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A NOVEL CYCLIZATION REACTION CATALYZED BY THE GRIGNARD REAGENT(1).

THE INTRAMOLECULAR LINKING OF AN AROMATIC RING TO THE α-POSITION OF KETOXIME

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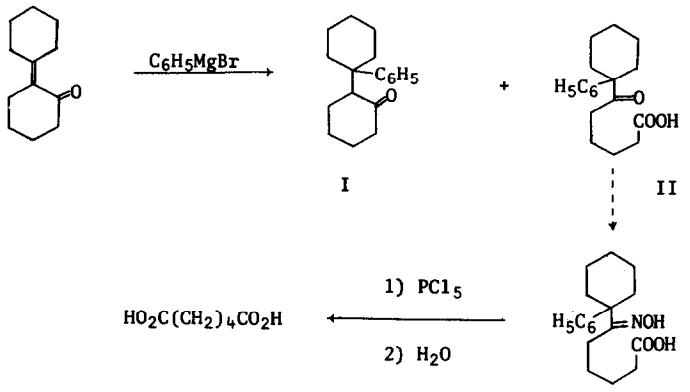
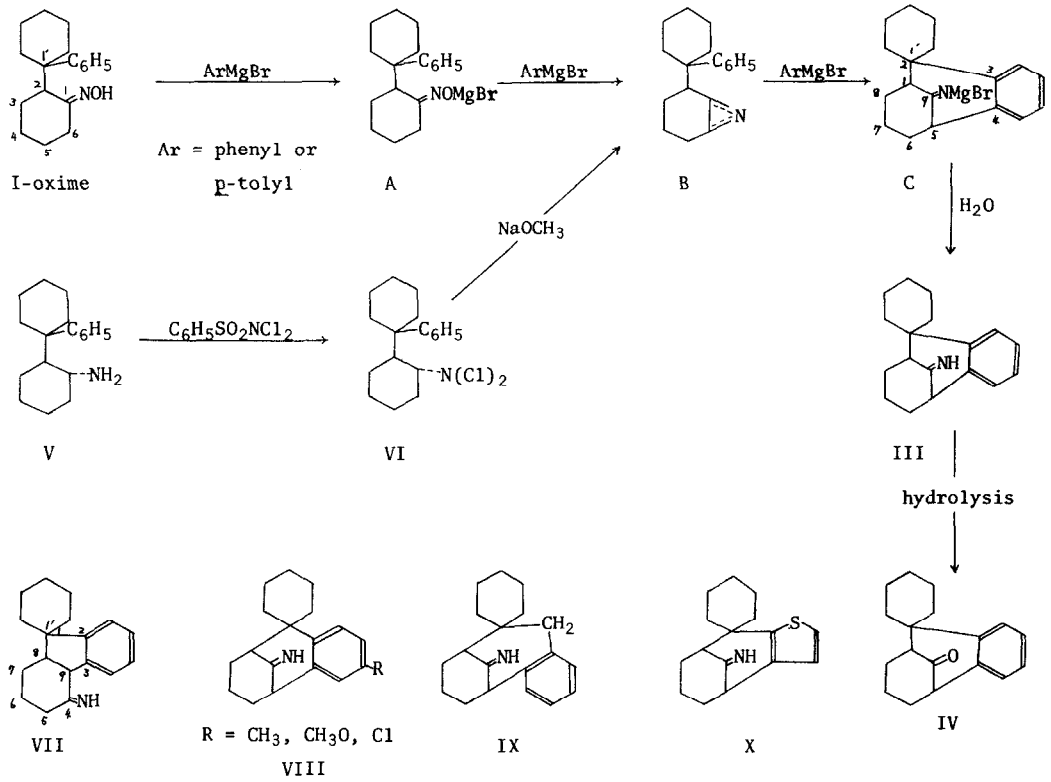
The Grignard reaction of ketoximes has been well-known as a preparation method of aziridines(3). The present study demonstrates that the cyclization of a certain kind of ketoximes involving an aryl group is catalyzed by arylmagnesium halide. 2-Cyclohexylidencyclohexanone(4) was reacted with phenylmagnesium bromide in the stream of nitrogen using purified ether as a solvent to afford 2-(1-phenyl)cyclohexylcyclohexanone(I), m.p. 64-68°(methanol), yield 65-75% and 6-(1-phenyl)cyclohexyl-6-oxo-n-hexanoic acid(II), m.p. 81°(petroleum benzine), yield 5-7%. Structural proof for II was given by the I.R.spectrum, 3100-2500 cm^{-1}(CO_2H), 1717 cm^{-1}(C=O), 940-920 cm^{-1}(CO_2H) and by the finding that II-oxime, m.p. 127-128°(ether-petroleum ether) afforded adipic acid through the Beckmann rearrangement, followed by hydrolysis. Further proof for the structure of II and the formation mechanism will be discussed elsewhere(5).



