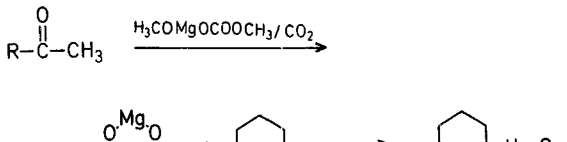
A New General Method of Preparation of 2-Piperidylmethyl and 2-Pyrrolidinylmethyl Ketones from Methyl Ketones; A Modification of the Schöpf Reaction

J. Martin Grisar, George P. Claxton, and Kenneth T. Stewart

Merrell-National Laboratories, Division of Richardson-Merrell Inc., Cincinnati, Ohio 45215, U.S.A.

Reported here is a new method of synthesizing piperidylmethyl and pyrrolidinylmethyl ketones. It consists of reaction of internal enolate magnesium salts of β-keto-acids in dimethylformamide (readily obtained from methyl ketones and magnesium methyl carbonate)[1,2] with 2,3,4,5-tetrahydropyridine[3,4] or 3,4-dihydro-2*H*-pyrrole[5], generated *in situ* from the trimers. This reaction is a modification of the Schöpf reaction[6].



Schöpf and coworkers explored the reaction of β-keto-acids with 2,3,4,5-tetrahydropyridine under "physiological" conditions to establish pathways of plant alkaloid biogenesis[6,7]. Synthetic application of this reaction, however, has been limited due to low water solubility of many β-keto-acids[8,9,10] and the requirement to maintain a pH below 11 to avoid self-condensation of 2,3,4,5-tetrahydropyridine[10,11]. Both these limitations are overcome by our new modification.

A typical reaction is described in the experimental part. Compounds prepared by this method are listed in the Table. The reactions with acetophenones substituted by hydroxy-, amino-, carboxy-, sulfo-, and nitro groups were unsuccessful, and only low yields were obtained with cyano- and dimethylaminosulfonyl-substituted acetophenones. Several attempts to carry out the reaction with 4,4'-methylene-bis-acetophenone, 4,4'-(1,6-hexanediyl)-bis-acetophenone, and 2,7-diacetylfluorene failed. Aromatic alkyl, alkoxy, thioalkyl, and chlorine substitution does not interfere with the reaction.

Of particular interest are compounds **5**, **6**, and **7** that contain one or more olefinic C=C double bonds since these products cannot be prepared by an alternative method using 2-pyridylmethyllithium followed by reduction of the pyridine ring[12]. We also explored the reaction with 2-, 3-, and 4-acetylpyridine and of 4-(4-pyridylmethyl)- and 4-(2-pyridylmethyl)-acetophenone but were able to obtain the desired product in only one case (**8**, 8%). The influence of steric hindrance was explored with the preparation of **9** that required forced conditions.

The use of 3,4-dihydro-2*H*-pyrrole resulted in formation of compounds **10** and **11**, while 3,4-dihydroisoquinoline and acetophenone gave **12**[13], and 6,7-dimethoxy-3,4-dihydroisoquinoline and 4-methoxyacetophenone gave **13**. 6-Methyl-2,3,4,5-tetrahydropyridine[14] and 5-(4-fluorophenyl)-3,4-dihydro-2*H*-pyrrole[15] were found not to undergo the condensation indicating that substitution at the imine C-atom interferes with condensation.

The reaction with ketones other than methyl ketones was also explored. The following compounds did not yield condensation products with 2,3,4,5-tetrahydropyridine and were recovered unchanged: 1-indanone, 2-indanone, 1-tetralone, 1,2-bis[4-methoxyphenyl]-1-oxoethane, 1,3-dioxo-1-phenylbutane, and 1,3-dioxo-1,3-diphenylpropane. This is surprising since 1-indanone and 1-tetralone are known to form β-keto-acids with magnesium methyl carbonate[2,16]. These experiments indicate that the condensation of Δ^1-pyrroline, 2,3,4,5-tetrahydropyridine, and other cyclic imines with chelates obtained by reaction of ketones with magnesium methyl carbonate is limited to the use of methyl ketones.

1,1-Diphenyl-2-oxo-3-(2-piperidyl)-propane Hydrochloride (4):
Magnesium methyl carbonate (1.2 mol, 2 *M* in dimethylformamide) was heated to 120° under carbon dioxide, 63.0 g (0.3 mol) of 1,1-diphenylacetone were added, and the mixture was stirred at 120° for 4 h under a stream of nitrogen to allow methanol that is formed to escape. After the mixture was cooled and saturated with carbon dioxide, 2,3,4,5-tetrahydropyridine (30.0 g, 0.36 mol; as α-trimer) was added, and the mixture was stirred at room temperature for 6 days in an atmosphere of carbon dioxide. The mixture was poured into conc. hydrochloric acid (375 ml) and ice, the resulting solution was extracted with dichloromethane, the extract was dried with sodium sulfate, and the solvent was evaporated to give 101.3 g of oil. The material crystallized from isopropanol, a second crop was obtained, and the combined crops were again recrystallized from isopropanol-water; yield: 37.9 g (37%); m.p. 197–199° (dec).

