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Synthesis of *N*-H vinylaziridines: a comparative study

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Synthesis of *N*-H vinylaziridines: a comparative study

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Abstract—Vinylaziridines are useful and versatile synthetic intermediates, as the relief of ring-strain provides a driving force for efficient ring-opening or ring-expansion reactions. Furthermore the vinyl group can be derivatized into interesting functionalities. The ring-closure of vicinal amino alcohols constitutes a straightforward route to aziridines. Several methods exist for this transformation, although many cannot be applied to vinylaziridines due to their acid lability. This comparative study describes the most effective sequences for the formation of *N*-H vinylaziridines. © 2014 Elsevier Science. All rights reserved

1. Introduction

Aziridines are useful and versatile synthetic intermediates, as the relief of ring-strain provides a driving force for efficient ring-opening or ring-expansion reactions.^{1,2} The importance of aziridines is also well recognized in asymmetric synthesis, where the need for chiral auxiliaries and ligands is continuously increasing.³ Vinylaziridines constitute an important subclass of aziridines. They have proven to be useful intermediates for various types of natural and synthetic compounds.^{4,5} Vinylaziridines can be selectively ring-opened at the allylic position, take part in conjugate addition reactions,⁶ Wittig and Claisen rearrangements,^{7,8} and furthermore the vinyl group can be derivatized into interesting functionalities.⁹

Existing enantioselective synthetic routes to aziridines include asymmetric aziridination of alkenes and ring-closure of vicinal hydroxy azides or amino alcohols.^{1,10} In an ongoing project, efficient syntheses of both vicinal amino alcohols and *N*-H vinylaziridines are of great importance, and ring-closure of amino alcohols became the most straightforward route to aziridines. There are several procedures for ring-closure of β -amino alcohols to *N*-substituted aziridines, and the plethora of methods encouraged us to perform a comparative study to find out which is the most effective in the formation of *N*-H vinylaziridines. These compounds are rather acid labile, which limits the number of applicable protocols and makes purification on silica gel cumbersome. We chose amino alcohol **1** as model substrate, and the desired transformation to aziridine **2** is shown in Scheme 1.

Scheme 1: Ring-closure of amino alcohol **1** to aziridine **2**.

The transformation can be conducted in three general ways: 1) direct ring-closure of amino alcohol **1** to yield aziridine **2** is the most effective strategy, but suffers from the low reactivity of **1**;¹⁰ 2) Activation of the hydroxy group of **1** into a better leaving group, which should facilitate ring-closure; 3) protection of the amino moiety of **1** should also increase the reactivity towards ring-closure, although a deprotection step is needed to yield **2**. The two latter methods need high-yielding reaction steps to compete with the direct ring-closure, as several steps are needed to achieve the desired transformation.

2. Results and Discussion

2.1. Direct ring-closure

Direct ring-closure of amino alcohols to provide aziridines is known to be difficult, and previous reports show moderate yields of the corresponding *N*-H aziridines.¹ Initial investigations of the ring-closure of **1** to aziridine **2** using Mitsunobu conditions^{11,12} were disappointing, but moderate yields could be obtained in toluene at reflux.¹³ A carbamate byproduct was irregularly formed in considerable amounts due to reaction between the amino alcohol and DEAD.¹² This could be prevented by changing the azo compound ethyl group to the bulkier isopropyl group in DIAD. The reaction rate could be increased by change of solvent to THF; this might reflect the observation of improved solubility of **1**. Unfortunately, purification of **2**

Keywords: amino alcohols; vinylaziridines; ring-closure.

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demanding repeated flash chromatography to remove the formed triphenylphosphine oxide, which decreased the yield considerably.¹⁴ In our experience *N*-H vinylaziridines are unstable on silica, and careful purification on deactivated silica improve the yields. Small-scale reactions were purified to give aziridine **2** in 80% yield, whereas large-scale reactions gave **2** in 70% yield.¹⁵ In an attempt to avoid the tedious purification, polymer bound triphenylphosphine was used. As expected, this decreased the reaction rate, but gave an easily purified crude product. Due to byproduct formation, the isolated yield of **2** was slightly lower.

