

The Reaction of *N*-Benzylpyroglutamic Acid with Phenyl Grignard (1)

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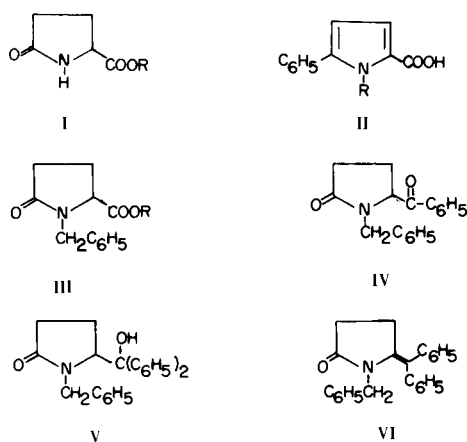
Needing 5-arylpyrrole-2-carboxylic acids (II, R = H) for other studies (2), it occurred to us that these might be synthesized from the readily available pyroglutamic acid, (I, R = H) if the amide carbonyl were susceptible to attack by an aryl Grignard or lithium reagent. To accomplish the conversion of I to II, it would be necessary to mask the amide hydrogen with a group such as benzyl, which could be removed after the intermediate dihydropyrrole, which should result from the reaction of an aryl Grignard with III, was oxidized to a pyrrole. It was assumed that the carboxylic acid group would be sufficiently deactivated, by conversion to a magnesium salt with excess Grignard, to favor reaction with amide carbonyl.

Accordingly, *N*-benzylpyroglutamic acid (III, R = H) was prepared. Initial experiments designed to alkylate the dianion of I (R = H) were unsuccessful, yielding mixtures, from which III (R = H) could be isolated in poor yield. However, the methyl ester (I, R = CH₃) was readily obtained (3) and this could be benzylated on nitrogen to III (R = CH₃) then hydrolyzed in good yield to form *N*-benzylpyroglutamic acid (III, R = H).

Treating III (R = H) with two moles of phenyl Grignard reagent produced not the desired compound, but the ketone IV, *N*-benzyl-5-benzoyl-2-pyrrolidone, in about 40% yield. About 50% of the starting III (R = H) could be recovered, even after exposure to the Grignard for twenty-four hours. Increasing the ratio of Grignard to as much as 4/1 did not appreciably improve the yield. Apparently the metal reagent complexes with the initially formed magnesium salt in some manner, deactivating the amide carbonyl to attack, but allowing attack on the carboxyl group. This evidently was not converted to ketone directly in the reaction, since only traces of the tertiary alcohol V were obtained, even when a three molar excess of Grignard was used. Phenyllithium gave nearly identical results in these experiments.

When ketone IV was treated with a slight excess of two moles of phenyl Grignard reagent, and the product worked up with dilute acid, a nearly quantitative yield of tertiary alcohol V was obtained. Once again, no product derived from attack on the amide carbonyl was evident, and at least two moles of Grignard were needed to complete the

Chart 1



reaction. Working up this reaction by treatment with more concentrated acid led to dehydration to give *N*-benzyl-5-diphenylmethylidene-2-pyrrolidone (VI) as a by-product. Although V was not easily dehydrated, compound VI was formed in quantitative yield from V in polyphosphoric acid, but was unstable, melting with decomposition, deteriorating on storage, and failing to give a satisfactory elemental analysis. A fresh sample showed an nmr consistent with structure VI (overlapping triplets for the four protons of the pyrrolidone ring) and an exact mass consistent only for the molecular formula of VI.

EXPERIMENTAL

Melting points were obtained on a Mel-Temp capillary melting point apparatus and are uncorrected for stem exposure. Infrared spectra were obtained on a Perkin-Elmer Model 137 infrared spectrometer. Nmr spectra were measured on Varian Associates A-60 and HA-100 instruments using deuteriochloroform as solvent and tetramethylsilane as a reference. Mass spectra were measured on Varian Associates M.A.T. CH-7 spectrometer or an Associated Electrical Industries MS-9 spectrometer at 70 eV. Microanalysis were obtained courtesy of Midwest Microlab, Ltd., Indianapolis, Indiana. All organometallic reactions were done in a dry nitrogen atmosphere.

Methyl Pyroglutamate. (I, R = CH₃).