1-Adamantanyl 2-Piperidylmethyl Ketone Hydrochloride (9):
Only a 6% yield was obtained when the reaction was carried out as described in the preceding example. To overcome the steric hindrance, chelate formation was extended to a period of 28 h at 120° under a stream of nitrogen, and the condensation was extended to a period of 5 days at room temperature under carbon dioxide.

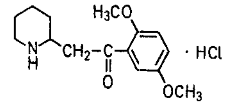
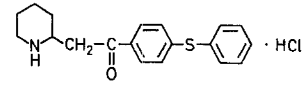
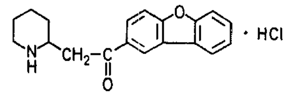
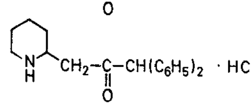
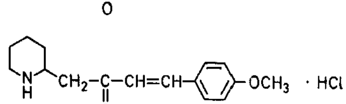
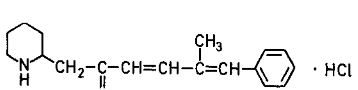
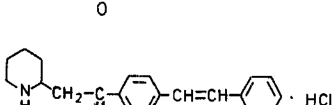
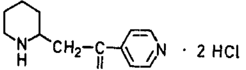
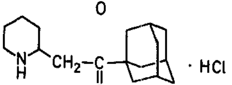
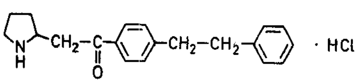
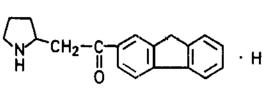
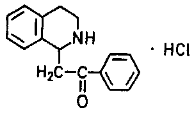
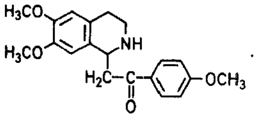
4-(2-Phenylethyl)-ω-(2-pyrrolidinyl)-acetophenone Hydrochloride (10):
Magnesium methyl carbonate (0.4 mol, 2 *M* in dimethylformamide) was heated to 120° under carbon dioxide and 4-(2-phenylethyl)-acetophenone (22.4 g, 0.1 mol) was added. The mixture was stirred at 120° for 4 h under a stream of nitrogen to allow the methanol that is formed to escape. The mixture was then allowed to cool under carbon dioxide, Δ^1-pyrroline (8.3 g, 0.12 mol) (probably as trimer) was added and stirring was continued at room temperature under carbon dioxide for 40 h. The mixture was poured into concentrated hydrochloric acid (200 ml) and ice (800 g), the precipitate was collected, and recrystallized twice from isopropanol-water; yield: 20.7 g (63%).

1-Phenacyl-1,2,3,4-tetrahydroisoquinoline Hydrochloride (12):
Magnesium methyl carbonate (0.27 mol, 2.2 *M* in dimethylformamide) was heated to 120° under carbon dioxide, acetophenone (8.0 g, 0.067 mol) was added, and the mixture was stirred at 120° for 4 h under a stream of nitrogen to allow the methanol that is formed to escape. The mixture was then allowed to cool under carbon dioxide, 3,4-dihydroisoquinoline hydrochloride (12.4 g, 0.08 mol) was added, and stirring was continued at room temperature in an atmosphere of carbon dioxide for 40 h. The mixture was poured into cold 3 *N* hydrochloric acid, the product extracted into dichloromethane, the extract dried with sodium sulfate, and the solvent evaporated. The residue was recrystallized from isopropanol; yield: 11.5 g (60%).

2,3,4,5-Tetrahydropyridine Trimer:
Acetic acid (120 g, 2.0 mol) was added dropwise to piperidine (170 g, 2.0 mol) with cooling to keep the temperature below 10°. This solution was added dropwise over 1 h to an aqueous solution of calcium hypochlorite [$Ca(ClO)_2$, 2.2 mol)] at 0° to −5° and stirring was continued for 15 min. The mixture was extracted