2.2. Selective activation of the hydroxy group prior to ring-closure

Selective activation of the hydroxy group prior to ring-closure is difficult, as the amino group is more reactive towards activating agents such as tosyl chloride. One solution to this delicate problem is reaction of **1** with chlorosulfonic acid to form sulfate ester **3** (Scheme 2), which can be ring-closed to aziridine **2** under basic conditions.¹⁶ Formation of salt **3** was nearly quantitative, but ring-closure with excess NaOH at reflux furnished **2** in moderate yield (Table 1, entry 1). Various solvents and bases were screened, and the best result was achieved in toluene/water with NaOH as base, which gave aziridine **2** in 65% isolated yield (entry 2). Attempts with milder conditions, such as lower temperature, decreased amount of NaOH or solvent change, decreased the yield (entry 3). The use of *n*-BuLi in THF resulted in 50% yield (entry 4); all other attempts were fruitless (entries 5-7). Ring-closure of **1** with activation of the hydroxy group accordingly yielded **2** in 63% over two steps, using the conditions stated in entry 2.

Scheme 2: Hydroxy group activation prior to ring-closure.

Table 1: Conditions for ring-closure of **3** to **2**.

Entry	Solvent ^a	Base	Yield of 2 (%) ^b
1	Water	NaOH ^c	58
2	Toluene / Water	NaOH ^c	76
3	THF / Water ^d	NaOH ^c	0
4	THF ^e	<i>n</i> -BuLi ^f	50
5	THF	NaOEt ^f	<5
6	Toluene	KOtBu ^f	0
7	Toluene	Et ₃ N ^g	<5

^aReaction performed at reflux unless otherwise stated.

^bIsolated yield except in entry 1.

^cExcess.

^d100 °C in sealed flask.

^e-50 °C to rt.

^f2.5 eq.

^g3 eq.

2.3. Selective protection of the amino group prior to ring-closure

Selective protection of the amino group prior to ring-closure is the most common way to synthesize aziridines from amino alcohols. The lability of *N*-H vinylaziridines limits the number of useful activating groups, as the conditions needed for deprotection of several activating groups are expected to destroy the aziridine moiety.¹⁷ Our choice was the triphenylmethyl (trityl) group, as it has been successfully employed in aziridination reactions and mild conditions are used for deprotection. Activation by tritylation proceeded almost quantitatively,¹⁸ and with trityl amino alcohol **4** in hand, several ring-closing methods were performed (Scheme 3). The Mitsunobu protocol described above afforded tritylaziridine **5**, easily purified, in 99% yield.

Scheme 3: Amino group activation prior to ring-closure.

In a second approach, **4** was mesylated to provide compound **6**, which ring-closed to yield **5** at elevated temperature (Scheme 4).¹⁹ With 1.0 eq MsCl, tritylaziridine **5** was formed in 88% yield together with 12% recovered **4**. An excess of MsCl (1.25 eq) gave a decreased yield of **5** along with byproducts.

Scheme 4: Ring-closure by *in situ* mesylation.

Trityl amino alcohols have been reported to react with sulfonyl chloride to form cyclic sulfamidates, which are converted *in situ* to aziridines at rt.²⁰ When trityl amino alcohol **4** was treated with carefully distilled surfonylchloride, sulfamidate **7** was indeed formed but ring-closure to aziridine **5** did not take place at rt. Instead **7** was recovered crude in quantitative yield (Scheme 5). Attempted purification by flash chromatography converted **7** to the desired aziridine **5** in 60% yield. The conversion could instead be performed in excellent yield by heating the reaction mixture to 70 °C for 1 h.

Scheme 5: Ring-closure via cyclic sulfamidate 7.

