BULLETIN OF THE CHEMICAL SOCIETY OF JAPAN VOL. 41 1440—1444 (1968)

Azirines. III. The Preparation of Azirine Derivatives by the Base-Catalyzed Rearrangement of Quaternary Hydrazones[1]

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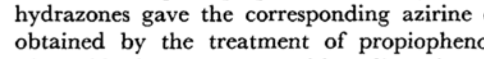
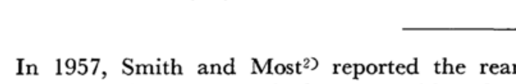
(Received December 27, 1967)

An attempt to prepare azirines by the base-catalyzed rearrangement of some quaternary hydrazones gave the corresponding azirine derivatives. Namely, 2-phenyl-3-methylazirine was obtained by the treatment of propiophenone dimethylhydrazone methiodide with potassium *t*-butoxide, but treatment with sodium isopropoxide gave 2,5-diphenyl-3,6-dimethylpyrazine or 2-phenyl-2-isopropoxy-3-methylaziridine, depending on the reaction conditions. 2-Phenyl-3,3-pentamethyleneazirine was obtained in a good yield by the treatment of cyclohexyl phenyl ketone dimethylhydrazone methiodide with sodium isopropoxide.

In 1957, Smith and Most[2] reported the rearrangement of quaternary hydrazones with a base to give aminoketones, but no intermediate azirine rings were isolated. Recently, Parcell[3] reported that 2-phenyl-3,3-dimethylazirine was isolated in a good yield by the treatment of isobutyrophenone dimethylhydrazone methiodide with sodium isopropoxide in isopropanol, but he did not describe the application of this reaction to other ketones or the effectiveness of other base-catalysts:



In a previous paper,[1] it was reported that 2,4-diphenylpyrrole, not 2-phenylazirine, was obtained by the treatment of acetophenone dimethylhydrazone methiodide (I) with methylsulfinyl carbanion as a base-catalyst:



I II

These results suggest that this rearrangement does not proceed along the same pathway for all ketones, and that the reaction is dependent upon the structures of the ketones or on the properties of the base-catalysts. Therefore, the object of the present study has been to examine the relationship between the azirine formation and the structures of the ketones or the properties of the base-catalysts.

When I was treated with a slightly less than one equivalent amount of sodium isopropoxide in isopropanol, 2,4-diphenylpyrrole (II) was obtained in a 32% yield, but 2-phenylazirine or its hydrolyzed product could not be isolated.

When propiophenone dimethylhydrazone methiodide (III), which possesses a *sec*-carbon atom in the α-position to the C=N double bond, was treated with a slightly less than one equivalent amount of sodium isopropoxide in isopropanol, 2,5-diphenyl-3,6-dimethylpyrazine (IV) was obtained in a 33% yield. The mechanism of the formation of IV is not clear, but it might be possible to consider that the reaction proceeds through the initial formation of the intermediate 2-phenyl-3-methylazirine,

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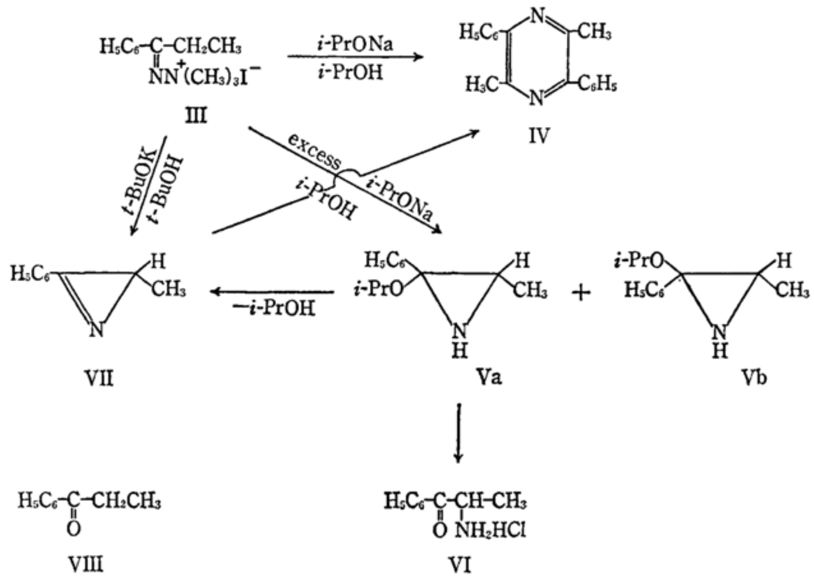
[1] Part I and II: S. Sato, H. Kato and M. Ohta, This Bulletin, **40**, 2936, 2938 (1967).

