An Improved Synthesis of 1-(1,2,3,6-Tetrahydro-1-methyl-4-pyridinyl)ethanone, Isoarecolone

J. Warren Beach

Department of Medicinal Chemistry, College of Pharmacy, The University of Georgia, Athens, GA 30602

Received August 15, 1997

A convenient synthesis of 1-(1,2,3,6-tetrahydro-1-methyl-4-pyridinyl)ethanone, isoarecolone, starting with 4-acetylpyridine is presented. 4-Acetylpyridine was protected as the ketal followed by reaction with iodomethane to give the quaterary salt. The quaterary salt was reduced with sodium borohydride followed by deprotection to give isoarecolone in 80% overall yield.

J. Heterocyclic Chem., **34**, 1861 (1997).

Introduction.

The apparent involvement of central nicotinic receptors in Alzheimer's and Parkinson's diseases has lead to an increased interest in central nicotinic receptor ligands[1-5]. Isoarecolone, although less potent than nicotine shows pharmacological and behavioral characteristics which may indicate that it has some selectivity for the minor subtypes of the central nicotinic receptor [6-10]. This selectivity may be useful as a tool to help understand the distribution and function of these minor subtypes. In addition isoarecolone may also serve as a good lead compound for the discovery of compounds with a high degree of selectivity for one or more of the receptor subtypes. To this end we needed a convenient synthesis of isoarecolone. A survey of the literature revealed two previous syntheses. The first, reported by Spivak and coworkers [9,10], started with 4-acetylpyridine which was converted to the quaternary salt with iodomethane followed by reduction with sodium borohydride to give 1-methyl-4-(2-hydroxyethyl)-1,2,3,6-tetrahydropyridine. Oxidation of the secondary alcohol to the ketone using chromium trioxide was accomplished in low yield. The second synthesis [11] employed the Wienreb-Nahm ketone synthesis [12] and involved conversion of 1,2,3,6-tetrahydropyridine-4-carboxylic acid to its corresponding acid chloride followed by reaction with *O,N*-dimethylhydroxylamine to give the amide. Reaction of this material with methyl magnesium chloride gave the ketone (isoarecolone) in 71% yield.

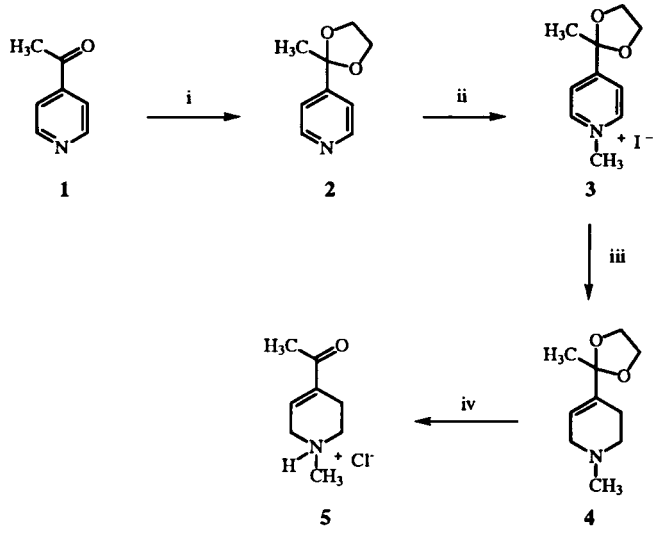
The first synthesis suffered from low yield as well as from the use of chromium which generally gives problems during workup and isolation of the product due to chromium tars. In addition chromium is an environmental hazard and poses disposal problems. The second synthesis gives good yields and is fairly straight forward, however it does not allow analogues to be synthesized with variation in the nitrogen substitution or substitution on the ring. For these reasons we employed a modification of the procedure for the synthesis of arecolone, reported by Coffen *et al* [13].

Chemistry.

The commercially available 4-acetylpyridine (**1**) was protected as its cyclic ketal **2** in high yield using ethylene glycol and a catalytic amount of *p*-toluenesulfonic acid with azeotropic removal of water. We found it more convenient to convert **1** into its hydrochloride salt than to use an excess of *p*-toluenesulfonic acid as was reported by Coffen *et al* [13]. The crystalline ketal **2** was pure enough to be taken directly to the next step but could be easily recrystallized from hexane. Reaction of the ketal **2** in refluxing acetone with iodomethane gave the quaternary salt **3** in excellent yield. Reduction of **3** with sodium borohydride in ethanol gave the protected isoarecolone **4** which was deprotected by dissolving **4** in dilute sulfuric acid. The free base of isoarecolone was found to be fairly unstable and was immediately converted to its hydrochloride salt **5** and crystallized from ethanol and diethyl ether. Compound **5** could be recrystallized from 2-propanol. Overall yield from **3** was 80%,

Other reaction of the quaternary salt **3** as well as the synthesis of compounds with different *N*-substitution will be reported in the near future.

