The Interaction of *cis* and *trans*-1-Cyclohexyl-2-phenyl-3-benzoylaziridine with Lithium *N*-Methylanilide

Philip Tarburton, D. K. Wall and Norman H. Cromwell (1)

Department of Chemistry, University of Nebraska, Lincoln, Nebraska 68588

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A reaction pathway for the rearrangement-dehydrogenation of *cis*-1-cyclohexyl-2-phenyl-3-benzoylaziridine into 2-cyclohexylamino-3-phenylindenone can now be suggested. Furthermore, a competing degradation pathway involving C-C bond scission accounts for the major product in these reactions and leads to ω-cyclohexylaminoacetophenone and benzaldehyde. Observed also is the fact that *trans*-1-cyclohexyl-2-phenyl-3-benzoylaziridine fails to undergo the rearrangement-dehydrogenation reaction.

J. Heterocyclic Chem., **13**, 411 (1976).

Sir:

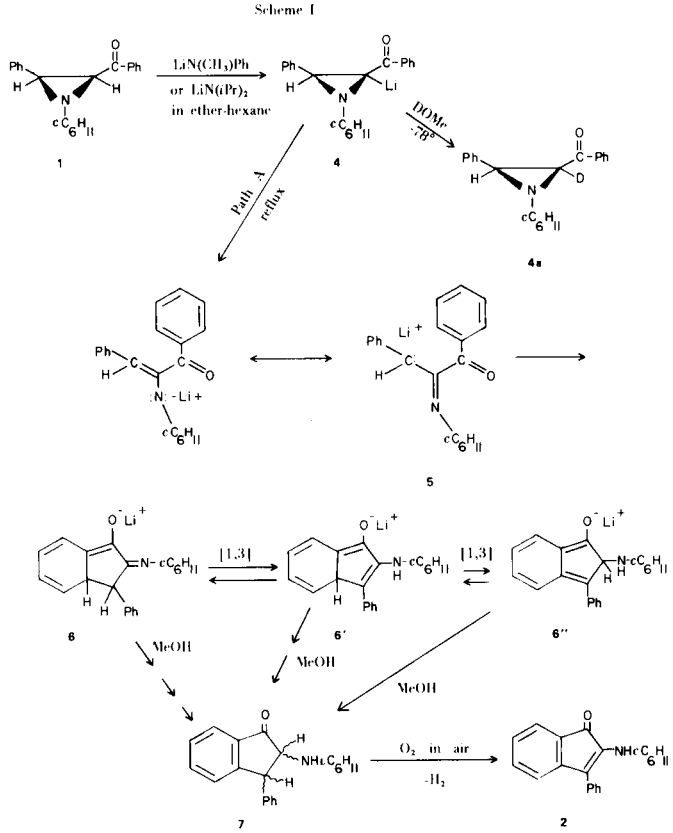
Over a decade has passed since the novel rearrangement-dehydrogenation of *cis*-1-cyclohexyl-2-phenyl-3-benzoylaziridine (**1**) into 2-cyclohexylamino-3-phenylindenone (**2**) in the presence of lithium *N*-methylanilide or lithium diisopropylamide was first announced in a preliminary communication (2). The corresponding *trans*-1-cyclohexyl-2-phenyl-3-benzoylaziridine (**1'**) is reduced to its corresponding *trans*-carbinol by the latter reagent (3), but undergoes neither reduction to carbinol nor rearrangement-dehydrogenation with the former reagent.

For the first time a reaction pathway for the transformation of **1** into **2** can now be suggested. Furthermore, a competing degradation pathway involving C-C bond scission accounts for the major product of the reaction, ω-cyclohexylaminoacetophenone (**3**). Finally, the inability of **1'** to undergo the rearrangement-dehydrogenation reaction with either of the aforementioned bases has been investigated further.

We have found that the sequence of reactions shown in Scheme I best illustrates a possible mechanism for the stereoselective rearrangement (*i.e.*, only the *cis* isomer rearranges) of **1** into **2**.