[3] R. F. Parcell, *Chem. & Ind.*, **1963**, 1396.

[2] P. A. S. Smith and E. E. Most, *J. Org. Chem.*, **22**, 358 (1957).



followed by dimerization to IV. Therefore, in order to clarify the above mechanism, the same reaction was attempted in the presence of an excess of sodium isopropoxide. In this case, if the reaction did proceed through an azirine, it might be expected to be trapped by the addition of isopropanol in the presence of a base-catalyst and so give a stable aziridine derivative. The reaction indeed gave 2-phenyl-2-isopropoxy-3-methylaziridine (V) in a 72% yield. This structure was supported by the results of elemental analysis; by the infrared absorptions at 3300 cm^{-1} for the NH group, at 1380 and 1370 cm^{-1} for the isopropyl group, and at 1120 cm^{-1} for the alkoxy group, and by the fact that hydrolysis by hydrochloric acid afforded α-aminopropiophenone. The vapor phase chromatography (vpc) analysis of this product suggested that it is a mixture of three components (A, B and C) in a ratio of 21 : 53 : 26.[4] Accordingly, its NMR spectrum was rather complex: it shows superimposed doublets at τ 8.85 (total of 9H, $J=7$ cps) for the methyl groups, a pair of singlets, at 8.18 and 8.08 (total of 1H), for the proton on the ring nitrogen and a pair of quartets centered at 7.04 and 6.65 (total of 1H, $J=7$ cps) and a pair of superimposed septets at 6.28 and 5.99 (total of 1H, $J=7$ cps) for the methine proton of the isopropyl group, besides a multiplet of the phenyl group at 2.5—2.9 (10H). The ratio of the *cis* and *trans* isomers was 2 : 1 judging from the vpc peak area ratio of 2.6 : 1 and by the NMR peak height ratio of the imine proton. These spectral data suggest that the product is a mixture of *cis* and *trans* isomers, Va and Vb.

Next, when the rearrangement of III was effected in the presence of an excess of potassium *t*-butoxide in place of sodium isopropoxide, an oily product boiling at 85—90°C/5 mmHg was obtained. Infrared spectrum of this product exhibits a band at 1740 cm^{-1} for the C=N bond of an azirine and one at 1690 cm^{-1} for the carbonyl, and the vpc peak shows the presence of two components (D and E) in a ratio of 55 : 45. The component E was found to have the same vpc retention time as an authentic specimen of propiophenone. The NMR spectrum of this product shows a double at τ 8.2 (3H) for the methyl group on the 3-position of the ring, a quartet at 7.8 (1H) for the hydrogen on the 3-position of the ring, a multiplet at 2—3 (10H) for the phenyl group and a triplet at 8.8 (3H) for the methyl group of propiophenone, and a quartet at 7.2 (2H) for the methylene group of propiophenone. These spectral data suggest that the component D is 2-phenyl-3-methylazirine (VII) and that the component E is propiophenone (VIII). The *t*-butanol addition product could not be isolated; this is probably because the addition of a bulky *t*-butyl group to the C=N double bond was more hindered than the addition of an isopropyl group.

Parcell reported that 2-phenyl-3,3-dimethylazirine was re-produced by the azeotropic distillation of isopropanol from a solution of the 2-phenyl-2-isopropoxy-3,3-dimethylaziridine in toluene in the presence of a catalytic amount of sodium isopropoxide.[3] Accordingly, compound V was treated by the same procedure in order to find out whether or not such a reaction can be used in the preparation of 3-monoalkylazirine. An oily product which boils at 75—82°C/1 mmHg was

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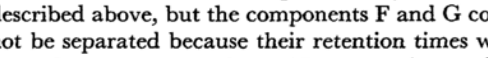
[4] Component A may be a decomposition product during the v.p.c. analysis, because the product gave a good elemental analysis and its spectrum did not show prominent peaks which may be assigned to the presence of an impurity.

