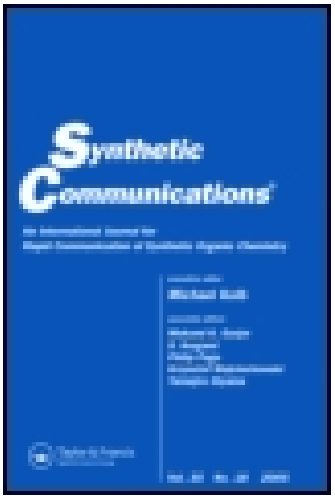

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IMINE DERIVATIVES OF FUMARALDEHYDE FROM OXIDATION OF A β-AZIRIDINYL ALCOHOL

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Abstract: Oxidation of a β-aziridinyl alcohol with tetrapropylammonium perruthenate yields a pyrrole and two unusual imine derivatives of fumaraldehyde.

In recent years, the use of aziridines in organic synthesis has become prevalent.[1] There are numerous examples of processes which involve ring-opening of aziridines, utilizing the inherent reactivity of the strained ring system, to synthesize complex natural products. There are also many reports of the use of aziridines as chiral auxiliaries or as chiral ligands for metal catalysts. For these systems, it is important that the aziridine ring be inert under the conditions of the reactions carried out. In both cases, it is important to define situations under which aziridines will and will not undergo ring-opening. In an attempt to oxidize β-aziridinyl alcohol **1** to the corresponding aldehyde, **2** (Figure 1), we have discovered an unexpected rearrangement that furthers our understanding of the stability of the aziridine ring system. The reaction also serves to illustrate the synthetic potential of the aziridine ring.

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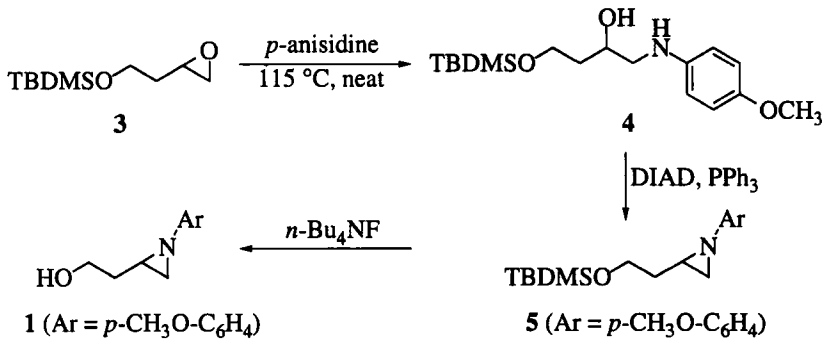
FIG. 1

Compound **1** was synthesized as shown in Figure 2. Silyl protected 3,4-epoxybutanol, **3**, made in two steps from commercially available 3-buten-1-ol,[2,3] was heated with two equivalents of *p*-anisidine at 115 °C.[4] Excess *p*-anisidine was removed by sublimation and the resulting aminoalcohol, **4**, was treated without further purification with triphenylphosphine and diisopropyl azodicarboxylate (DIAD) to form aziridine **5**.[5] The combined yield for these two steps was 51%. The silyl protecting group was then removed with tetrabutylammonium fluoride to afford alcohol **1** in 83% yield.

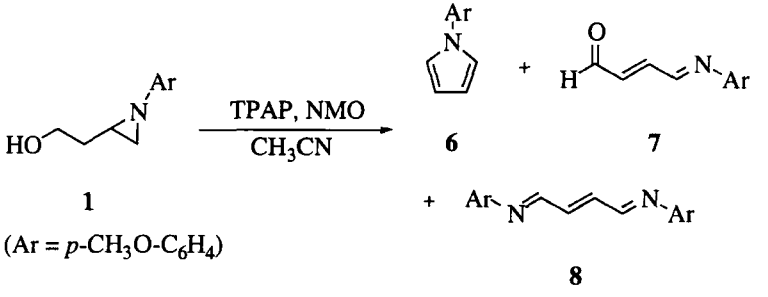
FIG. 2



We explored several methods for carrying out the transformation of **1** to **2**. Initial attempts using standard, mild methods, such as PDC and Swern oxidation, resulted in intractable product mixtures. We also attempted the reaction with tetrapropylammonium perruthenate (TPAP), a mild oxidant which reacts under non-acidic conditions.[6] Aldehyde **2**, was not isolated from oxidations conducted with

TPAP. Instead, three unexpected products were obtained (Figure 3). One product was identified as the known compound, 1-(*p*-methoxyphenyl)pyrrole, **6**.[7] The other two products have been assigned the structures **7** and **8** on the basis of their NMR spectra. The NMR spectra of imine **7** compare favorably to those of the only three closely related compounds which have been previously reported.[8-10] Only one published example of a compound similar to diimine **8** was found.[11-12]

