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Yuichi Kanaoka, Masanao Terashima, and Tetsuo Kimura : An Improved Synthesis of Some Ketones as an Intermediate of 3-Substituted Isoquinoline.

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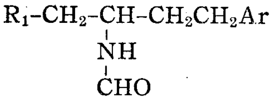
In the course of the synthesis of some 3-substituted tetrahydroisoquinolines, the preparation of ketones such as (VII) and (VIII) was attempted. Spoerri, *et al.*[1,2] had prepared (VII) and (VIII) by the stepwise hydrolysis of (I) and (II), through (III) and (IV), with overall yield of 6% and 13%, respectively.

$$R_1\text{-}\underset{}{\overset{R_2}{\overset{|}{C}}}H\text{-}COCH_2CH_2Ar$$

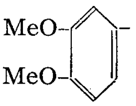
	R_1	R_2
(I)	Ph	CN
(II)	Ar	CN
(III)	Ph	$CONH_2$
(IV)	Ar	$CONH_2$
(V)	Ph	C(OEt)=NH
(VI)	Ar	C(OE)=NH
(VII)	Ph	H
(VIII)	Ar	H

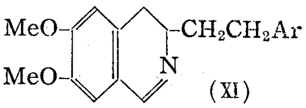


$$R_1\text{-}CH_2\text{-}\underset{\underset{CHO}{|}}{\underset{NH}{\underset{|}{C}}}H\text{-}CH_2CH_2Ar$$

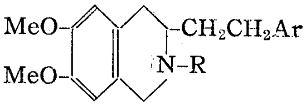
(IX) $R_1=Ph$
(X) $R_1=Ar$

$R_1CH_2COR_2$
(XIV)

Ar = 



(XI)



(XII) R=H
(XIII) R=Me

In the present modification, (VII) and (VIII) were obtained from (I) and (II) via (V) and (VI) by the application of imino-ester method and successive hydrolysis with respective yield of 78% and 80%.

Though Coan, *et al.*[3] used diluted sulfuric acid as hydrolyzing agent in their analogous study to synthesize some propanone derivatives, the present method may offer one route to prepare such ketones as (XIV) in view of the mild conditions and good yield. These ketones are considered to be key intermediates in the synthesis of 3-substituted (R_2) tetrahydroisoquinolines. Thus, (VIII) was cyclized in the usual manner to (XI) via (X), which was then converted to (XII) and (XIII). Cyclization of (IX) was unsuccessful.

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Experimemtal

1-Phenyl-4-(3,4-dimethoxyphenyl)butan-2-one (VII)—1-Phenyl-1-cyano-4-(3,4-dimethoxyphenyl)-butan-2-one (I) was prepared by the method essentially similar to that of Spoerri, *et al.* b.p$_{0.02\sim0.01}$ 180~200°. Yield, 75.6% [lit.,[1] b.p$_2$ 223~228°; yield, 38%]. IR $\nu_{max}^{liq.}$ cm^{-1}: 3390 (enolized OH), 2250 ($C\equiv N$), 2208 (conjugated $C\equiv N$), 1724 (C=O).

A solution of 10 g. of the foregoing nitrile (I) and 2.4 cc. of dehyd. EtOH in 54 cc. of dehyd. $CHCl_3$ was saturated with dry HCl gas under ice-cooling and the reaction mixture was kept in an ice-chest overnight, to which 0.8 cc. of water was added, solvent was removed *in vacuo*. The residual substance was mixed with 10% HCl (53.5cc.) and EtOH (53.5 cc.), and the mixture was refluxed on a steam bath for 4 hr. until the evolution of CO_2 ceased. Alcohol was removed until the reddish oil separated, the oily layer was taken up in benzene, washed with saturated aq. $NaHCO_3$, dried (Na_2SO_4), and evaporated. The residue was purified from benzene-hexane mixture as colorless needles of

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1) P. E. Spoerri, *et al.* : J. Am. Chem. Soc., **67**, 564(1945).

2) R. Carroll, P. E. Spoerri : *Ibid.*, **60**, 2656(1938).

3) S. B. Coan, E. I. Becker : *Ibid.*, **76**, 501(1954).

m.p. 44～46°. Yield, 7.2 g. or 73.3% (reported m.p. 49°). IR $\nu_{\max}^{\text{Nujol}}$: 1703 cm^{-1}(C=O).

1,4-Bis(3,4-dimethoxyphenyl)butan-2-one (VIII)—a) Hydrolysis of the amide (IV): A mixture of AcOH (5.5 cc.) and conc. HCl (55 cc.) was added to 1-cyano-1,4-bis(3,4-dimethoxyphenyl)butan-2-one (7.4 g.) (II) and the whole was kept at room temp. for 4 days. The mixture was poured into water (1 L.), extracted with $CHCl_3$, the extract washed (water), dried (Na_2SO_4), and evaporated. The residue was recrystallized from EtOH to form colorless prisms, m.p. 115° [2-carbamoyl-1,4-bis(3,4-dimethoxyphenyl)butan-2-one]. This amide (1.3 g.) was mixed with 10% HCl (78 cc.) and AcOH (10 cc.), and refluxed in an oil bath for 6 hr. On cooling, the bottom layer was taken up in benzene, washed with water, and evaporated, leaving a slightly brown syrup. The pure product, faint yellow needles, m.p. 73°, was obtained from MeOH. Yield, 0.85 g. or 74%.