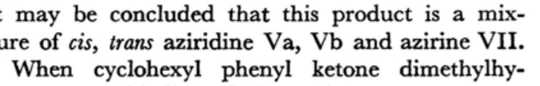
obtained. The infrared spectrum of this product exhibits a band at 3300 cm^{-1} for the NH group, at 1740 cm^{-1} for the C=N double bond of an azirine and one at 1120 cm^{-1} for the alkoxy group. These infrared data suggest that this product is a mixture of azirine (VII) and aziridine (V); the vpc peak shows the presence of four components (F, G, H and I) in a ratio of 50 : 2 : 40 : 8. The components H and I had the same vpc retention times as the components B and C (azirdidine Va,b) described above, and the component F had the same retention time as that of the component D (azirine VII) described above, but the components F and G could not be separated because their retention times were very close to one another. However, the product partly solidified on standing in a refrigerator for one week; the melting point of this solid was undepressed on admixture with compound IV. Thus, it may be concluded that this product is a mixture of *cis*, *trans* aziridine Va, Vb and azirine VII.

When cyclohexyl phenyl ketone dimethylhydrazone methiodide (IX), which possesses a *t*-carbon on the α-position of the C=N bond, was treated with sodium isopropoxide in isopropanol, 2-phenyl-3,3-pentamethyleneazirine (X) was isolated in an 80% yield. This compound was identified by elemental analysis and by its showing an infrared absorption at 1740 cm^{-1} for the C=N double bond of azirine.

In order to examine the applicability of this method to a cyclic ketone,⁵⁾ cyclohexanone dimethylhydrazone methiodide (XI) was treated with sodium isopropoxide in isopropanol. In this case no ring formation occurred, but XI dissociated to cyclohexanone and trimethylhydrazinium iodide (XIII).



IX X



XIII

XI XII

Compound XI probably dissociated because XI is a very unstable compound and is readily dissociated by isopropanol to XII and XIII; indeed, XIII was formed by an attempted recrystallization of XI from ethanol.

When this rearrangement was tried by means of methyl sulfinyl carbanion in DMSO, only an intractable red-brown resinous matter was formed. Similarly, an attempt to synthesize ethyl benzoylacetate dimethylhydrazone methiodide from ethyl benzoylacetate dimethylhydrazone and methyl iodide in ether gave only trimethylhydrazinium iodide.

In summary, it may be said that this method of preparing an azirine ring is affected by the activity of the hydrogen atom on the α-position of the C=N double bond, by the stability of the reaction product, and by the properties of catalyst and solvent. Namely, when the α-position was *t*-carbon, the reaction gave an azirine ring in a good yield, and when it was *sec*-carbon, it was attacked by the base to give unstable azirine, which was easily dimerized. When the α-position was primary carbon, the reaction gave a completely different product. Therefore, this method of preparation seems to be limited by the structure of the starting materials.

Experimental

The melting points were measured on a micro hot stage and are not corrected; all boiling points are uncorrected. The infrared spectra were taken on KBr tablets or neat liquid films. The vpc analysis was performed at a column temperature of 150°C, using a 150 cm column packed with 10% Apiezone Grease L on Diasolid A.

Propiophenone Dimethylhydrazone. A mixture of 25 g (0.18 mol) of propiophenone, 15 g (0.25 mol) of dimethylhydrazine, 2 g of anhydrous sodium acetate, and 2 drops of glacial acetic acid was heated, in a sealed tube, on an oil bath under reflux for 16 hr (bath temperature 120°C). After the two layers had been separated, the aqueous layer was extracted with ether, the combined organic layers were washed with water and dried over sodium sulfate, and the solvent was removed by distillation. The residual oil was distilled under reduced pressure to give 30 g (90%) of a pale yellow liquid boiling at 120—122°C/20 mmHg.

Found: C, 75.08; H, 8.92; N, 15.56%. Calcd for $C_{11}H_{16}N_2$: C, 74.95; H, 9.15; N, 15.96%.

Cyclohexyl Phenyl Ketone Dimethylhydrazone. A mixture of 10 g (0.053 mol) of cyclohexyl phenyl ketone,⁶⁾ 6 g (0.1 mol) of dimethylhydrazine, 1 g of anhydrous sodium acetate, and one drop of glacial acetic acid was treated in essentially the same manner to give 12 g of a pale yellow oil boiling at 115—118°C/1—2 mmHg.