Acidic detritylation of **5** to *N*-H aziridine **2** was the most difficult part of the sequence (Scheme 3). Treatment with TFA and water as a trityl scavenger furnished aziridine **2** in 79% yield.²¹ Formic acid in methanol worked equally well,²² whereas the combination of TFA and methanol gave only decomposition products.²³ The optimal reaction temperature was $-10\text{ }^{\circ}\text{C}$; reaction at rt gave **2** in moderate yield whereas lower temperature effected no reaction. Reductive detritylation using TFA / Et_3SiH proved inferior.²⁴ Thus, the three-step transformation of amino alcohol **1** into aziridine **2** was achieved in 77% via Mitsunobu cyclization, in 69% via mesylation and in 76% via cyclic sulfamidate.²⁵

3. Conclusion

Direct ring-closure under Mitsunobu conditions proved superior to other employed methods for small-scale reactions as *N*-H aziridine **2** was formed in 80% yield. This should be compared to 74% via sulfate ester **3** and 69–77% via tritylation of the amino group. For large-scale reactions, the convenience of easy purification could make the sulfate ester route preferable. Although the same advantage is achieved by the use of polymer-bound triphenylphosphine in the Mitsunobu reaction, this reagent does not give complete conversion for all substrates.²⁶

4. Experimental Section

4.1. General experimental conditions²⁷

Sulfonyl chloride was purified by distillation, collecting the fraction below $75\text{ }^{\circ}\text{C}$. This fraction was washed with crushed ice and dried over phosphorous pentoxide for 2 h. It was finally distilled at atmospheric pressure and the colorless fraction boiling at $69\text{ }^{\circ}\text{C}$ was collected. General workup: the reaction mixture was washed with water, the water phase was extracted three times with Et_2O . The organic phase was dried (Na_2SO_4) and concd *in vacuo*. Flash chromatography of vinylaziridines **2** and **5** was conducted with deactivated silica, using 10% triethylamine during packing of the column.

4.2. (2*R*,3*R*)-2-Phenethyl-3-vinyl-aziridine (**2**):¹³

4.2.1. Via Mitsunobu cyclization.

To a solution of PPh_3 (0.19 mg, 0.73 mmol) in THF (2 mL) at $0\text{ }^{\circ}\text{C}$ was added DIAD (0.14 mL, 0.73 mmol). After 20 min amino alcohol **1** (0.10 g, 0.52 mmol) in THF (1.5 mL) was added, and the resultant mixture was refluxed for 17 h. The solvent was evaporated at reduced pressure, Et_2O was added to the crude product, and the mixture was stored

overnight in the freezer. Precipitated Ph_3PO was removed by filtration and careful flash chromatography (pentane to pentane: EtOH 10:1, deactivated silica) afforded vinylaziridine **2** in 80% yield as a colorless oil.

4.2.2. By ring-closure of sulfate ester **3** with NaOH.

To sulfate ester **3** (66.0 mg, 0.243 mmol) was added water (0.3 mL), toluene (0.2 mL) and NaOH (0.9 g of 33%w/w solution) and the mixture was refluxed for 16 h, worked up and chromatographed (pentane: Et_2O 5:1 to Et_2O , deactivated silica) to give aziridine **2** (27.0 mg, 76%) as a colorless oil.

4.2.3. By ring-closure of salt **3** with BuLi.

To sulfate ester **3** (20.0 mg, 0.074 mmol) was added THF (0.6 mL), the mixture was cooled to $-50\text{ }^{\circ}\text{C}$ before addition of *n*-BuLi (1.6 M in hexanes, 46 μL , 0.074 mmol). The mixture was allowed to reach $0\text{ }^{\circ}\text{C}$ before addition of the remaining *n*-BuLi (1.6 M in hexanes, 69 μL , 0.110 mmol) and stirred at rt for 5 h. The solution was diluted with CH_2Cl_2 and washed twice with a 2M NaOH, the water phase was extracted three times with CH_2Cl_2 . The organic phase was dried, concd and chromatographed (pentane: Et_2O 5:1 to Et_2O , deactivated silica) to give aziridine **2** (6.3 mg, 50%) as a colorless oil.

