Synthetic Interconversions in Three-Membered Ring Heterocycles. An Alternate Synthesis of 2-Arylaziridinium Salts

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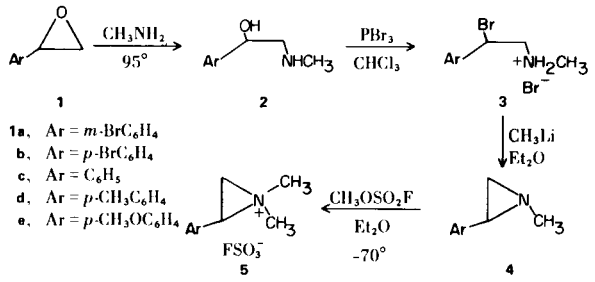
Received April 15, 1974 — Revised August 11, 1975

Various types of syntheses of aziridinium salts have been reported, including diazomethane insertion into iminium bonds (1) or NH^+ bonds (2), cyclization of β-haloethylamines with silver salts (3), and alkylation of aziridines with "alkyl perchlorates" (3,4), methyl tosylate (2), or, for sterically favorable cases, with alkyl iodides (5). Because of the renewed interest in this class of compounds, it seemed desirable to have available other methods which might be more suitable for a given compound. We now report a reaction sequence for the preparation of 2-arylaziridinium salts which, in our hands, was more reliable than that *via* diazomethane insertion (6,7) which can give piperazinium salt dimers (8).

Alkylation of 2-arylaziridines with methyl fluorosulfonate ("Magic Methyl") in ether has been found to proceed instantly at -70° to give, in most cases, analytically pure aziridinium salt products in very good yields. The success of the method is due to the fact that while reactants are soluble in ether at -70°, the aziridinium salt is very insoluble, resulting in complete separation of products from reactants. This method is advantagous for two additional reasons: 1) since these reactive salts can be produced at low temperatures and in the solid state, they are less likely to decompose, and 2) by adding the aziridine to a large excess of Magic Methyl, the tendency toward dimerization is suppressed.

Arylaziridine precursors, not available by the iodoalkyl azide route (9), were made from the bromoethylamine hydrobromides (10) by ring closure with two equivalents of methyllithium in ether, analogous to the formation of alkylaziridines from aminoalkyl iodides in the presence of butyllithium as reported by Levy and Brown (9). Use of this strong but relatively nonnucleophilic base with a bromide leaving group proved to be a more satisfactory way to obtain 2-arylaziridines than the classical Wenkert synthesis (11) which gave lower yields and was somewhat irreproducible. The synthetic steps are outlined in Scheme I. Epoxides not commercially available were readily obtained in 70-95% yields by treatment of the benzaldehyde with dimethylsulfonium methylide (12), or alternatively, by hydride reduction of phenacyl bromides in basic media (13).

SCHEME I



Aziridinium salts were characterized by their m.p., ir, nmr, elemental analysis, and chemical reactivity such as electrochemical reduction and solvolysis. The ir spectra showed an absence of +NH, iminium, and C=O bands consistent with the postulated structure, thus ruling out products formed by decomposition of the aziridinium salts. The possible formation of piperazinium salts was ruled out by lack of absorption in the δ 4-6 region in the nmr spectrum of the products (8). Chemical shifts were in good agreement with those reported by Keenan and Leonard (6) for fluoborate salts of **5b**, **c**, and **d**. In addition to characteristic aryl resonances, benzylic protons appeared as a triplet from δ 4.4-4.9 (the X portion of an AA′X system, with an apparent J = 8 Hz). Methylene protons (the AA′ portion of an AA′X system) appeared as doublet from δ 3.3-3.8 (J = 8 Hz). Methyl groups exhibited nonequivalent resonances differing by approximately 0.7 ppm (δ 3.2-3.5 and δ 2.5-2.7) due to the anisotropy of the aromatic ring. The resonance at higher field was assigned to the methyl *cis* to the aryl group (6,14).

The present synthetic sequence, starting from readily available benzaldehydes, provides a series of strained heterocycles with varying electronegativity of the "heteroatom". Such a series should prove useful for various physicochemical studies. The alkylation procedure, combined with newer methods of obtaining alkylaziridines (9,15), should provide a general synthesis of all *N*-methylaziridinium salts.

