1:1 EtOH−H_2O after 24 h at 25 °C. On the other hand, trimethylsilyl azide,[12] when used in aprotic solvents (THF, CH_2Cl_2), gave a mixture of the azides **2b** (prevalent) and **3b**. The reaction rate increased in the presence of tetrabutylammonium fluoride;[12c,d] in this case, the amount of the benzylic amine **3b** was also increased, such that this compound could be isolated by column chromatography.

The reactions with the primary amines benzylamine and *p*-anisidine in different conditions always gave mixtures of the isomeric products **2c**,**d** and **3c**,**d**. The best ratio in favor of **2c** (75:25) and **3d** (71:29) was obtained in the presence of the hydrated ceric salt in acetonitrile−water. In comparison, the use of anhydrous zinc triflate[13] or lithium perchlorate[13,14] in acetonitrile led to lower selectivities. Moreover, no reaction was observed with benzylamine and zinc triflate in dichloromethane. All the four compounds **2c**,**d** and **3c**,**d** could be isolated, preferably from the properly enriched reaction mixtures. Similarly, the reaction with dibenzylamine in the optimal reaction conditions gave the two products **2e** and **3e** in an almost 1:1 ratio, and they were separated chromatographically with some difficulty.

The positive effect of both the protic solvent and the cerium salt was particularly evident in the reactions of the aziridine **1** with aromatic thiols. In the case of 2-naphthalenethiol (1.1 equiv), the benzylic sulfide **2f** was obtained exclusively with high yield after heating in the presence of the hydrated cerium salt in 9:1 acetonitrile−H_2O at the reflux temperature for 2 h.[15] On the other hand, lower reaction rates and mixtures of **2f** and **3f** were observed in the absence of the catalyst in the same solvent mixture and in dichloromethane.[16] Similar results were obtained in the case of thiophenol, whereas the reaction with benzylthiol gave a mixture of the products **2h** and **3h** (70:30) in the optimized conditions. The reaction with *n*-butylthiol was even less satisfactory, as it afforded a mixture, from which only the prevalent sulfide **2i** and the alcohol **2a** were isolated by column chromatography. Finally, *t*-butylthiol was ineffective, as we only obtained the alcohols **2a** and **3a**, coming from the competitive ring opening by water.

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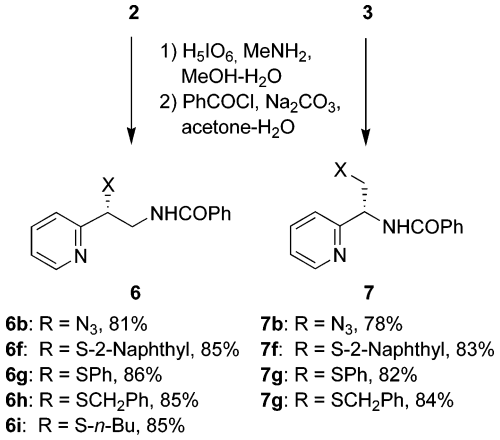
TABLE 1. Synthesis of 2-(2-Pyridyl)- and 1-(2-Pyridyl)-2-substituted Ethylamines 2 and 3 by Ring-Opening Reactions of the Aziridine 1

