MANNICH CYCLIZATION INVOLVING THE α-POSITION OF KETALS: SYNTHESIS OF 2-ARYL-4-PIPERIDONES AND 2-ARYL-3-ACYLPYRROLIDINES

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Abstract- A new method for the preparation of 2-aryl-4-piperidones and 2-aryl-3-acylpyrrolidines based on the acid-induced intramolecular cyclization between an iminium salt and the α-position of a ketal group is reported.

The acid-induced intramolecular cyclization between a cyclic iminium salt and the α-position of a ketal group has sometimes been used in alkaloid synthesis [1]. These reactions proceed through an enol ether as intermediate, which in acidic medium is in equilibrium with the corresponding ketal. The electrophilic attack of the iminium salt upon the enol ether double bond promotes the cyclization.

In a previous work [2] we described a cyclization of this type by using hydrogen chloride gas in the synthesis of 2-aryl-3-acetylpyrrolidines 14 from imino ketals 8 (see below, procedure A). In this paper we report a new and improved method for achieving these cyclizations and we extend the procedure to the synthesis of 2-aryl-4-piperidones [3,4].

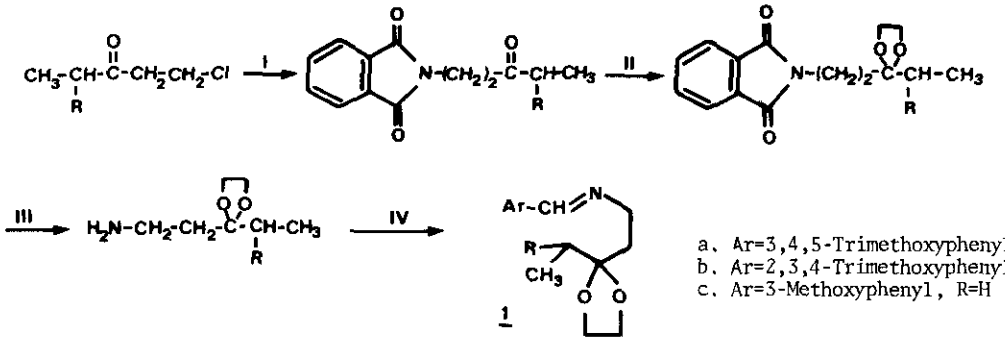
The preparation of the imino ketals 1 required for the synthesis of 4-piperidone systems has been carried out by the reaction sequence outlined in Scheme I [5].

Cyclizations were carried out by the following three alternative procedures, and the results obtained are summarized in Table I.

Procedure A: A stirred solution of the imine in anhydrous methylene chloride was saturated with hydrogen chloride gas for 90 minutes and refluxed under nitrogen for 21 hours. The mixture was basified with aqueous 20% potassium carbonate solution and extracted with methylene chloride.

Procedure B: A stirred mixture of the imine and anhydrous p-toluenesulfonic acid (1 eq.) in anhydrous benzene was refluxed under nitrogen for 3 hours. The cooled mixture was poured into aqueous 20% potassium carbonate solution and extracted with benzene.

Procedure C: To a stirred solution of the imine in anhydrous methylene chloride, a solution of methyl fluorosulfonate (1 eq.) in anhydrous methylene chloride was slowly added at -30°C under nitrogen. The mixture was stirred for 2 hours at -30°C and for 16 hours at room temperature. The solution was saturated with hydrogen chloride gas, stirred for 30 minutes at room temperature and for 3 hours at reflux. The solution was basified with aqueous 20% potassium carbonate solution and extracted with methylene chloride.



a. Ar=3,4,5-Trimethoxyphenyl, R=CH_3
b. Ar=2,3,4-Trimethoxyphenyl, R=H
c. Ar=3-Methoxyphenyl, R=H

Reagents: I, potassium phthalimide, DMF, reflux, 60-65%; II, p-TsOH, $(CH_2OH)_2$, C_6H_6, 85-95%; III, $H_2N\text{-}NH_2$, CH_3OH, reflux, 75-85%; IV, Ar-CHO, C_6H_6, reflux, 78-85%.

SCHEME I

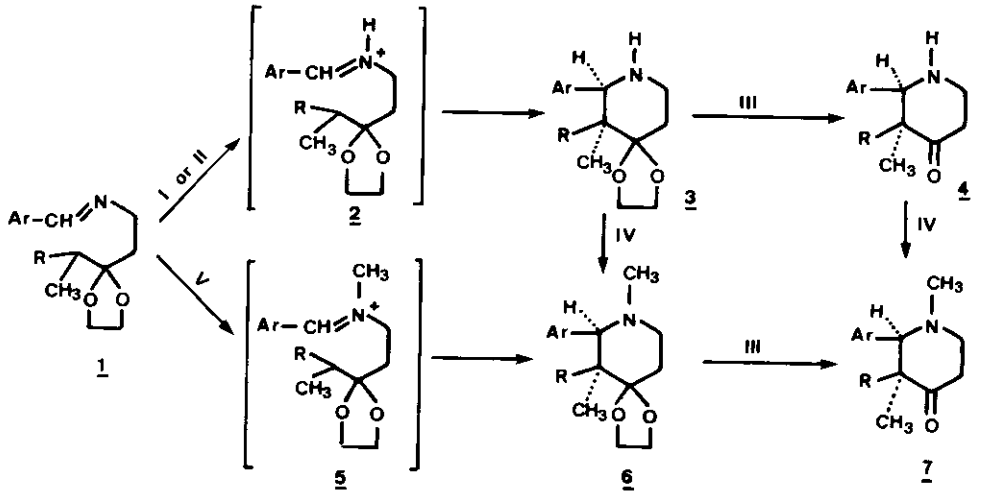
Table I. Acid-catalyzed cyclizations of imino ketals