I-Oxime, m.p. 127-128°(ethanol), was submitted to the Grignard reaction. Phenylmagnesium bromide was prepared in ether and then ether was replaced by toluene. To the Grignard reagent (more than 3 equiv.) was added the toluene solution of I-oxime and the mixture was refluxed for 2 hrs. The reaction mixture was treated with an aqueous solution of ammonium chloride and the toluene layer dried was saturated with anhydrous hydrogen chloride to cause the precipitation. Recrystallization from ethanol-ether gave colorless plates of $C_{18}H_{23}N\cdot HCl$(III·HCl), m.p. 282-284°, yield 71.8%; the free base($C_{18}H_{23}N$), m.p. 101°(petroleum ether). Hydrolysis of III·HCl in hydrochloric acid gave a ketone of $C_{18}H_{22}O$(IV), m.p. 79-81°(petroleum ether), m/e 254(M^+). In place of phenylmagnesium bromide, the use of p-tolylmagnesium bromide also resulted in the formation of the same product(III·HCl).



The molecular formula of IV corresponds to the compound which has two hydrogens less than I. But the absence of olefinic double bond and the presence of a carbonyl group were indicated by the usual chemical tests. The I.R.spectrum of IV contained a band at 753 cm^{-1} characteristic for disubstituted benzene showing a contrast to bands at 739 cm^{-1} and 704 cm^{-1} due to monosubstituted benzene in I. These observations led us to postulate the structure of IV to be spiro[bicyclo[3.3.1]-3,4-benzononane-9-one-2,1'-cyclohexane]. The postulation was supported by the N.M.R.spectroscopy as described below. The N.M.R.spectrum(60 Mc, CCl_4) of IV exhibited signals characteristic for benzene protons (2.85τ, 4H, A_2B_2type, m.), two methine protons(6.63, 7.10τ, each 1H, m.) and cyclohexane protons

(7.95-8.52τ, 16H, m.), while the splittings of the methine signals were not clear. The reduction of the ketone(IV) with lithium aluminum hydride afforded an alcohol(V), m.p. 103-104° (petroleum ether) which showed bands at 3480 cm^{-1}(OH) in the I.R.spectrum and at 7.6τ(1H, m.), 7.1τ(1H, m.) and 6.0τ (1H, t., J=3.0 cps) in the N.M.R.spectrum. The first two signals in the N.M.R.spectrum are ascribable to each methine(C_1, C_5) and the last to H on C_9 bearing the hydroxyl group. The signal(6.0τ) appeared as triplet by the partial overlaping of double doublets due to the coupling with the two methine hydrogens on the neighboring C_1 and C_5. The ascription of the signal(6.0τ) was confirmed by the finding that it shifted to the down field, 5.1τ(1H, t.), in derivation to the O-tosylate, m.p.(decomp.) 113-115°(benzene).

Thus, all the data were in accordance with the postulated structure for IV and consequently III was assigned to the corresponding ketimine which showed absorption bands at 1650 cm^{-1}(=NH) and 755 cm^{-1}(disubstituted benzene). The formation of III was presumed to proceed through similar one to the mechanism(6, 7) of the Neber rearrangement where azirines have been proposed as intermediates. As mentioned above, the reaction required at least 3 equiv. of the Grignard reagent. This may suggest that the reagents withdrew three hydrogens at the oxime group, C_6 and the o-position of benzene ring on the pathway to the ketimine(III) via an azirine. See I → A → B → C → III.

It has been already known that treatment of N,N-dichloroamine with sodium alkoxide in alcohol affords α-aminoketone via the Neber rearrangement(8, 9). The reaction was applied here to get an information for the mechanism proposed. Thus, a suspension of powdered sodium methoxide (2 equiv.) in toluene was mixed with a toluene solution of N,N-dichloro-DL-trans-2-(1-phenyl)cyclohexylcyclohexylamine(VI) which was prepared by action of N,N-dichlorobenzenesulfonamide (1 equiv.) on DL-trans-2-(1-phenyl)cyclohexylcyclohexylamine(5)(V). To the mixture was added a toluene solution of phenylmagnesium bromide (3 equiv.) while refluxing. The product isolated from the reaction mixture which was made alkaline was found to contain the ketimine(III) on T.L.C. and the hydrolysate of the product to contain the ketone(IV) on G.L.C. See V → VI → B → C.

The observations provided a support to the mechanism proposed for the formation of III. The mechanism leaves a possibility that the ketimine of m.p. 101° might be spiro[bicyclo[4.3.0]-2,3-benzononane-4-imino-1,1'-cyclohexane](VII) which would be formed by bridging between the benzene ring and C_1 of I-oxime with the shift of the imino group to C_6. But it is excluded by the N.M.R. data above-stated and by the fact that the ketone(IV) did not condense with aldehydes showing absence of an active methylene group. In application of the present reaction, VIII, IX and X also were formed analogously.

References

1. Studies in Stereochemistry. XXXIX.
2. Present adress: Faculty of Pharmacy, Fukuoka University, Fukuoka, Japan.
3. P.E.Fanta, in Heterocyclic Compound with Three and Four-membered Rings, Ed. A. Weissberger, Interscience Publishers, New York, 1964, p. 537.
4. J.Reese, Ber., 75, 384(1942).
5. It will appear in Chem. Pharm. Bull. (Tokyo) in near future.
6. H.Henze and W.D.Compton, J. Org. Chem., 22, 1036(1957).
7. S.Eguchi and Y.Ishii, Bull. Chem. Soc. Japan, 36, 1434(1963).
8. H.E.Baumgarten and F.A.Bower, J. Am. Chem. Soc., 76, 4561(1954).
9. H.E.Baumgarten and E.P.Willams, in Organic Syntheses, Vol.41, p. 82, John Wiley and Sons, Inc., New York (1961).