John S. Ward* and Leander Merritt

Lilly Research Laboratories, Lilly Corporate Center,
Indianapolis, Indiana 46285

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Good yields of arecolone and isoarecolone were obtained by treating the *N,O*-dimethylamides of arecaidine and isoarecaidine, respectively, with methylmagnesium chloride. Other substituted arecolones were synthesized by this same strategy.

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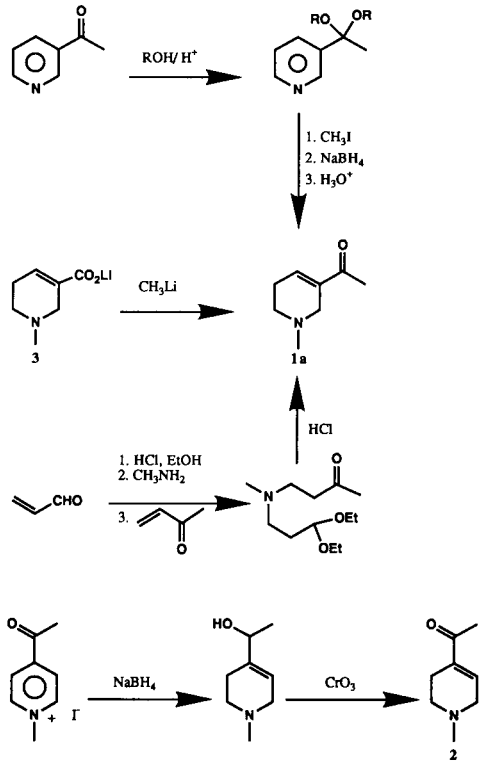
Arecolone, **1a**, is an important intermediate in the syntheses of cholinergic agonists and antagonists as well as other pharmaceuticals [1-3]. A reliable large scale synthesis of arecolone (Scheme 1) has been developed that starts from 3-acetylpyridine and in five steps, involving a protection and deprotection scheme to protect the ketone function, produces **1a** in 35% yield [2]. More modest yields of **1a** have been obtained by the method of Wohl and Prill starting from acrolein [4]. Small quantities of **1a** have also been obtained by the reaction of the lithium salt of arecaidine with methyllithium [1]. While the first approach described produces acceptable quantities of **1a**, this scheme is not convergent with respect to producing a series of 1,2,5,6-tetrahydropyridyl ketones such as compounds **1b-i**.

Scheme 1

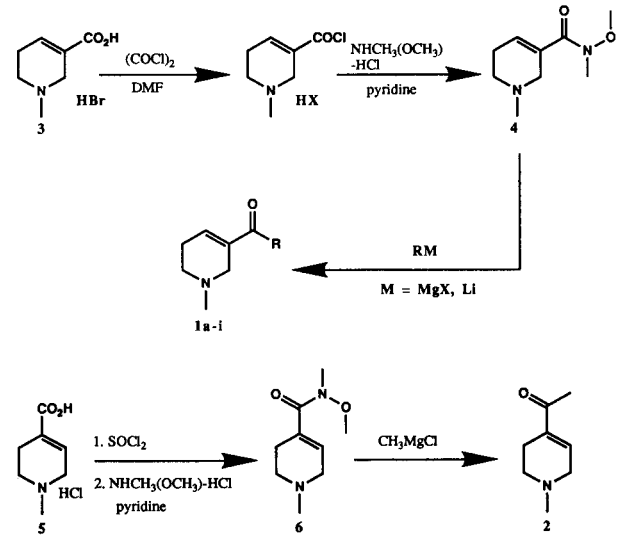



Isoarecolone, **2**, a nicotinic agonist and intermediate in the syntheses of other nicotinic agonists [1,5], has been synthesized (Scheme 1) in low yield by reducing the corresponding quaternized 4-acetylpyridine to 4-(2-hydroxyethyl)-1-methyl-1,2,3,6-tetrahydropyridine followed by oxidation of the secondary alcohol to the ketone [1]. This too is a rather indirect synthetic pathway and lacks the convergence that would be desirable in producing a series of 1,2,-3,6-tetrahydropyridyl ketones.

This paper reports convenient new synthetic routes to **1a** and **2** that produce these compounds in improved yields. In addition these routes are equally applicable to the syntheses of series of 1,2,5,6-tetrahydropyridyl- and 1,2,3,6-tetrahydropyridyl ketones.