Scheme 1: Synthesis of Isoarecolone



i) HCl / EtOH; Ethylene glycol, *p*-TsOH, Toluene reflux. ii) CH_3I/acetone reflux. iii) $NaBH_4$/ EtOH, 0-5°C. iv) Dilute H_2SO_4, concentrated HCl/EtOH.

EXPERIMENTAL

Melting points are uncorrected. The ^1H and ^{13}C nmr spectra were recorded at 400 MHz and 100 MHz, respectively at ambient temperature. Carbon and proton assignments were based on the following experiments: Carbon, Proton, DEPT, COSY, and HETCOR. Combustion analyses were carried out by Atlantic Microlab,Inc., Norcross, Georgia.

4-(2-Methyl-1,3-dioxolan-2-yl)pyridine (**2**).

A solution of 4-acetylpyridine (**1**) (38 g 0.314 mole) in toluene was treated dropwise with concentrated hydrochloric acid (25 ml) until the reaction mixture was strongly acidic. The toluene was removed under reduced pressure and the residue was co-evaporated with toluene and 2-propanol to a crystalline solid. The solid in toluene (500 ml) was treated with 1,2-ethanediol (60 ml) and *p*-toluenesulfonic acid (3.8 g). The reaction mixture was refluxed with azeotropic removal of water. After 3 hours water production had ceased, the reaction mixture was cooled and the toluene was removed under reduced pressure. The residue was treated with ethyl acetate (300 ml) and potassium carbonate (40 g). After stirring for 15 minutes, water was added slowly to dissolve the potassium carbonate. The layers were separated and the aqueous layer was extracted twice with ethyl acetate (100 ml x 2). The ethyl acetate layers were combined, washed with brine, dried (sodium sulfate anhydrous), filtered, and concentrated to give the ketal **2** (50 g, 96%) as a crystalline solid from hexane, mp 49-50°; ^1H nmr (deuteriochloroform): δ 1.60 (s, 3 H, CH_3), 3.70 (m, 2 H,CH_2 ketal), 4.05 (m, 2 H CH_2 ketal), 7.38 (d, 2 H, J = 6 Hz, Pyr C-3-H and C-5-H), 8.6 (d, 2 H, J = 6 Hz, Pyr C-2-H and C-6-H); ^{13}C nmr (deutrochloroform) δ 27.3 (CH_3), 65.1 (O-*C*H_2*C*H_2-O), 108.1(O-*C*(CH_3)-O), 120.6 (C-3 and C-5), 150.3 (C-2 and C-6), 152.3 (C-4).

Anal. Calcd for $C_9H_{11}NO_2$: C, 65.40; H, 6.70; N, 8.50. Found: C, 65.56; H, 6.69; N, 8.44.

1-Methyl-4-(2-methyl-1,3-dioxolan-2-yl)pyridinum Iodide (**3**).

To a solution of **2** (48 g, 0.291 mole) in acetone (300 ml) was add iodomethane (30 ml, 0.482 mole) and the reaction mixture was refluxed overnight. The reaction mixture was cooled, diluted with diethyl ether (200 ml) and the solid filtered to give **3** (85 g 95%), after recrystallization from methanol as a yellow solid, mp 153-155°, ^1H nmr (dimethyl-d_6 sulfoxide): δ 1.64 (s, 3 H, CH_3), 3.80 (m, 2 H, CH_2 ketal), 4.10 (m, 2 H, CH_2 ketal), 4.40 (s, 3 H, N-CH_3), 8.14 (d, 2 H, J = 6.7 Hz, Pyr C-3-H and C-5-H), 9.05 (d, 2 H, J = 6.7 Hz, Pyr C-2-H and C-6-H); ^{13}C nmr (dimethyl-d_6 sulfoxide): δ 25.7 (CH_3), 47.9, (CH_3-N), 65.0 (O-*C*H_2*C*H_2-O), 107.0, (O-*C*(CH_3)-O), 123.8 (C-3 and C-5), 146.0 (C-2 and C-6), 160.8, (C-4).

Anal. Calcd. for $C_{10}H_{14}NO_2I$: C, 39.1; H, 4.6; N, 4.6. Found: C, 39.14; H, 4.55; N, 4.50

1-Methyl-4-(2-methyl-1,3-dioxolan-2-yl)-1,2,3,6-tetrahydropyridine (**4**).

To a suspension of **3** (8 g, 0.026 mole) in absolute ethanol (250 ml) cooled in an ice/salt bath was added sodium borohydride portionwise, until tlc indicated disappearance of starting material. The reaction mixture was allowed to stir for 1 hour and then quenched by addition of glacial acetic acid until hydrogen evolution had ceased. The reaction solvent was removed under reduced pressure and the residue was partitioned between diethyl ether and water and the aqueous layer was exhaustively extracted with ether. The ether layers were combined, dried over anhydrous potassium carbonate, filtered and concentrated to give **4** (4.25 g, 90%) as a light green-yellow oil. It was used in the next reaction without further purification; ^1H nmr (deuteriochloroform): δ 1.45 (s, 3 H, CH_3), 2.20 (m, 2 H, C-5-H), 2.36 (s, 3 H, N-CH_3), 2.51 (t, 2 H, J = 5.7 Hz, C-6-H), 2.90 (m, 2 H, C-2-H), 3.82 (m, 2 H, CH_2 ketal), 3.93 (m, 2 H, CH_2 ketal), 5.82 (m, 1 H, C-3-H); ^{13}C nmr (deuteriochloroform): δ 23.8 (CH_3), 25.1 (C-5), 45.7, (CH_3-N), 52.1 (C-6), 54.1 (C-2), 64.7 (O-*C*H_2*C*H_2-O), 108.7, (O-*C*(CH_3)-O), 120.4 (C-3), 136.2, (C-4).