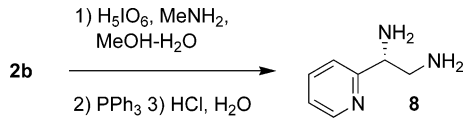
reagent (equiv)	additive (mol %)	solvent, *T*, *t*	ratio **2**/**3**[a]	**2**, yield %[b]	**3**, yield %[b]
H_2O	*p*-TsOH (20)	CH_3CN-H_2O (9:1), reflux, 6 h	82:18	**2a**, 77	**3a**, 14
H_2O	$CeCl_3 \cdot 7H_2O$ (30)	CH_3CN-H_2O (9:1), reflux, 8 h	86:14	**2a**, 71	**3a**, 8
NaN_3 (1.5)	−	CH_3CN-H_2O (9:1), reflux, 6 h	−	−	−
NaN_3 (1.1)	CAN (10)	CH_3CN-H_2O (9:1), 25 °C, 24 h	100:0	**2b**, 91	−
NaN_3 (1.1)	CAN (10)	CH_3CN-H_2O (9:1), reflux, 5 h	100:0	**2b**, 94	−
NaN_3 (1.1)	$CeCl_3 \cdot 7H_2O$ (10)	CH_3CN-H_2O (9:1), 25 °C, 18 h	100:0	**2b**, 92	−
NaN_3 (1.1)	$CeCl_3 \cdot 7H_2O$ (10)	CH_3CN-H_2O (9:1), reflux, 4 h	100:0	**2b**, 91	−
NaN_3 (2)	$AlCl_3$ (10)	$EtOH-H_2O$ (1:1), 25 °C, 24 h	100:0	**2b**, 62	−
$TMSN_3$ (2)	−	CH_3CN, 25 °C, 20 h	91:9	**2b**, 87	**3b**[c]
$TMSN_3$ (2)	−	CH_2Cl_2, 25 °C, 48 h	80:20	**2b**, 73	**3b**, 16
$TMSN_3$ (2)	*n*-Bu_4NF (20)	THF, 25 °C, 20 h	65:35	**2b**, 58	**3b**, 31
$PhCH_2NH_2$ (2)	$CeCl_3 \cdot 7H_2O$ (50)	CH_3CN-H_2O (9:1), reflux, 6 h	75:25	**2c**, 67	**3c**[c]
$PhCH_2NH_2$ (2)	$Zn(OTf)_2$ (10)	CH_3CN, reflux, 8 h	51:49	**2c**, 38	**3c**, 40
$PhCH_2NH_2$ (2)	$Zn(OTf)_2$ (10)	CH_2Cl_2, reflux, 6 h	−	−	−
$PhCH_2NH_2$ (2)	$LiClO_4$ (10)	CH_3CN, reflux, 8 h	40:60	**2c**[c]	**3c**[c]
4-$CH_3OC_6H_4NH_2$ (1.2)	$LiClO_4$ (10)	CH_3CN, reflux, 24 h	69:31[d]	**2d**, 62	**3d**, 27
4-$CH_3OC_6H_4NH_2$ (1.2)	$CeCl_3 \cdot 7H_2O$ (50)	CH_3CN, reflux, 24 h	71:29	**2d**, 51	**3d**, 24
$(PhCH_2)_2NH$ (2)	$CeCl_3 \cdot 7H_2O$ (50)	CH_3CN-H_2O (9:1), reflux, 5 h	53:47	**2e**, 48	**3e**, 41
2-naphthylSH (1.1)	$CeCl_3 \cdot 7H_2O$ (30)	CH_3CN-H_2O (9:1), reflux, 2 h	100:0	**2f**, 92	−
2-naphthylSH (3)	−	CH_3CN-H_2O (9:1), reflux, 5 h	75:25	**2f**, 57	**3f**, 18
2-naphthylSH (3)	−	CH_2Cl_2, 25 °C, 24 h	70:30	**2f**, 54	**3f**, 19
PhSH (1.1)	$CeCl_3 \cdot 7H_2O$ (30)	CH_3CN-H_2O (9:1), reflux, 4 h	96:4	**2g**, 84	**3g**, 3
PhSH (3)	−	CH_2Cl_2, 25 °C, 2 h	50:50	**2g**, 42	**3g**, 45
$PhCH_2SH$ (1.1)	$CeCl_3 \cdot 7H_2O$ (30)	CH_3CN-H_2O (9:1), reflux, 2 h	70:30	**2h**, 65	**3h**, 23
n-BuSH (1.1)	$CeCl_3 \cdot 7H_2O$ (30)	CH_3CN-H_2O (9:1), reflux, 4 h	−[e]	**2i**, 57; **2a**, 12	−
t-BuSH (1.1)	$CeCl_3 \cdot 7H_2O$ (30)	CH_3CN-H_2O (9:1), reflux, 4 h	81:19	**2a**, 62	**3a**, 9
t-BuSH (1.1)	*p*-TsOH (50)	CH_3CN-H_2O (9:1), reflux, 4 h	85:15	**2a**, 79	**3a**, 11

[a] Determined by ^1H NMR analysis of the crude product. [b] Yield of product isolated by column chromatography (SiO_2). [c] The product was not isolated. [d] The reaction was incomplete (about 60% conversion of **1c**). [e] A complex mixture of products was observed, and only **2i** and **2a** were isolated by column chromatography (SiO_2).

SCHEME 2. Preparation of *N*-Benzoyl 2-Substituted-2- and -1-(2-pyridyl)ethylamines



SCHEME 3. Preparation of (*R*)-1-(2-Pyridyl)-1,2-ethanediamine 8



A few of the compounds **2** and **3** were subjected to routine oxidative cleavage of the N-substituent to obtain the corresponding homobenzylic and benzylic amines, which were immediately converted to the benzamides **6** and **7** with good overall yields (Scheme 2).

Moreover, the azide **2b** was converted to the 1-(2-pyridyl)-1,2-diamine **8** by the three-step sequence described in Scheme 3, avoiding purification of the intermediates. In particular, after the usual oxidative cleavage of the N-substituent, we tried the reduction of the azide group with lithium aluminum hydride at 0 °C, but a complex mixture of products was obtained. Alternatively, the *β*-azido amine was treated with triphenylphosphine, and then hydrolysis of the intermediate ylide gave the primary diamine **8**. It should be observed that the analogous process carried out on the isomeric azide-amine **3b** would give the enantiomer of the amine **8**.

In conclusion, the ring-opening reaction of the 2-(2-pyridyl)-aziridine **1** with heteronucleophiles in optimized experimental conditions, i.e., in an acetonitrile−water mixture as the solvent and in the presence of a catalytic amount of cerium trichloride heptahydrate, proved to be a useful route to a variety of laterally difunctionalized pyridines, which could be useful for medicinal and bio-organic applications. It is our intention to investigate the potential of such compounds and their derivatives to act as ligands of (organo)metallic species in asymmetric synthesis and catalysis or as chiral organocatalysts.