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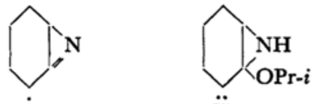
5) Hassner and Fowler reported the synthesis of fused azirines by photolysis of the corresponding vinyl azides but the azirine fused to a six-membered ring could not be isolated probably because of a highly strained structure of the expected compound. In our experiment, however, if the desired fused azirine I was formed, it may readily add a molecule of isopropanol to give isolable stable fused aziridine II under the reaction conditions.



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A. Hassner and F. W. Fowler, *Tetrahedron Letters*, **1967**, 1545.

6) V. Meyer and W. Scharvin, *Ber.*, **30**, 1942 (1897).

Found: C, 77.98; H, 9.75; N, 11.98%. Calcd for $C_{15}H_{22}N_2$: C, 78.21; H, 9.63; N, 12.16%.

Ethyl Benzoylacetate Dimethylhydrazone. A mixture of 19.2 g (0.1 mol) of ethyl benzoylacetate, 12 g (0.2 mol) of dimethylhydrazine, 2 g of anhydrous sodium acetate, and 2 drops of glacial acetic acid was treated in the same manner to give 11 g (48%) of a pale yellow liquid boiling at 130—135°C/1 mmHg.

Found: C, 66.72; H, 7.47; N, 11.97%. Calcd for $C_{13}H_{18}O_2N_2$: C, 66.64; H, 7.74; N, 11.96%.

Propiophenone Dimethylhydrazone Methiodide (III). To a solution of 25 g of propiophenone dimethylhydrazone in 50 m*l* of absolute ethanol, there was added 80 g of methyl iodide, and then the mixture was refluxed for five hours. After cooling, the white crystals which separated out were collected, further crops being obtained by dilution with ether. Recrystallization from ethanol gave 31 g of white prisms melting at 157—159°C.

Found: C, 45.15; H, 5.78; N, 8.88%. Calcd for $C_{12}H_{19}N_2I$: C, 45.30; H, 6.02; N, 8.80%.

Cyclohexyl Phenyl Ketone Dimethylhydrazone Methiodide (IX). To a solution of 12 g of cyclohexyl phenyl ketone dimethyl hydrazone in 30 m*l* of dry ether, there was added 15 g of methyl iodide; the mixture was refluxed for one hour, and then allowed to stand overnight at room temperature. The crystals which separated out were collected and then washed with acetone to give 9.5 g of colorless prisms melting at 148—149°C.

Found: C, 50.66; H, 6.38; N, 7.10%. Calcd for $C_{16}H_{24}N_2I$: C, 50.18; H, 6.46; N, 7.52%.

Cyclohexanone Dimethylhydrazone Methiodide (XI). To a solution of 20 g of cyclohexanone dimethylhydrazone²⁾ in 30 m*l* of dry ether, 50 g of methyl iodide was added; the mixture was then treated in essentially the same manner as above to give 23 g of very hygroscopic white needles melting at 95—103°C.

Found: C, 36.92; H, 6.76%. Calcd for $C_9H_{19}N_2I$: C, 38.31; H, 6.78%.

2,4-Diphenylpyrrole (II). 15 g of I was added to a solution of 1.4 g (0.06 g-atom) of sodium in 150 m*l* of isopropanol at 40°C. Stirring was continued for one hour, after which the solvent was removed on a rotary evaporator. The residual oil solidified on cooling, and the solid was recrystallized from methanol-water to give 1.6 g of 2,4-diphenylpyrrole as pale yellow leaflets melting at 177—179°C. The IR spectrum was identical with that of an authentic sample.¹⁾

2,5-Diphenyl-3,6-dimethylpyrazine (IV). To a solution of 0.65 g (0.028 g-atom) of sodium in 60 m*l* of isopropanol, 10 g (0.031 mol) of III were added at 40°C; the mixture was then stirred for one hour at 40°C. The solvent was removed on a rotary evaporator. The residual paste was extracted with *n*-hexane, and the extracts were dried over sodium sulfate. The solvent was then removed by distillation under reduced pressure to give an oily residue. The residual oil which solidified on cooling was washed with *n*-hexane and was recrystallized from ethanol to give 1.2 g of colorless leaflets melting at 125—126°C (lit. 124—125°C).⁷⁾ (Found: C, 83.48; H, 6.12; N, 10.48%). Picrate, mp 153—154°C (lit. 153—154°C).⁶⁾

2-Phenyl-2-isopropoxy-3-methylaziridine (V). To a solution of 0.9 g (0.034 g-atom) of sodium in 80 m*l* of isopropanol, 10 g (0.03 mol) of III were added at 40°C, after which the mixture was stirred for one hour. The solvent was removed on a rotary evaporator. The residual paste was extracted with *n*-hexane, and the extracts were dried over sodium sulfate. The solvent was then removed by distillation under reduced pressure, and the residual oil was distilled under reduced pressure, giving 4.3 g (72%) of V boiling at 105—108°C/8—9 mmHg. IR: 3350 (NH), 1380, 1370 (isopropyl) and 1120 cm^{-1} (alkoxy).