EXPERIMENTAL (16)

General Method of Preparing Aryl Epoxides. Synthesis of **1a**, **d**, **e**.

Following the Corey procedure (12), dimethylsulfonium methylide was prepared by adding 51.0 g. (0.25 mole) of trimethylsulfonium iodide in 200 ml. of dry dimethyl sulfoxide to a cooled solution containing an equimolar amount of sodium methylsulfinyl carbanion in 200 ml. of 1:1 dimethyl sulfoxide-tetrahydrofuran. The benzaldehyde (0.20 mole) was added at a moderately rapid rate and the reaction mixture stirred for 60 minutes. The product was extracted with ether, washed with water, and dried over sodium sulfate giving **1d** in 95% yield as a colorless liquid (13), ir (film): ν max 3030, 3000-2860, 1515, 880, 815 cm^{-1}; nmr (dichloromethane): δ 2.35 (s, 3H, CH_3), 2.74 (H_A of ABX pattern), 3.09 (H_B, J_{AB} = 5.5), 3.77 (H_X, J_{AX} = 2.6, J_{BX} = 4.3), 7.36 (s, 4H, ArH).

For **1a**, distillation gave the product in 68% yield, b.p. 78° (0.022 Torr) [lit. (13), b.p. 100° (1.5 Torr)]; ir (film): ν max 3050, 3000-2900, 1600, 1510, 1480, 870, 780, 683 cm^{-1}; nmr (carbon tetrachloride): δ 2.66 (H_A of ABX pattern), 3.08 (H_B, J_{AB} = 6.0), 3.78 (H_X, J_{AX} = 2.5, J_{BX} = 4.3), 7.45 (m, 4H, ArH).

Distillation of the product gave **1e** in 73% yield, b.p. 76° (0.037 Torr) [Lit. (17), m.p. 20°]; ir (film): ν max 3030, 3000-2900, 2820, 1600, 1500, 1240, 823, 800 cm^{-1}; nmr (dichloromethane): δ 2.75 (H_A of ABX pattern), 3.05 (H_B, J_{AB} = 5.5), 3.81 (H_X, J_{AX} = 2.5, J_{BX} = 3.9), 3.83 (s, 3H, OCH_3), 7.28 (d of d, 4H, J_{AB} = 9.0 ArH).

p-Bromoepoxyethylbenzene (**1b**).

Sodium borohydride reduction (13) of 2,4′-dibromoacetophenone followed by cyclization of the bromohydrin with sodium hydroxide gave a 95% yield of **1b** as an orange oil [lit. (18), b.p. 79-80° (1 Torr)]; ir (film): ν max 3050, 3000-2900, 1597, 1490, 1070, 1008, 980, 875, 825, 758 cm^{-1}; nmr (dichloromethane): δ 2.71 (H_A of ABX pattern), 3.09 (H_B, J_{AB} = 5.5), 3.79 (H_X, J_{AX} = 2.5, J_{BX} = 4.1), 7.54 (d of d, 4H, J_{AB} = 9.0, ArH).

General Method of Preparing Arizidines.

Epoxides (0.14 mole) were reacted with 21.2 g. (0.27 mole) of a 40% aqueous methylamine solution for 5 hours at 110° in a stainless steel bomb (Parr, Series 4000 Pressure Reaction apparatus) (11b). Evaporation of water and excess methylamine, followed by distillation gave the amino alcohols as viscous liquids which crystallized on standing. Since **2** decomposed on attempted distillation, it was purified directly by recrystallization from hexane.

Following the method of Chapman and Triggle (10), the bromoamine hydrobromides were prepared by reacting 0.05 mole of amino alcohol with 0.065 mole of phosphorous tribromide. Precipitation of the product with ether and recrystallization from 2-propanol gave the bromoamine hydrobromides.

Cyclization to the aziridine was carried out in a flame-dried, round-bottomed flask fitted with a pressure-compensated dropping funnel, magnetic stirrer, and reflux condenser. Under a positive pressure of nitrogen, the flame-dried flask was charged with 0.02 mole of amine hydrobromide in 25 ml. of dry ether and the dropping funnel with 17.7 ml. (0.035 mole) of a 2.0*M* solution of methyllithium in ether (used as supplied by Alpha Inorganics). The methyllithium was added dropwise over a period of 30 minutes at 0°, after which the reaction mixture was heated under gentle ether reflux for 1.5 hours. Enough water was carefully added to decompose excess methyllithium, the reaction mixture filtered, and the ether layer dried over sodium sulfate. Evaporation of solvent and distillation of the residue gave the aziridine.