These synthetic approaches (Scheme 2) employed the ketone synthesis developed by Weinreb and Nahm [6]. Oxalyl chloride, in the presence of a catalytic amount of dimethylformamide, converted commercially available arecaidine hydrobromide, **3**, to its acid chloride. After removal of excess oxalyl chloride, the acid chloride reacted with *N,O*-dimethylhyroxylamine to give the corresponding amide **4** in 88% yield. This amide could be purified by hplc or isolated as its hydrochloride salt, but was normally used in subsequent reactions without further purification.

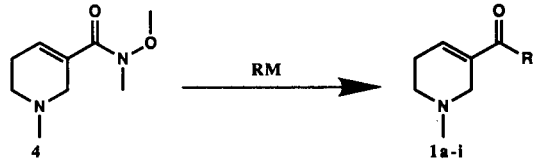
Scheme 2

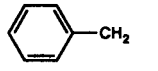
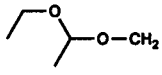
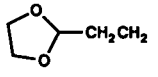



In the presence of one to three equivalents of organolithium or Grignard reagent at 0°, amide **4** gave

arecolones **1a-i** in the yields shown in Table I. Reactive Grignard reagents gave good yields of arecolones, for example **1a,f**, whereas less reactive Grignard reagents produced poorer results. The low yields obtained using the less reactive Grignard reagents could be improved by conducting the reaction at ambient temperature or by using the corresponding organolithium reagent. For example, *n*-butylmagnesium chloride gave **1d** in 15% and 35% yield at 0° and ambient temperature, respectively, while *n*-butyllithium produced **1d** in 54% yield. Similarly, phenylmagnesium chloride gave **1e** in 30% yield whereas phenyllithium gave **1e** in 63% yield.

Table I




| 1 | R | M | Equivalents of RM | Temp °C | % Yield |
|---|---|---|---|---|---|
| a | $CH_3$ | MgCl | 2 | 0 | 79 |
| b | $CH_3CH_2$ | MgBr | 3 | 0 | 5 |
| c | $CH_3CH_2CH_2$ | MgCl | 2.2 | 0 | 11 |
| d | $CH_3CH_2CH_2CH_2$ | MgCl | 2 | 0 | 15 |
| | $CH_3CH_2CH_2CH_2$ | MgCl | 1.5 | 22 | 35 |
| | $CH_3CH_2CH_2CH_2$ | Li | 1.75 | 0 | 54 |
| e |  | MgCl | 1.6 | 0 | 30 |
| | | Li | 1.75 | 0 | 63 |
| f |  | MgCl | 1.85 | 0 | 43 |
| g |  | Li | 9 | 0 | 60 |
| h |  | Li | 1 | -78 | 46 |
| i |  | Li | 1.4 | -78 | 44 |

Isoarecolone, **2**, was conveniently produced by converting 1,2,3,6-tetrahydropyridine-4-carboxylic acid hydrochloride, **5**, obtained from commercially available ethyl ester in 70% yield, to its acid chloride with thionyl chloride and treating the acid chloride with *N,O*-dimethylhydroxylamine to give the Weinreb amide **6** in 88% yield. Amide **6**, in the presence of three equivalents of methylmagnesium chloride in tetrahydrofuran, gave isoarecolone **2**, isolated in 71% yield as its hydrochloride salt.

The commercial availability of starting materials and the good, but unoptimized, yields of arecolone and isoarecolone obtained from these reaction seqences show that these approaches are improved alternatives to the synthetic pathways previously used to obtain these compounds. In addition, the convergence of these approaches with respect to the production of a variety of substituents attached to the tetrahydropyridyl ketones should aid the development of structure-activity relationships in pharmaceuticals employing these compounds as intermediates.

## EXPERIMENTAL

Melting points were determined on a Mel-Temp apparatus and are uncorrected. A Waters PrepLC/500A using PrepPAK-500 silica gel cartridges, with the solvents specified, were used for hplc separations. Merck F254 silica gel plates were used for tlc. All reactions, exclusive of extraction procedures, were conducted under an argon atmosphere. A QE300 was employed for nmr measurements using the solvents described. No particular attempt was made to optimize reaction conditions for most of the reactions described.

*N*-Methoxy-1-,*N*-dimethyl-1,2,5,6-tetrahydro-3-pyridinecarboxamide (**4**).