Thus treatment of 2.0 g. (0.0066 mole) of **1** in 20 ml. of anhydrous ether with 0.04 mole of lithium *N*-methylanilide in anhydrous ether and hexane (prepared from *N*-methylaniline and butyllithium) under a nitrogen atmosphere, followed by (A), addition of 50 ml. of methanol (distilled under a nitrogen atmosphere) and (B), exposure to oxygen in the air, leads to the formation of 0.39 g. of **2** in 20% yield. These deeply purple colored crystals, obtained from column chromatography of the reaction

Scheme I



mixture employing a 9:1 petroleum ether (b.p. 30-60°)/-benzene mixture on alumina (4), had m.p. 119-120°; nmr (carbon tetrachloride, TMS): δ = 6.4-7.7 (m, 9H), 2.7-3.3 (m, 1H, N-H), 0.94-2.10 (m, 11H). Subsequent treatment of **2** with deuterium oxide showed a peak to

form at δ = 4.5 (indicative of deuterium hydroxide) and the peak at δ = 2.7-3.3 (m, 1H, N-H) had vanished. The ultraviolet-visible spectrum (methanol) had two general absorption regions with λ max at 265 nm (ε = 57,600) and 525 nm (ε = 13,500); ir (carbon tetrachloride): ν = 3370 (N-H) and 1720 (C=O) cm^{-1}; mol. wt. (mass spectrum) = 303.

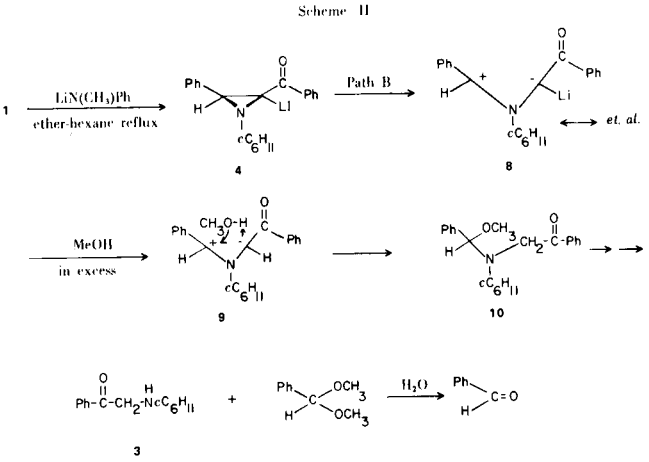
Anal. Calcd. for $C_{21}H_{21}NO$: C, 83.13; H, 6.98; N, 4;60; Found: C, 83.09; H, 7.16; N, 4.62.

cis-α-Lithio-1-cyclohexyl-2-phenyl-3-benzoylaziridine (**4**) was detected by reacting 2.0 g. of **1** in 20 ml. of anhydrous ether with 0.04 mole of lithium *N*-methylanilide in anhydrous ether and hexane (prepared from butyllithium and *N*-methylaniline) under a nitrogen atmosphere at very low temperature (*i.e.*, a dry ice-acetone bath was used to bring the temperature down to -78°). The reaction mixture was stirred at this very low temperature for three hours and then for five more hours after 5.0 ml. of methanol-d_1 had been added. Later the mixture was warmed to 0° and stirred for two more hours and finally was stirred overnight at room temperature. The next day the tan solution was exposed to the air and no color change was observed. The mixture was next extracted with 10.0 ml. of deuterium oxide and the ether solution dried with magnesium sulfate. Nmr spectral studies revealed the peak indicative of the α-proton of **1**, that is the δ = 3.23 peak, to have diminished to 20% of its original height relative to the constant area of the cyclohexyl group (δ = 0.84-2.04 (m, 11H)). This implies the production of **4a** in 80% yield.