Aziridine **4a** was prepared in 74% yield from the bromoamine hydrobromide as a colorless liquid, b.p. 67° (0.08 Torr); ir (film): ν max 3040, 3000-2900, 2850, 2780, 1600, 1565, 1475, 1060 cm^{-1}; nmr (carbon tetrachloride): δ 1.55 (H_A of ABX pattern), 1.75 (H_B, J_{AB} = 1.0), 2.21 (H_X, J_{AX} = 6.5, J_{BX} = 3.5), 2.50 (s, 3H, NCH_3), 7.54 (m, 4H, ArH).

Anal. Calcd. for $C_9H_{10}BrN$: C, 50.97; H, 4.75; N, 6.60. Found: C, 51.07; H, 4.82; N, 6.74.

Aziridine **4b** was prepared in 76% yield from the bromoamine hydrobromide as a viscous oil, b.p. 70° (0.20 Torr), which crystallized on cooling, m.p. 35-36°; ir (film): ν max 3040, 3000-2900, 2850, 2780, 1590, 1485 cm^{-1}; nmr (carbon tetrachloride): δ 1.60 (H_A of ABX pattern), 1.79 (H_B, J_{AB} = 1.0), 2.28 (H_X, J_{AX} = 7.0, J_{BX} = 3.5), 2.60 (s, 3H, NCH_3), 7.81 (d of d, 4H, J_{AB} = 9.0, ArH).

Anal. Calcd. for $C_9H_{10}BrN$: C, 50.97; H, 4.75; N, 6.60. Found: C, 51.12; H, 4.72; N, 6.67.

Aziridine **4c** was prepared in 52% yield from the bromoamine hydrobromide as a colorless liquid, b.p. 34-40° (1.0 Torr) [lit. (19), b.p. 39-40° (0.5 Torr)]; ir (film): ν max 3050, 3000-2780, 1605, 1490, 1450, 1385, 1210 cm^{-1}; nmr (carbon tetrachloride): δ 1.53 (H_A of ABX pattern), 1.7 (H_B, J_{AB} = 1.5), 2.22 (H_X, J_{AX} = 7.0, J_{BX} = 3.5), 2.51 (s, 3H, NCH_3), 7.42 (s, 5H, ArH).

Aziridine **4d** was prepared in 58% yield from the bromoamine hydrobromide with b.p. 51° (0.22 Torr); ir (film): ν max 3050-3020, 3000-2900, 2840, 2780, 1515, 1450 cm^{-1}; nmr (carbon tetrachloride): δ 1.47 (H_A of ABX pattern), 1.73 (H_B, J_{AB} = 1.5), 2.22 (H_X, J_{AX} = 5.5, J_{BX} = 3.5), 2.39 (s, 3H, CH_3), 2.52 (s, 3H, NCH_3), 7.37 (s, 4H, ArH).

Anal. Calcd. for $C_{10}H_{13}N$: C, 81.59; H, 8.90; N, 9.51. Found: C, 81.48; H, 9.00; N, 9.63.

Aziridine **4e** was prepared as a slightly impure liquid, b.p. 58-60° (0.16 Torr); ir (film): ν max 3040, 3000-2900, 2830, 2730, 1610, 1510, 1250, 1030, with impurity at 3700-3200 (w, br), 1690, 1650; nmr (carbon tetrachloride): δ 1.49 (H_A of ABX pattern), 1.75 (H_B, J_{AB} = 1.5), 2.22 (H_X, J_{AX} = 6.5, J_{BX} = 3.5), 2.53 (s, 3H, NCH_3), 3.93 (s, 3H, OCH_3), 7.39 (d of d, 4H, J_{AB} = 9.0, ArH), with impurities at 3.52, 3.99 and 4.03.

General Method for Preparing Aziridinium Fluorosulfonates.

In a drybox with nitrogen atmosphere a round-bottomed flask was charged with 0.114 mole of methyl fluorosulfonate ("Magic Methyl", Aldrich Chemical Co.) in 10 ml. of dry ether. It was then fitted with a pressure-compensated dropping funnel and cooled in powdered Dry Ice. A solution of 5.7 mmoles of the aziridine in 10 ml. of dry ether, previously cooled in Dry Ice, was then added dropwise with swirling. During the addition the product separated from solution. When addition was complete, an additional 20 ml. of ether was added and the product collected and washed several times with dry ether.