Finely ground arecaidine hydrobromide, **3**, 47 g (0.21 mole) was suspended in a mixture of 1 liter of dichloromethane and 10 drops of dimethylformamide. To the mixture was added 50 g (0.39 mole) of oxalyl chloride and the reaction mixture was heated to a gentle reflux for 8 hours. After stirring overnight, the solvent was evaporated, another 500 ml of dichloromethane was added, and the solvent evaporated. The residue was suspended in 1 liter of dichloromethane and 23.25 g (0.27 mole) of *N,O*-dimethylhydroxylamine hydrochloride was added. The reaction mixture was cooled to 0° and 54 ml of pyridine was added dropwise with stirring. After the addition, the cooling was removed and the reaction stirred 4 hours. The solvent was evaporated and the residue dissolved in 100 ml of ice-water. The *p*H was adjusted to 10 with 5 *N* sodium hydroxide and the mixture extracted 3x with 150 ml of dichloromethane. The organic extracts were washed with brine, dried, and evaporated to give a yellow liquid. The liquid was treated with 200 ml of ether, the mixture filtered, and the solvent evaporated. After thorough drying *in vacuo* to remove residual pyridine, 34.3 g of **4** was obtained (88% yield) of sufficient purity to be used in subsequent reactions. Analytically pure **4**-HCl was obtained by treating the crude material with hydrochloric acid in ethyl acetate, mp 134-135°; pmr (deuterium oxide): ppm 2.7 (2H, m), 3.01 (3H, s), 3.35 (3H, s), 3.2-3.7 (2H, br m), 3.75 (3H, s), 3.8-4.2 (2H, br m), 6.65 (1H, m).

*Anal.* Calcd. for $C_9H_{16}N_2O_2$-HCl: C, 48.98; H, 7.76; N, 12.69. Found: C, 49.20; H, 7.95; N, 12.57.

General Synthesis of Arecolones **1** from **4** and Grignard Reagents.

A solution of 1.85 g (0.01 mole) of **4** in 20 ml of dry tetrahydrofuran was cooled to 0° as a tetrahydrofuran or ether solution of more than one equivalent of the specified Grignard reagent was added. After 1.5 hours, the reaction mixture was poured into 30 ml ice-water containing enough 5 *N* hydrochloric acid to neutralize the amount of Grignard reagent used. The mixture was ex-

tracted 3x with 25 ml of dichloromethane and the combined organic extracts washed with brine. After drying and evaporating the solvent, the crude arecolone was further purified as described in the specific examples.

1-(1,2,5,6-Tetrahydro-1-methyl-3-pyridinyl)ethanone (**1a**, Arecolone).

From 1.85 g (0.01 mole) of **4** and 7 ml (0.021 mole) of 3 *M* methylmagnesium chloride in tetrahydrofuran was obtained 1.1 g of **1a** as a yellow liquid, 79% yield. The hydrochloride salt **5a**-HCl crystallized from 2-propanol, mp 213-214°; pmr (deuterium oxide): ppm 2.41 (3H, s), 2.79 (2H, m), 3.0 (3H, s), 3.13-3.3 (1H, m), 3.55-3.8 (2H, m), 4.1-4.25 (1H, m), 7.35 (1H, m).

*Anal.* Calcd. for $C_8H_{13}NO$-HCl: C, 54.70; H, 8.03; N, 7.77. Found: C, 54.78; H, 7.74; N, 7.92.

1-(1,2,5,6-Tetrahydro-1-methyl-3-pyridinyl)-1-propanone (**1b**).

From 1.85 g (0.01 mole) of **4** and 15 ml (0.03 mole) of 2 *N* ethylmagnesium bromide in tetrahydrofuran was obtained as a yellow liquid that was purified by hplc eluting with an 8 liter gradient starting with dichloromethane and going to 7.5% methanol-1% ammonium hydroxide. The hydrochloride salt **1b**-HCl crystallized from ethyl acetate as the dihydrate, 0.12 g, 5% yield, mp 112-114°; pmr (deuterium oxide): ppm 1.05 (3H, t), 2.75 (2H, m), 2.82 (2H, q), 3.0 (3H, s), 3.12-3.3 (1H, m), 3.5-3.85 (2H, m), 4.18 (1H, m), 7.35 (1H, m).

*Anal.* Calcd. for $C_9H_{15}NO$-$2H_2O$-HCl: C, 47.89; H, 8.93; N, 6.21. Found: C, 48.17; H, 8.65; N, 6.19.

1-(1,2,5,6-Tetrahydro-1-methyl-3-pyridinyl)-1-butanone (**1c**).