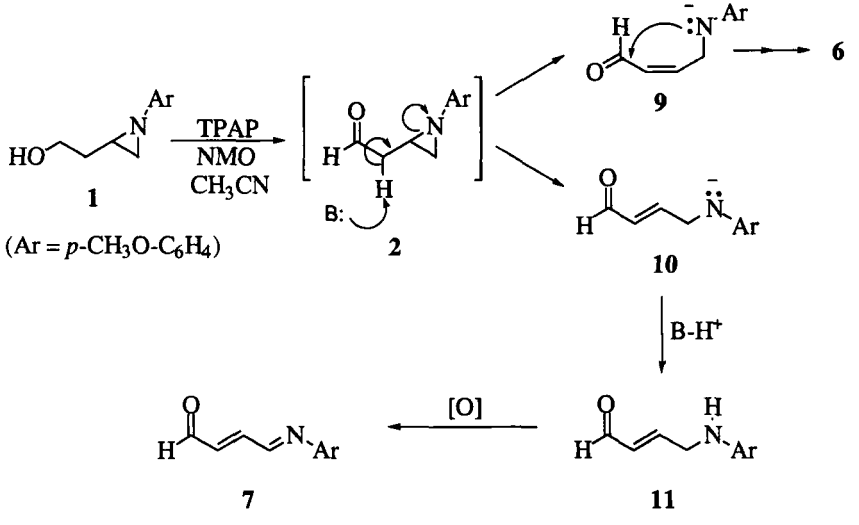
FIG. 3



We propose the following mechanism to account for the formation of products **6** and **7** (Figure 4). Initially, the alcohol is oxidized to aldehyde **2**, as expected. This aldehyde is rapidly deprotonated, resulting in opening of the aziridine ring to form a mixture of *cis*- and *trans*-alkenes, **9** and **10**. The *cis*-alkene undergoes cyclization to eventually form the pyrrole, **6**. The *trans*-alkene cannot cyclize so it is protonated to give the conjugated γ-aminoaldehyde, **11**. Finally, compound **11** is further oxidized by TPAP to imine **7**. It has been previously demonstrated that TPAP can oxidize secondary amines to the corresponding imines.[13]

The origin of the diimine, **8**, was more difficult to deduce. The TPAP oxidation of alcohol **1** was run several times under similar reaction conditions. In the initial trials, the relative amounts of the imine and the diimine obtained were variable. Further investigation revealed two factors that affect the ratio of imine to diimine.

FIG. 4



When the reaction was run with scrupulous exclusion of water, the solvent removed and the product mixture examined directly by NMR without exposure to alumina, none of the diimine product was present. Carrying out a similar procedure with reactions run in the presence of trace amounts of water showed small amounts of diimine in the product mixture. Finally, when a mixture of imine and diimine consisting of predominantly the imine was allowed to sit on alumina for several hours, the mixture that was subsequently eluted contained primarily the diimine.

We conclude that the diimine is produced slowly by reaction of the imine in the presence of water. Exposure of the imine to alumina serves to accelerate this process. Variability in the ratio of imine to diimine in our initial experiments was due to exposure of the reaction mixtures to alumina for varying amounts of time. The mechanism for the conversion of the imine to the diimine may involve simple hydrolysis of the imine, releasing *p*-anisidine which can then react with the free aldehyde functional group of another molecule of the imine to produce the diimine.

Alternately, direct transfer of a *p*-anisidine group from one imine molecule to another may occur without release of free *p*-anisidine.

We presumed that the base which was abstracting a proton from aldehyde **2** in our reaction mixtures was *N*-methylmorpholine, a byproduct of the reaction. NMO is included in the reaction mixture as a co-oxidant, allowing reactions to be run with catalytic amounts of TPAP. We hoped that carrying out the reactions with an alternate co-oxidant would allow us to isolate aldehyde **2**. Ley has recently reported that molecular oxygen may be used as a co-oxidant for TPAP.[14] We found that alcohol **1** is oxidized by TPAP/O_2, although the reaction is much slower than when NMO is used as the co-oxidant. However, even under these extremely mild conditions, the aldehyde undergoes further reaction and the only products isolated are pyrrole **6**, imine **7** and diimine **8**.

The reaction that we have described allows access to imine and diimine derivatives of fumaraldehyde, a pair of structural motifs whose synthesis has not been the subject of significant investigation. Furthermore, this work underscores the extremely sensitive nature of aziridine rings that are located β to a carbonyl group. In these experiments (and others we have previously carried out in attempts to form related β-aziridinyl esters), compounds of this type have been extremely susceptible to eliminative ring opening with concomitant formation of a conjugated alkene even under very mild conditions.