Found: C, 75.40; H, 8.86; N, 7.32%. Calcd for $C_{12}H_{17}ON$: C, 75.35; H, 8.96; N, 7.32%.

Hydrolysis of V. To a solution of 0.5 g of V in 20 m*l* of ether, 40 m*l* of 2 N hydrochloric acid was added, after which the mixture was stirred for 30 min. The reaction mixture was evaporated on a rotary evaporator at 50—60°C to a volume of 5—10 m*l*. The solid which separated out was collected by filtration, and then washed with ether and dried to give 0.3 g of white crystals melting at 187—189°C, while its picrate melted at 168—169°C. These melting points are identical with the literature values of α-aminopropiophenone hydrochloride and its picrate.⁸⁾

Found: C, 47.83; H, 3.50; N, 15.16%. Calcd for $C_{15}H_{14}O_8N_4$: C, 47.62; H, 3.73; N, 14.81%.

2-Phenyl-3-methylazirine (VII). a) To a solution of 1.4 g (0.036 g-atom) of potassium in 150 m*l* of *t*-butanol, 10 g (0.03 mol) of III was added at 50°C, after which the mixture was stirred for 1.5 hr at 50—55°C. The solvent was removed on a rotary evaporator, the residual paste was extracted with *n*-hexane, and the extracts were dried over sodium sulfate and distilled to give 1.2 g of a pale brown liquid boiling at 85—90°C/5 mmHg. IR: 1740 (C=N) and 1690 cm^{-1} (C=O).

b) To a solution of 0.1 g of sodium in 10 m*l* of isopropanol, 2 g of V and 15 m*l* of dry toluene were added. The mixture was slowly distilled through a short column on an oil bath until the toluene distilled off; the residual oil was then distilled under reduced pressure to give 1 g of a product boiling at 75—82°C/1—2 mmHg. IR: 3350 (NH), 1740 (C=N), 1380, 1370 (isopropyl) and 1120 cm^{-1} (alkoxy).

2-Phenyl-3,3-pentamethyleneazirine (X). To a solution of 0.46 g (0.02 g-atom) of sodium in 60 m*l* of isopropanol, 9.0 g (0.025 mol) of IX was added at 40°C, after which the mixture was stirred for one hour at 40°C. The solvent was then removed on a rotary evaporator. The residual paste was extracted with ether, the extracts were dried over sodium sulfate, and the solvent was removed by distillation under reduced pressure. The residual oil was distilled under reduced pressure, giving 3.5 g (80%) of X boiling at 110—111°C/1—2 mmHg.

Found: C, 84.07; H, 7.80; N, 7.45%. Calcd for $C_{13}H_{15}N$: C, 84.28; H, 8.16; N, 7.56%. IR: 1740 cm^{-1} (C=N).

Rearrangement of XI. To a solution of 1.2 g (0.05 g-atom) of sodium in 150 m*l* of isopropanol, 10 g (0.035 mol) of XI were added at 45—50°C, after which the mixture was stirred for one hour at 50°C. After cooling, the solid which separated out was collected by filtration; then it was washed with ether, dried, and recrystallized from ethanol to give 2.5 g of white

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7) A. Kolb, *Ann.*, **291**, 267 (1898).

8) S. Gabriel, *Ber.*, **41**, 1152 (1908).

prisms of trimethylhydrazinium iodide, mp 239°C (dec.).[2] The filtrate was treated with a 2,4-dinitrophenylhydrazine reagent. There was thus obtained cyclohexanone 2,4-dinitrophenylhydrazone, mp 159°C.

The author wishes to express his deep gratitude to Professor M. Ohta and Dr. H. Kato, Tokyo Institute of Technology, for their advice and guidance on this study. Thanks are also due to Dr. S. Ogihara, President of the Kyorin Pharmaceutical Co., Ltd., and to Dr. T. Irikura, Director of the Kyorin Chemical Laboratory, for their permission to publish this work.