Experimental Section

Procedures for the Ring Opening of the Aziridine 1. $CeCl_3 \cdot 7H_2O$-Catalyzed Hydrolytic Ring-Opening of Aziridine 1. Preparation of Pyridine-amine Diols 2a and 3a. $CeCl_3 \cdot 7H_2O$ (0.054 g, 0.15 mmol) was added to the solution of the aziridine **1** (0.100 g, 0.48 mmol) in a 1:1 CH_3CN-H_2O mixture (20 mL). The mixture was stirred at the reflux temperature for 8 h: TLC analysis showed that the starting material was totally consumed and two products were formed. A saturated aqueous solution of $NaHCO_3$ (10 mL) was added, and the organic materials were extracted with Et_2O (3 × 20 mL). The collected ethereal layers were dried over Na_2SO_4 and concentrated to leave a brown oily residue which was subjected to chromatography eluting with a EtOAc/MeOH/30% NH_4OH (98:2:1) mixture.

$CeCl_3 \cdot 7H_2O$-Catalyzed Ring-Opening of the Aziridine 1 by Heteronucleophiles. Preparation of Laterally Polyfunctionalized

Pyridines 2b−i and 3b−d,f−h. Typical Procedure. Sodium azide (0.034 g, 0.52 mmol) and $CeCl_3 \cdot 7H_2O$ (0.090 g, 0.24 mmol) were added to the solution of the aziridine **1** (0.100 g, 0.48 mmol) in a 9:1 CH_3CN-H_2O mixture (20 mL). The mixture was stirred at the reflux temperature for 2 h: TLC analysis showed that the starting material was totally consumed. The organic materials were extracted with EtOAc (3 × 20 mL). The collected ethereal layers were dried over Na_2SO_4 and concentrated to leave **2b** as a yellowish oil, Pure **2b** (0.109 g, 71%) was obtained by column chromatography on a short SiO_2 column eluting with a cyclohexane/EtOAc mixture.

Oxidative Cleavage of the N-Auxiliary. Preparation of the β-Substituted Primary Amines and Benzamides 6a,b,e,f,h,i and 7b,e,f,h. Typical Procedure. To the valinol derivative **2b** (0.240 g, 0.96 mmol) dissolved in MeOH (5 mL) was added 40% $MeNH_2$ in water (1.2 mL), then a solution of H_5IO_6 (0.768 g) in H_2O (5 mL) was added dropwise. After stirring for 2 h at room temperature, the reaction was complete, as determined by TLC analysis. Most of the solvent was evaporated at reduced pressure, and then the organic materials were extracted with Et_2O (3 × 20 mL). The collected ethereal layers were dried over Na_2SO_4 and concentrated to leave the primary amine as a yellow oil. This was dissolved in acetone (5 mL), and then Na_2CO_3 (0.200 g), H_2O (5 mL), and benzoyl chloride (167 μL, 1.44 mmol) were added while magnetically stirring. After stirring for 12 h, the organic materials were extracted with Et_2O (3 × 20 mL). The collected ethereal layers were dried over Na_2SO_4 and concentrated to leave the benzamide **6b** as a yellow oil. The product was subjected to column chromatography (SiO_2) eluting with a 1:1 mixture of cyclohexane−EtOAc to give pure **6b** as a yellow oil: 0.205 g (81%).

Preparation of the (*R*)-1-(2-Pyridyl)-1,2-ethanediamine 8. To the valinol derivative **2b** (0.202 g, 0.81 mmol) dissolved in MeOH (5 mL) was added 40% $MeNH_2$ in water (1.0 mL), and then a solution of H_5IO_6 (0.648 g) in H_2O (5 mL) was added dropwise. After stirring for 2 h at room temperature, the reaction was complete, as determined by TLC analysis. Most of the solvent was evaporated at reduced pressure, and then the organic materials were extracted with Et_2O (3 × 20 mL). The collected ethereal layers were dried over Na_2SO_4 and concentrated to leave the primary amine as a yellow oil. This was dissolved in THF (5 mL) and was cooled to 0 °C, and PPh_3 (0.177 mg, 0.67 mmol) was added. Then, the solution was warmed at room temperature for 2 h and water (2 mL) was added. After 16 h, $NaHCO_3$ (sat. solution, 5 mL) was added and the organic materials were extracted with CH_2Cl_2 (3 × 20 mL). The collected organic layers were dried over Na_2SO_4 and concentrated to leave a red solid. Pure **8** (0.074 g, 67%) was obtained by column chromatography on a short neutral Al_2O_3 column eluting with a EtOAc/MeOH (9:1) mixture.

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Supporting Information Available: General methods, analytical data, and copies of ^1H NMR and ^{13}C NMR spectra for all the new compounds prepared. This material is available free of charge via the Internet at http://pubs.acs.org.

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