4.2.4. By detritylation of tritylaziridine **5** with TFA.

Tritylaziridine **5** (85.0 mg, 0.205 mmol) was dissolved in CH_2Cl_2 (10 mL) and cooled to $-10\text{ }^{\circ}\text{C}$ before addition of water (100 μL). TFA (20 μL) was added and the solution was left to reach $0\text{ }^{\circ}\text{C}$ during 30 min followed by 30 min at $0\text{ }^{\circ}\text{C}$. The solution was stirred for 10 min with 2M NaOH (5 mL), worked up and chromatographed (pentane: Et_2O 3:2 to Et_2O , deactivated silica) to give aziridine **2** (27.8 mg, 79%) as a colorless oil.

4.2.5. By detritylation of tritylaziridine **5** with formic acid.

Tritylaziridine **5** (63.2 mg, 0.152 mmol) was dissolved in CHCl_3 (7 mL) and cooled to $-15\text{ }^{\circ}\text{C}$ before addition of methanol (100 μL). Formic acid (1 mL) in CHCl_3 (1 mL) was added and the solution was allowed to reach $-5\text{ }^{\circ}\text{C}$ during 2 h, then 2M NaOH (3 mL) was added and the resulting mixture was stirred for 10 min. The reaction was worked up and purified as above to give aziridine **2** (20.5 mg, 78%) as a colorless oil.

4.3. (3*S*,4*R*)-4-Amino-1-phenyl-hex-5-en-3-ol sulfate ester (**3**):

Amino alcohol **1** (49.8 mg, 0.260 mmol) was dissolved in Et_2O (1.5 mL) and cooled to $0\text{ }^{\circ}\text{C}$. Chlorosulfonic acid (21.2 μL , 0.319 mmol) was slowly added under vigorous stirring, and a yellow precipitate was formed. The solution was stirred for 4.5 h, concentrated *in vacuo* and the residue was washed twice with ether, twice with isopropanol and twice with Et_2O . After drying under vacuum, salt **3** was obtained as a yellow solid (66.0 mg, 97%). mp $>250\text{ }^{\circ}\text{C}$; ^1H NMR (400 MHz, d_6 DMSO): δ 8.04 (br s, 3H), 7.31–7.16 (m, 5H), 5.82 (m, 1H), 5.41 (m, 2H), 4.40 (ddd, 1H, $J = 6.5, 4.5, 2.1\text{ Hz}$), 3.93 (m, 1H), 2.74 (m, 1H), 2.62 (m, 1H),

1.78-1.62 (m, 2H); ^{13}C NMR (100 MHz, d_6 DMSO): δ 141.7, 130.5, 128.5, 128.4, 125.9, 121.7, 75.2, 56.1, 32.9, 31.0; $[\alpha]_D$: -29.1 (c 0.79, DMF); HRMS (FAB-) Exact mass calcd for $\text{C}_{12}\text{H}_{16}\text{NO}_4\text{S}$ (M-H): 270.0800. Found: 270.0794.

4.4. (3*S*,4*R*)-1-Phenyl-4-(trityl-amino)-hex-5-en-3-ol (4):

Amino alcohol **1** (50 mg, 0.26 mmol) and tritylchloride (80 mg, 0.26 mmol) were dissolved in CH_2Cl_2 (0.5 mL), and cooled to 0 °C before addition of Et_3N (73 μL , 0.52 mmol). The mixture was stirred at 0 °C for 15 min, worked up and chromatographed (pentane: EtOAc 20:1 to 5:1) to give tritylated amino alcohol **4** (112 mg, 99%) as a colorless oil. ^1H NMR (400 MHz, CDCl_3): δ 7.52 (m, 6H), 7.27-7.12 (m, 12H), 7.02 (m, 2H) 5.75 (m, 1H), 5.10 (m, 2H), 3.11 (dd, 1H, J = 7.6, 2.8 Hz), 2.53-2.41 (m, 2H), 2.35 (br s, 1H), 2.27 (ddd, 1H, J = 13.9, 10.1, 6.5 Hz), 1.92 (d, 1H, J = 5.7 Hz), 1.55-1.43 (m, 1H), 1.39-1.27 (m, 1H). ^{13}C NMR (100 MHz, CDCl_3): δ 146.7, 142.0, 136.2, 128.8, 128.3, 127.9, 127.8, 126.5, 125.7, 117.1, 72.5, 71.6, 59.7, 36.0, 32.4; IR (neat): 3452, 3059, 3027, 2929 cm^{-1} ; $[\alpha]_D$: -28.9 (c 0.18, CH_2Cl_2); HRMS (EI+) Exact mass calcd for $\text{C}_{31}\text{H}_{31}\text{NO}$ (M): 433.2406. Found: 433.2391.