Another important experiment was the transformation of **1** into **2** using azobenzene in lieu of oxygen as the hydrogen acceptor. This key experiment, for the first time, offers positive evidence that the immediate precursor of **2** is 2,3-dihydro-2-cyclohexylamino-3-phenylindenone (**7**). The evidence for this is two-fold. Visible spectroscopy studies show that azobenzene reacts to become hydroazobenzene upon addition to the reaction mixture (5) and concomitantly the reaction mixture itself develops a purple color indicating the formation of the unsaturated indenone **2**. Furthermore, since it is believed that **6**, **6'**, and **6''** are in thermal equilibrium owing to the reversibility of their [1,3]suprafacial shifts, all paths, as it were, lead to **7**. Since an equilibrium has been established, the most stable thermodynamic isomer wins out. The benzenoid 2,3-dihydro intermediate **7** is expected to be more stable than any ot its quinoid analogs (8). Use of the known hydrogen acceptor, azobenzene, specifies the timing of the loss of hydrogen (*i.e.*, it is lost after protonation by methanol and *not* before). Hence, intermediates such as **6**, **6'**, and **6''** cannot be ruled out in the mechanistic sequence of Scheme I. Unfortunately, however, all attempts to trap **5** *via* methylation have failed so that it is suspected that this particular intermediate enjoys only a transient existence.

In Path A (See Scheme I) a mechanistic sequence for the formation of **2** has now been put forth; however, owing to the low yield of **2** (*e.g.*, 20%) an investigation as to the fate of the remainder of the starting material **1** was important. Recent laboratory work has revealed the major product of this reaction to be ω-cyclohexylaminoacetophenone (**3**) and a possible pathway for its formation may now be put forth; see Scheme II (9):

Scheme II



All attempts to separate **3** from *N*-methylaniline were unsuccessful (4). The independent synthesis of **3** (10) gave, m.p. 85-89.5°; nmr (carbon tetrachloride, TMS): δ = 7.20-8.16 (m, 5H), 4.36 (d, 2H), 4.15 (m, 1H, N-H), 0.90-2.11 (m, 11H); treating with deuterium oxide gave nmr (carbon tetrachloride, TMS): δ = 7.20-8.16 (m, 5H), 4.34 (s, 2H), 4.72 (s, DOH), 0.90-2.11 (m, 11H); ir (carbon tetrachloride) gave ν = 3325 (N-H) and 1705 (C=O) cm^{-1}. Chromatography of the reaction product (4) afforded 1.65 g. of an oil which was shown by quantitative nmr to be 52% **3** and 48% *N*-methylaniline; 0.86 g. of **3** was calculated to be present (*e.g.*, **3** was formed in 60% yield) (11). This oil fraction showed ir (carbon tetrachloride): ν = 1705 cm^{-1}, indicative of the carbonyl in **3** as well as ν = 3325 cm^{-1} for the secondary amino group in both **3** and *N*-methylaniline. Finally, a trace amount of benzaldehyde was isolated in the work-up and the 2,4-DNP derivative gave the expected melting point of 237° thereby accounting for the formation of the other degradation product.

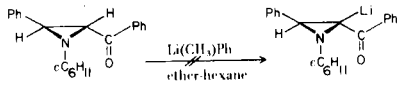
Since the thermal process of ring cleavage of carboaziridines involves stereospecific, conrotatory ring opening (12) the formation of an intermediate such as **8** in a refluxing ether-hexane mixture is not surprising. Furthermore, the presence of the lithium *N*-methylanilide is thought to facilitate C-C bond scission by forming the immediate precursor of **8**. The ylid **8** is probably quite stable because of resonance but upon addition of methanol

loses its carbon-lithium bond to become **9**, followed by a 1,3-dipolar addition of methanol to form the amide acetal **10**. This intermediate then fragments to form **3** as well as benzaldehyde acetal which upon exposure to water becomes benzaldehyde. Hence, a pathway (see Path B Scheme II) involving C-C bond scission accounts for the major products of this reaction.

We now turn our attention to the inertness of *trans*-1-cyclohexyl-2-phenyl-3-benzoylaziridine (**1'**) toward lithium *N*-methylanilide. A 1.40 g. (0.0131 mole) amount of lithium *N*-methylanilide in ether-hexane (prepared from butyllithium and *N*-methylaniline) was added to 2.0 g. (0.0066 mole) of the *trans*-aziridine **1'** which was dissolved in 20 ml. of anhydrous ether. After stirring the reaction mixture, 0.5 ml. (0.0138 mole) of deuteriosulfuric acid was added dropwise followed by the addition of 5.0 ml. of deuterium oxide. Work-up of the yellow reaction mixture gave 1.37 g. of the non-deuterated aziridine **1'** (68.5% recovery) as revealed by nmr. Repeating this same experiment with **1** afforded **2** in 20% yield, m.p. 118-120°. (The ir and nmr were identical to that expected for **2**).

