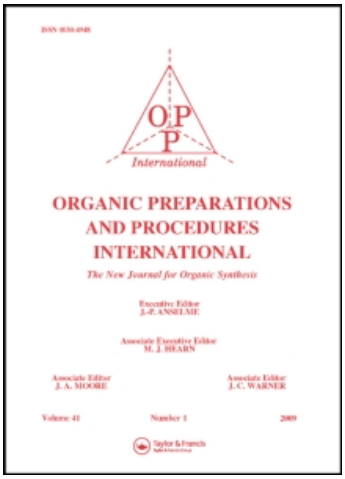

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AN IMPROVED PREPARATION OF 1-METHYL-4-CYANO-4-PHENYLPIPERIDINE

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AN IMPROVED PREPARATION OF 1-METHYL-4-CYANO-4-PHENYLPIPERIDINE

Submitted by Dino Gnecco*†, J. L. Terán†, Raúl G. Enríquez††, William F. Reynolds††† and C. Marazano††††
(04/03/92)

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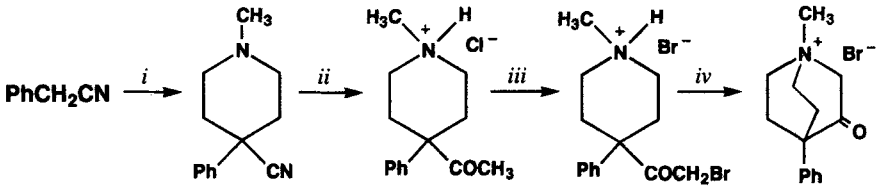
Several synthetic approaches are available for the preparation of 1-methyl-4-cyano-4-phenylpiperidine (**1**). These methods all involve refluxing the starting material in toluene or benzene for several hours which results in the formation of polymeric residues, making the purification process difficult and leading to low overall yields.[1] Since **1** is a key intermediate for the synthesis of derivatives which exhibit potent narcotic-analgesic or antihypertensive effects,[2] it would be highly desirable to have a better method for the synthesis of **1**. The present work describes modifications that significantly improve its preparation.

Reaction of phenylacetonitrile and *bis*-(β-chloroethyl)methylamine hydrochloride in anhydrous ether with sodium amide at -5° afforded **1** in yields which were on average 30-40% higher than those previously reported.[1]



1 2 3 4

i) $NaNH_2$, Et_2O, -5°, $(ClCH_2CH_2)_2NMe$ ii) MeLi, then HCl i iii) Br_2, HOAc i iv) $NaHCO_3$, acetone

1-Methyl-3-keto-4-phenylquinuclidinium bromide (**4**) and intermediates **2** and **3** were prepared from **1** according to Perrine's method.[3] The physical and spectral data of **1**, **2** and **3** are reported for the first time.

EXPERIMENTAL SECTION

Mps. are uncorrected. IR spectra were recorded in KBr on a FTIR-8101M Shimadzu Fourier transform infrared spectrophotometer. NMR spectra were obtained at room temperature dissolved in $CDCl_3$, D_2O or DMSO-d_6 using TMS or the sodium salt of 3-(trimethylsylil)-1-propanesulfonic acid as internal standard on Varian VXR-300S and 500 MHz Unity Plus spectrometers. **Caution**: Care should be exercized when preparing compound **1** due to the toxicity of *bis*-(β-chloroethyl)methylamine hydrochloride and derivatives.

1-Methyl-4-cyano-4-phenylpiperidine (1).- To *bis*-(β-chloroethyl)methylamine hydrochloride (4.0 g, 20.8 mmol) and sodium amide (3.3 g, 83.2 mmol) in a 250 mL round bottom flask in 50 mL of anhydrous ether with magnetic stirring and an inert atmosphere of Argon at -5°, was added dropwise a solution of phenylacetonitrile (5 mL, 43.4 mmol) in 50 mL of anhydrous ether. After 50 min at room temperature, the reaction was complete. The mixture was cooled to 0° and upon addition of 15 mL of H_2O, two phases separated. The organic phase was washed with a saturated solution of ammonium chloride until neutral. After drying over anhydrous sodium sulfate and removal of solvent *in vacuo*, a yellowish oil (7.90 g, 95%) consisting of a mixture of the free base of **1** with unreacted phenylacetonitrile was obtained. The crude product was dissolved in 10 mL of ethanol and 2 mL of concentrated HCl were added which afforded the hydrochloride of **1** (4 g, 80% based on reacted phenylacetonitrile) as colorless needles, mp. 223-225°. 1-Methyl-4-cyano-4-phenylpiperidine hydrochloride ^{1}H NMR (DMSO-d_6): δ 2.49 (m, 4H), 3.31 (s, 3H), 3.30 (br, t, 2H), 3.60 (d, J_{gem}=12.3 Hz, 2H), 7.60 (m, 5H). The hydrochoride of **1** (1 g) could be converted quantitatively into the free base (yellow oil).