4.5. (2*R*,3*R*)-2-Phenethyl-1-trityl-3-vinyl-aziridine (5):

4.5.1. Via Mitsunobu cyclization.

Triphenylphosphine (42.2 mg, 0.161 mmol) was dissolved in THF (1 mL) and cooled to 0 °C. DIAD (31.7 μL , 0.161 mmol) was added and the solution stirred for 15 minutes. Trityl amino alcohol **4** (50.0 mg, 0.115 mmol) was added in THF (1 mL), the mixture was heated at reflux for 16 h and concd in vacuo. Flash chromatography (pentane: EtOAc 50:1 to 8:1, deactivated silica) gave aziridine **5** (42.7 mg, 99%) as a colorless oil. ^1H NMR (400 MHz, CDCl_3): δ 7.44 (d, 6H, J = 7.1 Hz), 7.25-7.12 (m, 12H), 7.02 (d, 2H, J = 7.1 Hz), 5.08 (m, 1H), 4.70 (m, 1H), 4.50-4.37 (m, 1H), 2.70-2.53 (m, 3H), 2.06-1.93 (m, 2H), 1.77-1.65 (m, 1H); ^{13}C NMR (100 MHz, CDCl_3): δ 146.3, 141.9, 136.1, 130.0, 128.4, 128.3, 127.3, 126.6, 125.7, 117.1, 72.7, 46.2, 40.9, 34.3, 33.7; IR (neat): 3059, 3027, 2928, 2856 cm^{-1} ; $[\alpha]_D$: +90.1 (c 0.96, CH_2Cl_2); HRMS (CI+) Exact mass calcd for $\text{C}_{31}\text{H}_{30}\text{N}$ (M+H): 416.2378. Found: 416.2378.

4.5.2. Via mesylate 6.

Trityl amino alcohol **4** (50.1 mg, 0.115 mmol) was dissolved in THF (1 mL). Et_3N (48 μL , 0.346 mmol) and mesyl chloride (9.0 μL , 0.117 mmol) were added and the solution was stirred at rt for 1 h, followed by heating at reflux for 36 h. The mixture was diluted with CH_2Cl_2 and washed twice with sat. aq NaHCO_3 solution, dried, concd and chromatographed (pentane: EtOAc 50:1 to 20:1, deactivated silica) to give aziridine **5** (42.7 mg, 88%) as a colorless oil. Starting material **4** was recovered in 12 % yield.

4.5.3. Via cyclic sulfamidate 7.

Trityl amino alcohol **4** (137.6 mg, 0.318 mmol) was dissolved in toluene (6 mL). Et_3N (133 μL , 0.954 mmol) was added and the mixture cooled to -50 °C. Freshly

distilled sulfonylchloride (32 μL , 0.398 mmol) was slowly added as a solution in toluene (1.5 mL) after which the solution became white. After 1 h stirring the temperature was raised to rt, the flask was sealed and the solution was heated to 70 °C for 1 h, at which time the color had become yellow. Workup and purification as described above gave aziridine **5** (127.4 mg, 97%) as a colorless oil.

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25. In a similar reaction sequence, the trityl group was replaced by the 2,4-dinitrobenzenesulfonyl group (Ns'), which proved unsuccessful.^{28,29} Although both the protection and the ring-closure were fast reactions, the yields were poorer than in the tritylation sequence. Furthermore, deprotection of the Ns'-aziridine to **2** was unsuccessful, instead affording the corresponding ring-opened diamine.
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