EXPERIMENTAL

General: All reagents were purchased from either Acros or Aldrich Chemical Company and used without further purification, except where noted. Reactions were carried out under argon using standard glassware and apparatus. Prior to use, tetrahydrofuran was freshly distilled off of sodium benzophenone.

Dichloromethane and acetonitrile were distilled off of CaH_2 and stored over 4Å molecular sieves. Column chromatography was conducted using either ICN silica gel 32-63, 60 Å or Fisher adsorption alumina (80-200 mesh). NMR spectra were run at 300 MHz and 75 MHz for ^1H and ^{13}C, respectively. Elemental analyses were conducted by Atlantic Microlabs, Norcross, GA. High resolution mass spectra were obtained in the Mass Spectrometry Laboratory, School of Chemical Sciences, University of Illinois.

1-(4-methoxy)phenylamino-4-*tert*-butyldimethylsilyloxy-2-butanol (4). Epoxide **3**[2,3] (1.20 g, 5.94 mmol) and *p*-anisidine (1.46 g, 11.9 mmol) were combined and heated at 115 °C for 7 h. Excess *p*-anisidine was removed by sublimation using a Kügelrohr apparatus (1 mm Hg, 60°C) affording 1.78 g (92%) of the amino alcohol as a dark brown oil, which was used without further purification. ^1H NMR ($CDCl_3$) δ 0.07 (6H, s), 0.89 (9H, s), 1.72 (2H, m), 3.02 (1H, dd, J = 7.7, 12.3 Hz), 3.16 (1H, dd, J = 3.9, 12.3 Hz), 3.55 (2H, br), 3.73 (3H, s), 3.88 (2H, m), 4.07 (1H, m), 6.61 (2H, m), 6.76 (2H, m); ^{13}C NMR ($CDCl_3$) δ –5.6, 18.1, 25.8, 36.4, 51.1, 55.7, 62.2, 70.2, 114.5, 114.7, 114.8, 116.4, 142.6, 152.2; exact mass *m/z* calcd for $C_{17}H_{31}NO_3Si$ 325.2073, found 325.2068.

1-(4-methoxy)phenyl-2-(2-*tert*-butyldimethylsilyloxy)ethyl-aziridine (5). Amino alcohol **4**, dissolved in 21 mL of THF, was added to a cooled (0 °C) solution of triphenylphosphine (3.5 g, 13 mmol) in 21 mL of THF. Diisopropyl azodicarboxylate (2.6 mL, 2.7 g, 13.4 mmol) was then added dropwise, the solution was allowed to warm to room temperature and then stirred for 3.5 h. The protected aziridine, **5**, was isolated by column chromatography (alumina, 7.5% EtOAc/hexanes) to yield 1.5 g (55%) of light yellow oil. IR 1600, 2900, 3050 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.07 (3H, s),0.08 (3H, s), 0.91 (9H, s), 1.64 (1H, m), 1.83 (1H, m), 1.99 (1H, m), 2.05 (1H, m), 2.22 (1H, m), 3.74

(3H, s), 3.86 (2H, m), 6.77 (2H, m), 6.94 (2H, m); ^{13}C NMR ($CDCl_3$) δ -5.4, 18.2, 25.9, 34.3, 36.3, 37.4, 55.4, 61.2, 114.1, 121.5, 148.5, 154.9. Anal. Calcd for $C_{17}H_{29}NO_2Si$: C, 66.40; H, 9.51; N, 4.55. Found: C, 66.59; H, 9.51, N, 4.56.

1-(4-methoxy)phenyl-2-aziridineethanol (1). To a cooled (0 °C) solution of the protected aziridine, **5**, (0.25 g, 0.81 mmol) in 2.2 mL of THF, tetra-*n*-butylammonium fluoride (1.2 mL of 1.0 M solution in THF, 1.2 mmol) was added dropwise. The solution was stirred for 2 h and then added to a mixture of EtOAc (20 mL) , H_2O (7 mL), and saturated NH_4Cl (3 mL). The layers were separated and the aqueous layer was extracted with an additional 10 mL of EtOAc. The combined organic layers were washed with saturated NaCl, dried over $MgSO_4$ and purified by column chromatography (alumina, 25% then 75% EtOAc/hexanes) to obtain 0.13 g (83% yield) of clear colorless oil. IR 3350, 2950, 1600 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.64 (1H, m), 2.00 (1H, m), 2.06 (1H, m), 2.18 (1H, m), 2.21 (1H, m), 3.55 (1H, br), 3.72 (3H, s), 3.80 (2H, t), 6.73 (2H, m), 6.92 (2H, m); ^{13}C NMR ($CDCl_3$) δ 32.9, 33.8, 38.0, 55.4, 60.4, 114.2, 121.5, 147.5, 155.2; exact mass *m/z* calcd for $C_{11}H_{15}NO_2$ 193.1103, found 193.1101.