From 1.85 g (0.01 mole) of **4** and 8 ml (0.022 mole) of 2.8 *M* propylmagnesium chloride in ether was obtained a yellow oil that was purified by hplc eluting with an 8 liter gradient beginning with dichloromethane and going to 7.5% methanol-1% ammonium hydroxide. The liquid obtained was treated with dry hydrochloric acid in ether and the resulting solid recrystallized from ethyl acetate to give 0.22 g of **1c**-HCl, 11% yield, mp 106-108°; pmr (deuterium oxide): ppm 0.9 (3H, t), 1.62 (2H, m), 2.78 (4H, m), 3.0 (3H, s), 3.2-4.2 (4H, m), 7.35 (1H, m).

*Anal.* Calcd. for $C_{10}H_{17}NO$-HCl: C, 58.96; H, 8.91; N, 6.88. Found: C, 58.66; H, 8.93; N, 6.77.

1-(1,2,5,6-Tetrahydro-1-methyl-3-pyridinyl)-1-pentanone (**1d**).

From 1.85 g (0.01 mole) of **4** and 10 ml (0.02 mole) of 2 *M* *n*-butylmagnesium chloride in tetrahydrofuran was obtained as a yellow oil that was purified by hplc as in example **1b**. The 0.4 g of liquid obtained was converted to an oxalate salt, **1d**-oxalate, that crystallized from ethanol as a white solid, 0.4 g, 15% yield, mp 175-176°; pmr (deuterium oxide): ppm 0.9 (3H, t), 1.32 (2H, m), 1.58 (2H, m), 2.75 (4H, m), 3.0 (3H, s), 3.25 (1H, m), 3.62 (1H, m), 3.7 (1H, d), 4.19 (1H, d), 7.35 (1H, m).

*Anal.* Calcd. for $C_{11}H_{19}NO$-$C_2H_2O_4$: C, 57.55; H, 7.80; N, 5.16. Found: C, 57.18; H, 7.75; N, 5.15.

Preparation of **1d** from Butylmagnesium Chloride at Ambient Temperature.

A solution of 1.85 g (0.01 mole) of **4** in 20 ml of dry tetrahydrofuran was stirred at ambient temperature during dropwise addition of 7.5 ml (0.015 mole) of 2 *M* *n*-butylmagnesium chloride in tetrahydrofuran. The reaction became warm during the addition. After the reaction had cooled to ambient temperature, the reaction was poured in 30 ml of ice-water containing 4 ml of 5 *N* hydrochloric acid. The mixture was extracted 3x with 25 ml of dichloromethane, the extracts washed with brine, dried, and the solvent evaporated to give a yellow oil. Purification by hplc as in example **1b** gave 0.75 g of yellow oil that was converted to 0.94 g of **1d**-oxalate, 35% yield.

Preparation of **1d** from **4** and Butyllithium.

A solution of 1.85 g (0.01 mole) of **4** in 20 ml of tetrahydrofuran was cooled to 0° as 11 ml (0.0175 mole) of 1.6 *M* *n*-butyllithium in hexane was added dropwise. After 30 minutes the excess butyllithium was destroyed with 1 ml of 2-propanol followed by 17 ml of 1 *N* hydrochloric acid. The volatile organics were evaporated and the aqueous residue extracted 3x with 25 ml of dichloromethane. The extracts were dried and the solvent evaporated to give 1.6 g of a yellow liquid that was converted to 1.47 g of **1d**-oxalate, 54% yield.

1-(1,2,5,6-Tetrahydro-1-methyl-3-pyridinyl)phenone (**1e**).

From 4 g (0.022 mole) of **4** in 100 ml of tetrahydrofuran and 18 ml (0.036 mole) of 2 *M* phenylmagnesium chloride in ether was obtained as a yellow oil that was purified by hplc using an 8 liter gradient starting with dichloromethane and going to 10% methanol. The 1.55 g of **1e** obtained as a yellow liquid was converted to the tan solid **1e**-oxalate, 1.9 g, after crystallization from ethanol, 30% yield, mp 157-158°; pmr of **1e** (deuteriochloroform): ppm 2.48 (5H, s), 2.58 (2H, t), 3.35 (2H, m), 6.65 (1H, m), 7.35-7.67 (5H, m).

*Anal.* Calcd. for $C_{13}H_{15}NO$-$C_2H_2O_4$: C, 61.85; H, 5.88; N, 4.81. Found: C, 61.61; H, 6.04; N, 4.72.

Preparation of **1e** from **4** and Phenyllithium.