Anal. Calcd for $C_{13}H_{17}ClN_2$: C, 66.07; H, 7.26; N, 11.86; Cl, 14.81
Found: C, 65.95; H, 7.10; N, 11.50; Cl, 14.71

TABLE 1. Physical and Spectral Data for Compounds **1**, **2**, **3** and **4**

Cmpd	mp. (°C)	Yield (%)	IR (KBr) (cm^{-1})	^{1}H NMR (δ)
1	oil	80	3010, 2940, 2230, 1600	$CDCl_3$: 2.04 (m, 4H), 2.31 (s, 3H); 2.42 (ddd, J= 12.6, 12.3, 4.5 Hz, 2H); 2.89 (br, dt, J_{gem} = 12.6 Hz; 2H); 7.22-7.38 (m, 3H); 7.40-7.43 (d, J_{ortho}=7.2 Hz, 2H)
2	oil	85	3030, 2920, 1705	$CDCl_3$: 1.91 (s, 3H), 2.13 (m, 4H), 2.25 (s, 3H), 2.48 (br, d, 2H), 2.68 (br, m, 2H), 7.34 (m, 5H)
2•HCl[a]	239-240	95	2960, 1690, 1500	D_2O: 1.86 [1.88] (s, 3H)[b], 2.03 (br m, 2H); 2.61 [2.73] (s, 3H)[c]; 2.80 (m,br, 4H); 3.42 (br t, 2H); 7.34 (m, 5H)
3•HBr[d]	189-190	85	3013, 1705, 1500	D_2O: 2.31(br m, 2H); 2.78 [2.90][e] (s, 3H); 3.08 (br, m, 4H); 3.58 (br, t, 2H), 4.20[f], 4.28[g], 2H; 7.37-7.58 (m, 5H)
4[h]	174-176	95	2955, 1740, 1630	D_2O: 2.70 (m, 4H), 3.29 (s, 2H), 3.37(s, 3H); 4.05 (m, 4H); 7.22-7.45 (m, 5H)

a) Calcd. for $C_{14}H_{20}ClNO$: C, 66.37; H, 7.96; N, 5.53; Cl, 13.81. Found: C, 66.30; H, 8.00; N, 5.52; Cl, 13.80. b, c) N-CH_3 and $COCH_3$ groups gave each one two singlets with approximately equal ratios arising from the two possible isomers. d) the free base of **3** is not reported since it readily undergoes cyclization *in situ* upon neutralization of its hydrobromide to yield **4**; e) the N-CH_3 group gives rise to two singlets. f, g) two singlets for bromomethyl group were observed. h) lit.[2a] 170-172°.

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REFERENCES

1. a) H. R. Le Sueur and P. Haas. *J. Chem. Soc.*, **97,** 967 (1910); b) O. Eisleb and O. Schaumann, *Deut. Med. Worrsch.*, **65**, 967, *Chem. Abstr.*, **36**, 5465[3] (1939); c) O. Eisleb, *Ber.*, **74,** 1443 (1941); d) A. T. Nielsen, *J. Org Chem.*, **31,** 1053 (1966); e) J. Carrol, A. N. Fergusson and J. B. Lewis, *ibid.*, **31**, 2957 (1966); f) D. S. Watt, *Tetrahedron*, **24,** 175 (1968).

2. a) E. Hong, US Patent 3,860,717; *Chem. Abstr.*, **82**, 149531z (1975); b) L. E. Mather and P. J. Meffin., *Clin. Pharmacokinet.*, **3**, 352 (1978); *Chem. Abstr.*, **90**, 40w (1979).

3. T. D. Perrine, *J. Org. Chem.*, **22**, 1484 (1957).

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EFFICIENT *IN SITU* ESTERIFICATION OF CARBOXYLIC ACIDS USING CESIUM CARBONATE

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The esterification of carboxylic acids is a fundamental process in organic synthesis[1] and may effected by the reaction of carboxylate anions with alkyl halides.[2] Compared to other alkali metal carboxylate salts, cesium salts have been shown to be especially efficient in esterification[3-6] and macrocyclization reactions.[7] However, these reactions usually required high boiling solvent (DMF) in the presence of water[3-5] or cesium fluoride/DMF system[6] which are undesirable in terms of convenience. We now report a highly effective method for the esterification of carboxylic acids in acetonitrile with readily available cesium carbonate under non-aqueous conditions.

Acetonitrile was used as a reaction medium because of its appropriate boiling point as well as high dielectric constant and polar aprotic nature. The latter two properties should provide good solubility for the cesium carboxylate salt and concomitant rate enhancement of the reaction. Reflux of the carboxylic acids with alkyl iodides (1.0-5.0 equiv.) and cesium carbonate (1.5 equiv.) in

$$\underset{\mathbf{1}}{RCO_2H} + \underset{\mathbf{2}}{R'X} \xrightarrow[CH_3CN,\ reflux]{Cs_2CO_3} \underset{\mathbf{3}}{RCO_2R'}$$