Procedure for Oxidation of 1 with TPAP. Vacuum dried *N*-Methylmorpholine-*N*-oxide (0.63 g, 5.38 mmol) and activated, powdered 3 Å molecular sieves (0.36 g) were dissolved in 25 mL of dry acetonitrile. Aziridine **1** (0.35 g, 1.81 mmol) was dissolved in 8 mL of dry acetonitrile and added to the solution of sieves and *N*-Methylmorpholine-*N*-oxide. TPAP (64 mg, 0.181 mmol) was added and the mixture was stirred at room temperature until TLC showed complete consumption of starting material (1.5 h). ^{1}H NMR of the crude reaction mixture showed three main components. One was a product which has proven unisolable and has therefore not been identified. The other two products were pyrrole **6** and imine **7** in a ratio of 20:80. There was no detectable diimine, **8**, in

this crude product mixture. The crude product mixture was then flushed through a plug of alumina to remove excess TPAP and NMO. ^{1}H NMR of this mixture indicated the presence of pyrrole **6**, imine **7** and diimine **8** in a ratio of 19% to 66% to 15%. The peaks due to the unidentified compound in the NMR of the crude reaction mixture were no longer present. The combined yield of the three products was 68% after they had been flushed through alumina. A more careful column was run (alumina, 5% to 50% EtOAc in hexane) to isolate the three products (pyrrole **6**, imine **7** and diimine **8**).

Imine 7. ^{1}H ($CDCl_3$) δ 3.82 (s, 3H), 6.57 (dd, 1H, J = 7.8, 15.9 Hz), 6.92 (m, 2H), 7.28 (m, 2H), 7.32 (dd, 1H, J = 9.0, 15.9 Hz), 8.39 (d, 1H, J = 9.0 Hz), 9.77 (d, 1H, J = 7.8 Hz); ^{13}C δ 55.5, 114.6, 123.0, 138.3, 143.1, 149.3, 155.4, 160.0, 193.2; exact mass *m/z* calcd for $C_{11}H_{11}NO_2$ 189.0790, found 189.0790.

Dimine 8. ^{1}H ($CDCl_3$) δ 3.82 (s, 6H), 6.91 (m, 4H), 7.00 (dd, 2H, J = 2.8, 5.7 Hz), 7.23 (m, 4H), 8.31 (dd, 2H, J = 2.8, 5.7 Hz); ^{13}C δ 55.5, 114.5, 122.6, 141.0, 143.9, 157.6, 159.1; exact mass *m/z* calcd for $C_{18}H_{18}N_2O_2$ 294.1368, found 294.1363.

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REFERENCES

1. For a recent review: Tanner, D. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 599.
2. Pirrung, M. D. and Webster, N. *J. Org. Chem.* **1987**, *52*, 3603.

3. Mori, K. and Ikunaka, M. *Tetrahedron* **1984**, *40*, 3471.

4. Chamchaang, W. and Pinhas, A. *J. Org. Chem.* **1989**, *55*, 2943.

5. Pfister, J. R. *Synthesis* **1984**, 969.

6. Griffith, W. P. and Ley, S. V. *Aldrichimica Acta* **1990**, *23*, 13.

7. Faigl, F., Fogassy, K., Thurner, A. and Toke, L. *Tetrahedron* **1997**, *53*, 4883.

8. Tsuchiya, T., Arai, H., Hasegawa, H. and Igeta, H. *Tetrahedron Lett.* **1974**, 4103.

9. Severin, T., Lerche, H. and Zimmermann, B. *Chem. Ber.* **1985**, *118*, 4760.

10. Zimmermann, B., Lerche, H. and Severin, T. *Chem. Ber.* **1986**, *119*, 2848.

11. Kovtun, Y. P. and Romanov, N. N. *Khim. Geterotsikl. Soedin.* **1989**, 553. (*CA* **111**: 232647)

12. Kawashima, Y. and Kagawa, N. Japanese Patent 04 09,045, 1992. (*CA* **116**: 245197)

13. Goti, A. and Romani, M. *Tetrahedron Lett.* **1994**, *35*, 6567.

14. Lenz, R. and Ley, S. V. *J. Chem. Soc., Perkin Trans. 1* **1997**, 3291.

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