A solution of 1.85 g (0.01 mole) of **4** in 20 ml of tetrahydrofuran was cooled to 0° as 9.8 ml (0.0175 mole) of 1.8 *M* phenyllithium in cyclohexane-ether was added dropwise. After 35 minutes the reaction was quenched with 1 ml of 2-propanol followed by 17.5 ml of 1*N* hydrochloric acid. Further processing as in example **5d** provided 1.84 g of **1e**-oxalate, 63% yield.

1-(1,2,5,6-Tetrahydro-1-methyl-3-pyridinyl)-2-phenylethanone (**1f**).

From 2 g (0.0109 mole) of **4** and 10 ml (0.02 mole) of 2 *M* benzylmagnesium chloride in tetrahydrofuran was obtained as a yellow liquid that was purified by hplc as in example **1e** to give 1 g of **1f** as a clear yellow liquid, 43% yield; pmr (deuteriochloroform): ppm 2.41 (3H, s), 2.41-2.57 (4H, m), 3.17 (2H, m), 3.97 (2H, s), 7.05 (1H, m), 7.15-7.38 (5H, m). The oxalate salt crystallized from 2-propanol to give 1.23 g of white solid **1f**-oxalate, mp 82-84°.

*Anal.* Calcd. for $C_{14}H_{17}NO$-$C_2H_2O_4$: C, 62.94; H, 6.27; N, 4.59. Found: C, 62.75; H, 6.21; N, 4.59.

1-(1,2,5,6-Tetrahydro-1-methyl-3-pyridinyl)-2-butyn-1-one (**1g**).

A solution of 3.15 g (0.017 mole) of **4** in 75 ml of dry tetrahydrofuran was cooled to 0° as 7 g (0.152 mole) of 1-lithiopropyne was added in 1 g portions in 5 minute intervals. After addition, the reaction ws stirred 20 minutes then carefully poured into 100 ml of an ice-brine mixture. The mixture was extracted 3x with 50 ml of dichloromethane, the extracts washed with brine, dried, and the solvent evaporated to give 2.7 g of a yellow liquid. The liquid was converted to 2.6 g of **1g**-oxalate, 60% yield, mp 147° dec; pmr (deuterium oxide): ppm 2.08 (3H, s), 2.8 (2H, m), 3.0 (3H, s), 3.17-3.27 (1H, m), 3.61 (1H, m), 3.75 (1H, d), 4.2 (1H, d), 7.61 (1H, m).

*Anal.* Calcd. for $C_{10}H_{13}NO\text{-}C_2H_2O_4$: C, 56.71; H, 5.97; N, 5.53. Found: C, 56.65; H, 5.80; N, 5.35.

(+ −)-2-(1-Ethoxyethoxy)-1-(1,2,5,6-tetrahydro-1-methyl-3-pyridinyl)ethanone (**1h**).

A solution of 9.3 g (0.0237 mole) of (ethoxyethyloxymethyl)tributylstannane [7] in 75 ml of tetrahydrofuran was cooled to −78° followed by dropwise addition of 16 ml (0.0256 mole) of 1.6 *N* *n*-butyllithium in hexane. After 5 minutes, 4 g (0.0217 mole) of **4** in 5 ml of tetrahydrofuran was added in one portion. The reaction was stirred another 15 minutes then poured into a mixture of 25 ml of ether and 25 ml of brine. The organics were separated and the aqueous phase extracted 2x with 50 ml of ether. The combined organics were dried and the solvent evaporated to give a yellow liquid that was chromatographed by hplc using an 8 liter gradient beginning with dichloromethane and going to 15% methanol. This gave 2.5 g of **1h** as a yellow liquid, 50% yield; pmr (deuteriochloroform): ppm 1.19 (3H, t), 1.37 (3H, d), 2.41 (3H, s), 2.41-2.55 (4H, m), 3.15 (2H, m), 3.5 (1H, m), 3.64 (1H, m), 4.5 (2H, s), 4.82 (1H, q), 6.92 (1H, m). The oxalate salt was crystallized from 2-propanol, mp 80-82°.

*Anal.* Calcd. for $C_{12}H_{21}NO_3\text{-}C_2H_2O_4$: C, 52.99; H, 7.31; N, 4.41. Found: C, 52.73; H, 7.05; N, 4.40.

1-(1,2,5,6-Tetrahydro-1-methyl-3-pyridinyl)-3-(1,3-dioxolan-2-yl)-1-propanone (**1i**).