Although the failure of the *trans*-carboaziridine **1'** to react with this base is surprising, the fact that up to 68.5% of the starting material is recovered gives credence to the argument that the intermediate **4'** *does not* form (see Scheme III) thereby preventing epimerization of **4'** into **4**, deuterium exchange, or rearrangement of **4'** into the indenone **2**. The most probable factor preventing the

Scheme III



1' 4'

reaction of the lithium base with **1'** is a steric interplay between the base and **1'** thereby preventing the formation of **4'**. We intend to investigate this matter further by variations of size and strength of the base and by variations of the structure of the 1-alkyl-2-aryl-3-aroylaziridines to learn if the rearrangement-dehydrogenation of the *trans* analog may finally be affected.

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REFERENCES AND NOTES

(1) To whom inquiries should be addressed.

(2) A. E. Poland, M. C. McMaster, R. C. Badger, and N. H. Cromwell, *J. Am. Chem. Soc.*, **87**, 2510 (1965).

(3) D. K. Wall, J. L. Imbach, A. E. Pohland, R. C. Badger, and N. H. Cromwell, *J. Heterocyclic Chem.*, **5**, 77 (1968).

(4) The yellow liquid last eluted from the column was found to be an inseparable mixture of **3** and *N*-methylaniline.

(5) The Reaction of **1** with Lithium *N*-Methylanilide Using Azobenzene as the Proton Acceptor: Upon addition of 2.0 g. (0.0066 mole) of **1** in 20 ml. anhydrous ether to 0.04 mole of lithium *N*-methylanilide in ether-hexane (prepared from butyllithium and *N*-methylaniline) a red solution resulted which was refluxed for 12 hours. Upon addition of deoxygenated methanol (*i.e.*, it was distilled under a nitrogen atmosphere) with 0.0012 mole of azobenzene a purple solution developed almost immediately. Prior to exposure to the air, visible spectra of varying concentrations of the reaction mixture revealed λ max = 525 (in methanol) indicative of **2**, but no general absortion was observed around λ = 440 nm indicating azobenzene was not present (6). Upon work-up of the solution and exposure to the air for 24 hours, visible spectroscopy studies revealed λ max = 440 and 525 nm, indicating that azobenzene had indeed returned (7). Chromatography using a 9:1 petroleum ether (b.p. = 30-60°)/-benzene mixture on alumina allowed two solids, one orange and one purple, to be obtained (4). Nmr, ir, and melting point studies revealed the orange solid to be azobenzene, while the deeply purple colored crystals obtained had m.p. 119-120° as well as ir and nmr identical to that expected for **2**.

(6) We had suspected that the reaction azobenzene $+H_2 \rightarrow$ hydrazobenzene had occurred owing to the fact that no general absorption near 440 nm could be found.

(7) Upon exposure to the air the reaction hydrazobenzene $\xrightarrow[\text{several hours}]{O_2}$ azobenzene had taken place.

(8) For a discussion of this phenomenon see Badger, "Aromatic Character", Cambridge University Press, London, 1969.

(9) This scheme is similar to the pathway proposed by P. B. Woller and N. H. Cromwell, *J. Heterocyclic Chem.*, **5**, 579 (1968) for a somewhat analogous thermally induced cleavage reaction of aziridinyl esters.

(10) N. H. Cromwell and G. D. Mercer, *J. Am. Chem. Soc.*, **79**, 3815 (1957).

(11) The nmr spectrum of **3** is given above and the nmr spectrum of *N*-methylaniline is available in the Sadtler file. The nmr spectrum obtained from the yellow oil was identical to these two superimposed upon one another.

(12) For more details on this subject see P. B. Woller and N. H. Cromwell, *J. Org. Chem.*, **35**, 888 (1970).