Aziridinium salt **5a**, the only one to separate as an oil, crystallized on trituration with dry ether giving an 82% yield from the aziridine, m.p. 55-57°; ir (Nujol): ν max 3050, 3000-2900, 1575, 1460, 1300-1260, 1070 cm^{-1}; nmr (dichloromethane): δ 2.50 (s, 3H, *cis*- $+NCH_3$), 3.32 (s, 3H, *trans*- $+NCH_3$), 3.55 (d, 2H, J = 8.0 Hz, $+NCH_2$), 4.56 (t, 1H, J = 8.0 Hz, +NCH), 7.50 (m, 4H, ArH).

Anal. Calcd. for $C_{10}H_{13}BrFNO_3S$: C, 36.83; H, 4.02; N, 4.30. Found: C, 36.67; H, 4.07; N, 4.22.

Aziridinium salt **5b** was prepared in 88% yield, m.p. 84-86°; ir (Nujol): ν max 3120, 3050, 3000-2900, 1600, 1490, 1300, 1090 cm^{-1}; nmr (TFA, external TMS): δ 2.33 (s, 3H, *cis*- $+NCH_3$),

2.99 (s, 3H, *trans*- +NCH_3), 3.18 (d, 2H, J = 8.0 Hz, +NCH_2), 4.15 (t, 1H, J = 8.0 Hz, +NCH), 7.27 (d of d, 4H, J = 9.0 Hz, ArH).

Anal. Calcd. for $C_{10}H_{13}BrFNO_3S$: C, 36.83; H, 4.02; N, 4.30. Found: C, 36.73; H, 4.18; N, 4.20.

Aziridinium salt **5c** was prepared in 89% yield, m.p. 69-70°; ir (Nujol): ν max 3110, 3050, 3000-2900, 2850, 1585, 1460, 1220-1110, 1060 cm^{-1}; nmr (dichloromethane): δ 2.57 (s, 3H, *cis*- +NCH_3), 3.29 (s, 3H, *trans*- +NCH_3), 3.52 (d, 2H, J = 8.0 Hz, +NCH_2), 4.54 (t, 1H, J = 8.0 Hz, +NCH), 7.45 (s, 5H, ArH).

Anal. Calcd. for $C_{10}H_{14}FNO_3S$: C, 48.57; H, 5.70; N, 5.66. Found: C, 47.17; H, 5.76; N, 5.51.

Aziridinium salt **5d** was prepared in 91% yield, m.p. 58-60°; nmr (dichloromethane): δ 2.27 (s, 3H, CH_3), 2.47 (s, 3H, *cis*- +NCH_3), 3.48 (d, 2H, J = 8.0 Hz, +NCH_2), 4.44 (t, 1H, J = 8.0 Hz, +NCH), 7.26 (d of d, 4H, J = 9.0 Hz, ArH).

Anal. Calcd. for $C_{11}H_{16}NSO_3F$: C, 50.56; H, 6.17; N, 5.36. Found: C, 50.65; H, 6.25; N, 5.23.

Attempted Isolation of *N,N*-Dimethyl-2-(*p*-methoxyphenyl)aziridinium Fluorosulfonate (**5e**).

Following the general procedure described above, 60 mg. (0.36 mmole) of aziridine **4e** was treated with 64 mg. (0.56 mmole) of methyl fluorosulfonate. The product, a white crystalline solid, separated at -70°. On warming above -50°, however, the product oiled out and decomposed to the piperizinium salt (m.p. >250°). An nmr in methylene chloride at -70° gave the following somewhat broad signals: δ 2.42 (s, 3H, *cis*- +NCH_3), 3.13 (s, 3H, *trans*- +NCH_3), 3.71 (br.d, 2H, +NCH_2), 4.12 (s, 3H, OCH_3), 5.27 (1H, +NCH, under dichloromethane), 6.79-7.50 (br m, 4H, ArH).

Acknowledgment.

Partial support of this work by Research Corporation is gratefully acknowledged. The authors also thank Prof. C. F. Hammer for helpful discussions on spectroscopy and Guy J. Jordan for assistance in experimental aspects of this work.

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