b) Hydrolysis of the iminoester: A solution of 3.7 g. of the above-mentioned nitrile (II) in 70 cc. of dehyd. Et_2O-dioxane mixture (1:1) was saturated with dry HCl gas with ice-cooling. The whole was kept in an ice-chest overnight and the theoretical amount of water was added. Evaporating the solvent *in vacuo*, the residue was dissolved in dehyd. benzene, filtered, benzene was removed from the filtrate, and the mixture of 10% HCl (40 cc.) and EtOH (40 cc.) was added to the residual brown oil. The whole was then refluxed on a steam bath for 4 hr., until evolution of CO_2 ceased. Removing the solvent *in vacuo*, separated oil was extracted with benzene, washed (10% K_2CO_3), dried, and evaporated to give (VIII) as faint yellow needles of m.p. 73° (from MeOH). Yield, 2.7 g. or 80%. This was identical with the one obtained by above-described a) method.

N-[1-Benzyl-1-(3,4-dimethoxyphenethyl)methyl]formamide (IX)—A mixture of the ketone (VII) (7.2 g.) and formamide (9.1 g.) was heated under reflux in an oil bath at 180～185° for 11.5 hr. On cooling, 50% EtOH was added to the mixture, which was kept in an ice-chest overnight, separating an almost colorless solid, which were collected on a filter, washed with water, and dried. Purified from EtOAc, it formed colorless needles of m.p. 107.5～108°. Yield, 6.2 g. or 78.5%. *Anal.* Calcd. for $C_{19}H_{23}O_3N$: C, 72.84; H, 7.35; N, 4.47. Found : C, 73.05; H, 7.44; N, 4.52. IR $\nu_{\max}^{\text{Nujol}}$ cm^{-1} : 3360 (N-H), 2735(C-H of formyl), 1661(Amide-I), 1520(Amide-II).

Attempted cyclization of (IX) to give the corresponding isoquinoline derivative with $POCl_3$ or P_2O_5 in various conditions was fruitless.

N-[1-(3,4-Dimethoxybenzyl)-1-(3,4-dimethoxyphenethyl)methyl]formamide (X)—A mixture of (VIII) (30 g.) and formamide (20 g.) was refluxed in an oil bath at 180～183° for 9.5 hr. On cooling, the reaction mixture was diluted with 50% EtOH (ca. 50 cc.), kept in an ice-chest overnight. Separated colorless solid was collected on a filter and recrystallized from MeOH to colorless needles of m.p. 82～83°. Yield, 27.2 g. or 83.1%. *Anal.* Calcd. for $C_{21}H_{29}O_5N$: C, 67.56; H, 7.24; N, 3.57. Found: C, 67.3; H, 7.4; N, 3.5.

3-(3,4-Dimethoxyphenethyl)-6,7-dimethoxy-3,4-dihydroisoquinoline (XI)—(X) (22.3 g.) in dehyd. benzene (180 cc.) was heated with $POCl_3$ (46 cc.) under reflux in an oil bath for 4 hr. After removing solvent and unreacted reagent *in vacuo*, a slightly brown syrup was obtained. On treating with petr. ether to eliminate the excess reagent and then with dehyd. EtOH, it solidified to faint green-colored crystals. This hydrochloride was hygroscopic yellow pillars from dehyd. EtOH, m.p. 145～148°. Yield, 20.6 g. or 80%. The free base, obtained from above-mentioned hydrochloride, was recrystallized from benzene-hexane mixture, forming faint yellowish brown pillars, m.p. 100～101°. *Anal.* Calcd. for $C_{21}H_{25}O_4N$: C, 70.99; H, 7.04; N, 3.94. Found : C, 70.7; H, 7.1; N, 4.25. UV $\lambda_{\max}^{\text{EtOH}}$ mμ (log ε): 279.5(4.11), 310(3.90).

Methosulfate : Faint yellow pillars from MeOH-Et_2O, m.p. 143～145°.

3-(3,4-Dimethoxyphenethyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (XII)—The hydrochloride (XI) (11.5 g.) was hydrogeneted catalytically over Adams' Pt in MeOH (ca. 250 cc.), one molar equivalent of H_2 being absorbed in 4 hr. Colorless crystals, which separated during hydrogenation, were recrystallized from water to form colorless plates, m.p. 228～230°. Yield, 10.4 g. or 90.4%. Free base (XII), which was obtained by basification of foregoing hydrochloride with 10% Na_2CO_3, was purified from benzene-hexane mixture and formed colorless pillars, m.p. 107.5～108.5°. *Anal.* Calcd. for $C_{21}H_{27}O_4N$: C, 70.59; H, 7.56; N, 3.92. Found : C, 71.0; H, 7.4; N, 3.9.

2-Methyl-3-(3,4-dimethoxyphenyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (XIII)— Methosulfate of (XI) was converted to the corresponding methiodide, which was isolated as a brown syrup and not as a solid. This was treated with excess AgCl in MeOH as usual, resulting yellow filtrate was hydrogenated catalytically over Adams' Pt, one molar equivalent of H_2 being absorbed. MeOH was evaporated, leaving a slightly colored syrup, which was again dissolved in water and basified with K_2CO_3. Free base (XIII) was separated on a filter, recrystallized from benzene-hexane mixture to form colorless needles, m.p. 87～88°, which was not depressed on admixture with an authentic sample[4] prepared by the reducton of corresponding 2-formyl derivative.

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[4] Y. Kanaoka : This Bulletin, **7**, 657(1959).