Imino ketal	Procedure	Product	%Yield	Imino ketal	Procedure	Product	%Yield
1a	A	3a	50	1c	C	6c	50
1a	C(a)	7a	67	8a	A	10a	51(c)
1b	B	3b	87	8a	B	10a	78
1b	C	6b(b)	53	8a	C(a)	14a(d)	60
1c	A(a)	4c	55	8b	A(a)	11b	45(c)
1c	B	3c	58	8b	C(a)	14b(d)	41

(a) Further hydrolysis with 20% HCl in methanol at 60°C. (b) Impurified with 7b. Pure ethylene ketal 6b was obtained after several recrystallizations of the hydrochloride. (c) Yield from reference 2. (d) A 1:1 cis:trans mixture which was separated by recrystallization of the hydrochloride.

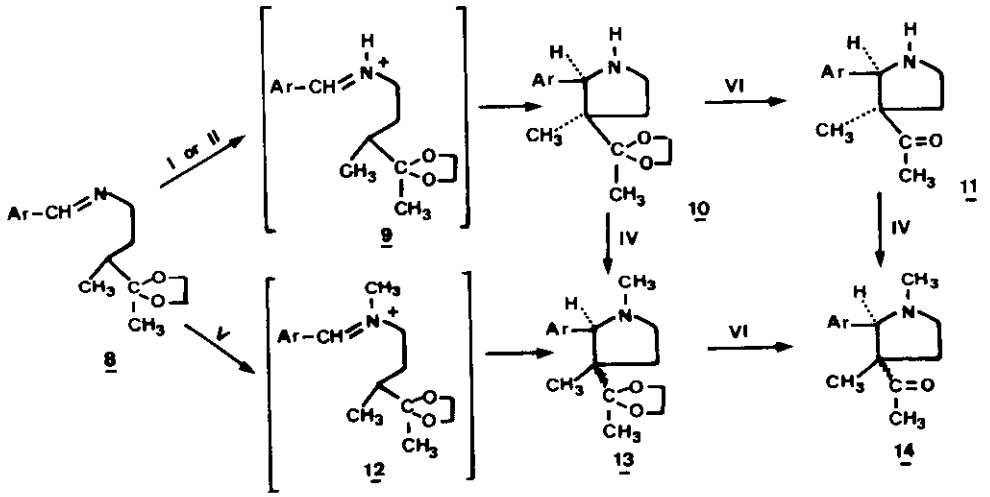
The 4,4-ethylenedioxypiperidines 3 were transformed into the corresponding 1-methyl-4-piperidones 7 by hydrolysis with 2N HCl followed by methylation or, alternatively, by methylation and further hydrolysis (Scheme II)[5]. Similarly, ketals 10 and 13 were converted into the corresponding 1-methyl-3-acetylpyrrolidines 14

SCHEME II



a. Ar=3,4,5-Trimethoxyphenyl, R=CH_3
b. Ar=2,3,4-Trimethoxyphenyl, R=H
c. Ar=3-Methoxyphenyl, R=H

SCHEME III



a. Ar=p-Chlorophenyl
b. Ar=3,4,5-Trimethoxyphenyl

Reagents for schemes II and III: I, HCl gas, CH_2Cl_2, reflux (Procedure A); II, p-TsOH, C_6H_6, reflux (Procedure B); III, 20% HCl, CH_3OH, 60°C; IV, ICH_3, acetone, K_2CO_3 anh., 0°C; V, (i) CH_3OSO_2F, CH_2Cl_2, -30°C; (ii) HCl gas, reflux (Procedure C); VI, 20% HCl, 60°C.

(Scheme III)[5]. In all cyclizations of imino ketals 1 the 2- and 3-substituents of the resulting piperidine ring are in a trans relation (equatorial C_3-methyl group, $\delta \sim 0.7$). In turn, the relative stereochemistry of the 2- and 3-substituents in the pyrrolidines obtained by cyclization of imino ketals 8 depends on the method of cyclization. Procedures A and B (cyclization of a $=\overset{+}{N}H-$ iminium salt) afford pyrrolidines with a cis C_2-H/C_3-methyl relationship, whereas procedure C (cyclization of a $=\overset{+}{N}CH_3-$ iminium salt) gives a 1:1 mixture of cis and trans isomers (see reference 2 for stereochemical assignment).

The above cyclizations are particularly useful when a Mannich condensation between an aldehyde and an amino ketone is not possible. This is the case in the synthesis of 3-acetylpyrrolidines 14 since the required γ-amino ketones spontaneously undergo intramolecular cyclization affording pyrrolines. Furthermore, the use of methyl fluorosulfonate allows a one-pot methylation, cyclization and hydrolysis from an imino ketal to give directly the corresponding N-methyl-4-piperidones or N-methyl-3-acylpyrrolidines.

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5. All compounds gave i.r., ^1H n.m.r. and elemental analyses consistent with the proposed structures.

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