with ethyl ether, the extract was dried (Na_2SO_4), and most of the ether was evaporated. (*Caution: N*-chloropiperidine tends to decompose spontaneously. Allow ~200 ml of ether to remain and avoid temperatures over 60°). This solution was added dropwise over 2.5 h to a vigorously stirred, refluxing solution of potassium hydroxide (264 g, 4.0 mol) in anhydrous ethanol (1250 ml) and stirring was continued for 2 h. The mixture was allowed to stand at room temperature during which time tetrahydropyridine trimerized. Precipitated potassium chloride was filtered off, washed with anhydrous ethanol, and the ethanol was distilled from the filtrate. (The distillate was saved since it frequently contains product that co-distilled as monomer). The residue was dissolved in water (750 ml) (to which the previously collected potassium chloride was added), extracted with ether, the extract was dried ($MgSO_4$), and the solvent evaporated. The product was crystallized from acetone; yield: 70–107 g (42–64%); m.p. 58–61° (Ref.[3,4], m.p. 60–62° for α-isomer, m.p. 70–73° for β-isomer; the β-isomer, usually obtained with m.p. 40–68°, can be converted to the more stable α-isomer by recrystallization from acetone, containing 2% water). The material was stored in a closed container over potassium hydroxide and was stable for over one year.

Table. 2-Piperidylmethyl, 2-Pyrrolidylmethyl, and 1-Tetrahydroisoquinolylmethyl Ketones

	Products	Yield[a] (%)	m.p.[b]	Elemental Analyses	I.R. (KBr) ν_{max} cm^{-1}	U.V. λ_{max} nm (ε)	^1H-N.M.R. (DMSO-d_6) δ ppm
1		75	186–188° (dec)	$C_{15}H_{21}NO_3 \cdot HCl$ (299.8) calc. C 60.1 H 7.4 N 4.7 found 60.1 7.4 4.7	1680	223[c] (16200)	7.19 (s, 3H), 3.90 (s, 3H), 3.77 (s, 3H)
2		50	149–151°	$C_{19}H_{21}NOS \cdot HCl$ (347.9) calc. C 65.6 H 6.4 Cl 10.2 found 65.8 6.3 10.0	1690	241[c] (8950), 310 (20000)	
3		32	218–220°	$C_{19}H_{19}NO_2 \cdot HCl$ (329.8) calc. C 69.2 H 6.1 Cl 10.7 found 69.1 6.1 10.5	1678	238[c] (31600), 256 (34500)	
4		37	197–199° (dec)	$C_{20}H_{23}NO \cdot HCl$ (329.9) calc. C 72.8 H 7.3 N 4.3 found 72.8 7.4 4.2	1700	260[c] (560), 292 (290)	5.51 (s, 1H)
5		43	188–189°	$C_{16}H_{21}NO_2 \cdot HCl$ (295.8) calc. C 65.0 H 7.5 N 4.7 found 65.0 7.5 4.7	1640	326[d] (26000)	7.72 (d, 2H, J=9 Hz), 7.71 (d, 1H, J=17 Hz), 7.01 (d, 2H, J=9 Hz), 6.80 (d, 1H, J=17 Hz), 3.83 (s, 3H)
6		48	179–180°	$C_{18}H_{23}NO \cdot HCl$ (305.8) calc. C 70.7 H 7.9 N 4.6 found 70.4 7.8 4.6	1660, 750, 695	328[c] (28200)	($CDCl_3$, CF_3COOD) 7.53 (d, 1H, J=16 Hz), 7.40 (s, 5H), 7.03 (s, 1H), 6.32 (d, 1H, J=16 Hz), 2.09 (s, 3H)
7		57	227–229°	$C_{21}H_{23}NO \cdot HCl$ (341.9) calc. C 73.8 H 7.1 N 4.1 found 73.8 7.0 4.0	1683	234[c] (3500), 332 (37700)	
8		8	202–205° (dec)	$C_{12}H_{16}N_2O \cdot HCl$ (277.2) calc. C 52.0 H 6.6 N 10.1 found 51.7 6.7 10.0	1690	221[c] (8400), 266 (1760), 283 (1920)	
9		37	240–241°	$C_{17}H_{27}NO \cdot HCl$ (297.9) calc. C 68.6 H 9.5 N 4.7 found 68.8 9.7 4.7	1701		
10		63	200–201° (dec)	$C_{20}H_{23}NO \cdot HCl$ (317.82) calc. C 72.8 H 7.3 N 4.3 found 72.7 7.3 4.2	1670	275[c] (18600)	
11		65[f]	243–244° (dec)	$C_{19}H_{19}NO \cdot HCl$ (313.8) calc. C 72.7 H 6.4 N 4.5 found 72.8 6.4 4.4	1650	315[c] (24400)	
12		60[f]	169–170°	$C_{17}H_{17}NO \cdot HCl$ (287.8) calc. C 71.0 H 6.3 N 4.9 found 70.9 6.2 4.8	1670	245[c] (15000)	5.11 (m, 1H)
13		62	157–159° (dec)	$C_{20}H_{23}NO_4 \cdot HCl$ (377.9) calc. C 63.6 H 6.4 N 3.7 found 63.4 6.4 3.6	1665	283[d] (29100)	5.0 (m, 1H), 3.87 (s, 3H), 3.76 (s, 3H), 3.69 (s, 3H)

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[a] Yields refer to analytically pure product unless otherwise indicated.