A solution of 17.6 g (0.066 mole) of di-*t*-butylbiphenyl in 200 ml of tetrahydrofuran was cooled to 0°. To the rapidly stirred solution was added in small pieces, 0.42 g (0.060 mole) of lithium wire. After 4 hours, the blue-green solution was cooled to −78° and a total of 6.9 g (0.038 mole) of 2-(2-bromoethyl)-1,3-dioxolane in 10 ml of tetrahydrofuran was added dropwise to produce a red solution [8]. After another 10 minutes, 5 g (0.027 mole) of **4** in 5 ml of tetrahydrofuran was added in one portion. The cooling was removed and when the temperature reached −10° the reaction was filtered through glass wool into 100 ml of a 1:1 mixture of brine and water. The mixture was extracted 3x with 75 ml of ether, the extracts dried, and the solvents evaporated. The residue was dissolved in 50 ml of ether and extracted 2x with 40 ml of cold 1 *N* hydrochloric acid. The combined acid extracts were washed with ether, made basic with 5 *N* sodium hydroxide, and extracted 4x with 30 ml of dichloromethane. The extracts were dried and the solvent evaporated to give 4.15 g of a brownish liquid that was purified by hplc using an 8 liter gradient starting with dichloromethane and going to 10% methanol. This gave 2.7 g of **1i**, 44% yield; pmr (deuteriochloroform): ppm 2.01 (2H, m), 2.3-2.52 (7H, m), 2.8 (2H, t), 3.15 (2H, m), 3.78-4.0 (4H, m), 4.91 (1H, t), 6.95 (1H, m). The oxalate salt crystallization from 2-propanol, mp 82-84°.

*Anal.* Calcd. for $C_{12}H_{19}NO_3\text{-}C_2H_2O_4$: C, 53.33; H, 6.71; N, 4.44. Found: C, 53.37; H, 6.83; N, 4.63.

*N*-Methoxy-*N*,1-dimethyl-1,2,3,6-tetrahydro-4-pyridinecarboxamide (**6**).

A mixture of 26.5 g (0.149 mole) of **5** and 100 ml of thionyl chloride was heated to reflux for 2 hours. The volatiles were evaporated, the residue treated with 200 ml of dichloromethane and the solvent evaporated. The resulting solid was suspended in 1.2 liters of dichloromethane, 16.25 g (0.167 mole) of *N,O*-dimethylhydroxylamine hydrochloride was added and the mixtue was cooled to 0°. Pyridine, 40.5 ml, was added dropwise, cooling was removed, and the reaction stirred 2 hours. The solvent was evaporated, the residue was suspended in 100 ml of ice-water, and the mixture made basic, *p*H 10, with 5 *N* sodium hydroxide. The mixture was extracted 3x with 100 ml of dichloromethane, the extracts were dried, and the solvent was evaporated. The residue was suspended in ether, the mixture filtered, and the solvent evaporated to give 24.25 g of **6** as a brown liquid, 88% yield; pmr (deuteriochloroform): ppm 2.4 (3H, s), 2.5 (2H, m), 2.58 (2H, t), 3.09 (2H, m), 3.2 (3H, s), 3.67 (3H, s), 6.25 (1H, m). This material was sufficiently pure to be used in subsequent reactions, but could be further purified by hplc eluting with an 8 liter gradient beginning with dichloromethane and going to 10% methanol. The hydrochloride salt crystallized from 2-propanol, mp 182-184°.

*Anal.* Calcd. for $C_9H_{16}N_2O_2\text{-}HCl$: C, 48.98; H, 7.76; N, 12.69. Found: C, 48.70; H, 7.67; N, 12.69.

1-(1,2,3,6-Tetrahydro-1-methyl-4-pyridinyl)ethanone (**2**).

The general procedure for the preparation of arecolones **1**, from Grignard reagents was used. From 2.14 g (0.0116 mole) of **6** and 8 ml (0.024 mole) of 3 *M* methylmagnesium chloride in tetrahydrofuran was obtained a brown liquid that was treated with hydrochloric acid to provide 1.46 g of **2**-HCl after recrystallization from 2-propanol, 71% yield, mp 166-167°; pmr of **2** (deuteriochloroform): ppm 2.3 (3H, s), 2.38-2.5 (5H, m + s), 2.57 (2H, t), 3.17 (2H, m), 6.8 (1H, m).

*Anal.* Calcd. for $C_8H_{13}NO\text{-}HCl$: C, 54.70; H, 8.03; N, 7.97. Found: C, 54.57; H, 8.25; N, 7.62.

Acknowledgment.

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