1-(1,2,3,6-Tetrahydro-1-methyl-4-pyridinyl)ethanone, Isoarecolone (**5**).

Crude **4** (3.75g, 0.020 mole) was dissolved in 1% aqueous sulfuric acid (150 ml) and allowed to stir for 2 hours at room temperature. The reaction mixture was cooled and solid potassium carbonate was added until the *p*H ≥ 9. The reaction mixture was transferred to a separatory funnel and extracted with ethyl acetate (3 x 150 ml). The organic layers were combined, washed with brine, dried (sodium sulfate, anhydrous), filtered and concentrated to give **5** as an oil. The oil was dissolved in absolute ethanol and treated with concentrated hydrochloric acid until the *p*H was slightly acidic. The ethanol was removed under reduced pressure to give a solid residue. The residue was taken up into warm absolute ethanol, allowed to cool, diluted with diethyl ether and the solid filtered to give **5** hydrochloride, which was recrystallized from 2-propanol (3.18 g, 89%), mp 166-167° (lit. 166-167° [11,14a], 176-178° [8,14b]); ^1H nmr (dimethyl-d_6 sulfoxide): δ 2.31 (s, 3 H, CH_3), 2.51 (m, 2 H, C-5-H), 2.80 (s, 3 H, N-CH_3), 3.30 (m, 2 H, C-6-H), 3.91 (m, 2 H, C-2-H), 6.96 (m, 1 H, C-3-H); ^{13}C nmr (dimethyl-d_6 sulfoxide): δ 20.6 (CH_3), 25.5 (C-5), 41.7 (N-CH_3), 49.2 (C-6), 50.5 (C-2), 132.8 (C-3), 135.7 (C-4), 197.3 (*C*O).

Anal. Calcd for $C_8H_{14}NOCl$: C, 54.7; H, 8.0; N, 8.0. Found: C, 54.65; H, 8.0; N, 8.05.

Acknowledgment.

This work was supported in part by funds from the Burroughs Wellcome Fund and the American Foundation for Pharmaceutical Education though the AACP Grant Program for New Investigators and is gratefully acknowledged.

REFERENCES AND NOTES

[1] D. A. Flynn and D. C. Mash, *J. Neurochem.*, **47**, 1948 (1986).

[2] P. J. Whitehouse, A. M. Martino, P. G. Antuono, P. Lowenstein, J. T. Coyle, D. L. Price and K. J. Kellar, *Brain Res.*, **371**, 146 (1986).

[3] E. K Perry, R. H. Perry, C. J. Smith, D. J. Dick, J. M. Candy, J. A. Edwardson, A. Fairbaim and G. Blessed, *J. Neurol. Neurosurg. Psychiatry*, **50**, 806 (1987).

[4] E. Giacobini, P. DeSarno, B. Clark and M. McIlhany, in Progress in Brain Research, A Nordberg, ed, Elsevier, Amsterdam, 1989, pp 335-343.

[5] E. D. Levin, *Psychopharmacology*, **108**, 417 (1992).

[6] P. Whiteaker, H. S. Garcha , S. Wonnacott and I. P. Stolerman, *Brit. J. Pharmacol.*, **116**, 2097 (1995).

[7] N. R. Mirza, Q. Pei, I. P. Stolerman and T. S. C. Zetterstrom, *Eur. J. Pharmacol..*, **295**, 207 (1996).

[8] C. Reavill, C. E. Spivak, I. P. Stolerman and J. A.Waters, *Neuropharmacology*, **26**, 789 (1987).

[9] J. A. Waters, C. E. Spivak, M. Hermsmeir, J. S. Yadav, R. F. Liang and T. M Gund,. *J. Med. Chem.*, **31**, 545 (1988).

[10] C. E. Spivak, T. M. Gund, R. F. Liang and J. A.Waters, *Eur. J. Pharmacol.*, **120**, 127 (1986).

[11] J. S. Ward and L. Merritt, *J. Heterocyclic Chem.*, **27**, 1709

(1990).

[12] S. Nahm and S. M. Wienreb *Tetrahedron Letters*, **22**, 3815 (1981).

[13] D. L. Coffen, U. Hengarter, D. A. Katonak, M. E. Mulligan, D. C. Burdick, G. L. Olson and L. J. Todaro. *J. Org. Chem.*, **49**, 5109 (1984).

[14a] Recrystallized from 2-propanol.

[14b] Recrystallized from acetone and absolute ethanol.