[b] Melting points are corrected and were determined in a Thomas Hoover capillary melting point apparatus. All compounds were recrystallized from isopropanol or isopropanol/water.

[c] in methanol.

[d] in ethanol.

[e] in chloroform

[f] yield includes a second crop.

[g] Ref.[13].

3,4-Dihydro-2*H*-pyrrole Trimer:

A solution of pyrrolidine (71.1 g, 1 mol) in ether (1000 ml) was added to *N*-chlorosuccinimide (140.3 g, 1.05 mol) and the mixture was stirred at room temperature under nitrogen for 24 h. A sufficient amount of water was added to dissolve the solids, the ether phase was separated and dried with sodium sulfate, and the ether was evaporated under nitrogen. (*Caution! N*-chloropyrrolidine tends to decompose spontaneously. Allow ~ 100 ml of ether to remain and avoid temperatures above 60°). this solution was added dropwise over 1.5 h to vigorously stirred, ice-cooled 2 *N* methanolic potassium hydroxide (1000 ml) and stirring was continued for 1 h. The methanol was then evaporated at 25–30° at reduced pressure of 200 torr, water was added, and the product was extracted continuously with ether. The solvent and the product were distilled under nitrogen at atmospheric pressure and fractions of b.p. 81–90° (38.0 g) and 91–97° (27.0 g) were collected (94% yield); the second fraction warmed up spontaneously, presumably due to exothermic trimerization, since it showed almost no I.R. absorption at 1650 cm^{-1}, as did the first fraction. Both fractions were used successfully in reactions with chelates of ketones with magnesium methyl carbonate.

6-Methyl-2,3,4,5-tetrahydropyridine:

The material was prepared by the procedure of Grundon and Reynolds[14].

I.R. (neat): $\nu_{max} = 1670\ cm^{-1}$;

^{1}H-N.M.R. ($CDCl_3$): $\delta = 3.55$ (m, 2H, $=N-C\underline{H}_2-$), 2.12 (m, 2H, $-C\underline{H}_2-C=N-$), 1.90 (t, $J = 1.75$ Hz $C\underline{H}_3-C=N-$), 1.63 ppm (m, 4H).

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[1] M. Stiles, H. L. Finkbeiner, *J. Amer. Chem. Soc.* **81**, 505 (1959).

[2] M. Stiles, *J. Amer. Chem. Soc.* **81**, 2598 (1959).

[3] C. Schöpf, A. Komzak, F. Braun, E. Jacobi, *Liebigs Ann. Chem.* **559**, 1 (1948).

[4] C. Schöpf, H. Arm, H. Krimm, *Chem. Ber.* **84**, 690 (1951).

[5] D. W. Fuhlhage, C. A. VanderWerf, *J. Amer. Chem. Soc.* **80**, 6249 (1958).

[6] C. Schöpf, F. Braun, K. Burkhardt, G. Dummer, H. Müller, *Liebigs Ann. Chem.* **626**, 123 (1959).

[7] C. Schöpf, *Angew. Chem.* **61**, 31 (1949).

[8] J. van Noordwijk, J. J. Mellink, B. J. Visser, J. H. Wisse, *Rec. Trav. Chim.* **82**, 763 (1963).

[9] J. H. Wisse, H. de Klonia, B. J. Visser, *Rec. Trav. Chim.* **83**, 1265 (1964).

[10] J. H. Wisse, H. de Klonia, B. J. Visser, *Rec. Trav. Chim.* **85**, 865 (1966).

[11] C. Schöpf, F. Braun, A. Komzak, *Chem. Ber.* **89**, 1821 (1956).

[12] G. P. Claxton, E. M. Roberts, J. M. Grisar, R. W. Fleming, *J. Med. Chem.* **15**, 500 (1972).

[13] *German Patent (DBP)* 1470084 (1968), E. Merck AG; *C. A.* **70**, 47319 (1969).

[14] M. F. Grundon, B. E. Reynolds, *J. Chem. Soc.* **1964**, 2445.

[15] S. S. Cheng, C. Piantadosi, J. L. Irvin, *J. Pharm. Sci.* **57**, 1910 (1968).

[16] R. W. Griffin, J. D. Gass, M. A. Berwick, R. S. Shulman, *J. Org. Chem.* **29**, 2109 (1964).