A mixture of I (R = H) (10.3 g., 0.08 mole), prepared from glutamic acid by the procedure of Hardegger and Ott (3), methanol (32 ml., 0.8 mole), benzene (20 ml.), and 10 drops of concentrated

sulfuric acid was refluxed 15 hours. The reaction mixture was cooled, adjusted to pH 6 with 20% sodium hydroxide solution, and concentrated by distillation under reduced pressure to a viscous liquid. The crude liquid was dissolved in chloroform (100 ml.) and the solution was filtered through a pad of Celite. The filtrate was concentrated by distillation under reduced pressure to give a yellow liquid, which distilled *in vacuo* to give 8.60 g. (75%) of the ester as a colorless liquid, b.p. 107-113° (0.06-0.12 mm) (reported b.p. 100° under high vacuum (3)); ir (neat): 3.10 μ (N-H), 5.70-6.10 μ (C=O, ester, lactam); nmr: δ 2.02-2.50 (m, 4H), δ 3.76 (s, 3H), δ 4.16-4.40 (m, 1H), δ 8.00 (s, 1H); ms: M⁺ 143.

Methyl *N*-Benzylpyroglutamate (III, R = CH₃).

A slurry of sodium hydride (9.7 g., 0.4 mole) (washed with petroleum ether to remove the mineral oil) in 300 ml. of dry benzene was treated dropwise with 42 g. (0.29 mole) of methyl pyroglutamate. After the addition of methyl pyroglutamate the solution was stirred at room temperature until hydrogen evolution ceased, then refluxed for 1.5 hours and allowed to stir at 45° for 16 hours. Benzyl bromide (30.7 g., 0.28 mole) was added, and the mixture brought to reflux. Additional benzyl bromide (30.7 g., 0.28 mole) was then added to the refluxing solution. After 24 hours, the mixture was filtered through Celite and the residue washed with methylene chloride, and the combined solutions concentrated to give 79 g. of an orange oil. Distillation yielded 49.5 g. (73%) of III (R = CH₃) as a clear, viscous liquid (b.p. 162-170°, 0.5-1.0 mm), which crystallized upon standing overnight, m.p. 63.5-65° (ether); ir (neat): 5.73 μ (C=O, ester), 5.90 μ (C=O, lactam); nmr: δ 1.73-2.68 (m, 4H), δ 3.61 (s, 3H), δ 3.93 (m, 1H), δ 3.95 and 4.97 (ABq, 2H, *J* = 7 Hz), δ 7.22 (s, 5H).

Anal. Calcd. for C₁₃H₁₅NO₃: C, 67.00; H, 6.49; N, 6.01; M.W. 233. Found: C, 67.04; H, 6.57; N, 6.06; M⁺ 233.

N-Benzylpyroglutamic Acid (III, R = H).

A solution of 4.1 g. (0.018 mole) III (R = CH₃) and 20 ml. of 1*N* sodium hydroxide was heated on a steam bath for one and one-half hours and then allowed to stand at room temperature overnight. The solution was acidified with concentrated hydrochloric acid and extracted with methylene chloride (3 x 15 ml.). The methylene chloride was removed under reduced pressure to give 4.6 g. of a viscous, clear oil which crystallized rapidly. Recrystallization (benzene) gave 3.4 g. (89%) of III (R = H), m.p. 122-123°; ir (potassium bromide): 3.6-4.4 μ (COOH), 5.8 μ (C=O, acid), 6.1 μ (C=O, lactam); nmr: δ 2.16-2.34 (m, 2H), δ 2.46-2.66 (m, 2H), δ 3.86-4.00 (m, 2H), δ 3.98-4.19 (t, 1H), δ 4.07 (d, 1H, *J*_{ab} = 14 Hz, C₆H₅-CH₂H_b), δ 5.23 (d, 1H, *J*_{ab} = 14 Hz, C₆H₅-CH₂H_b), δ 7.10-7.28 (m, 5H), δ 10.00 (s, 1H).

Anal. Calcd. for C₁₂H₁₃NO₃: C, 65.75; H, 5.98; N, 6.39; M.W. 219. Found: C, 65.81; H, 5.97; N, 6.48; M⁺ 219.

N-Benzyl-5-benzoyl-2-pyrrolidone (IV).

Nineteen ml. (55 mmoles) of a 2.9 *M* ether solution of phenylmagnesium bromide (Alpha Products) was added to 75 ml. of anhydrous ether. The Grignard reagent was cooled to 0° and a solution of 6.0 g. (27 mmoles) III (R = H) in 700 ml. ethyl ether/100 ml. of DME was added dropwise. The slurry was allowed to warm to room temperature and then stirred for 24 hours. The solution was then acidified with 2*N* hydrochloric acid and the aqueous layer was extracted with ethyl ether (2 x 75 ml.). The combined ether extracts were washed with 2*N* sodium hydroxide (2 x 75 ml.), dried over anhydrous magnesium sulfate and the solvent removed, yielding a pale brown oil. This oil was allowed to set over the week-

end. A small amount of crystals (0.1 g.) were collected and later identified as V. Vacuum distillation of the oil (b.p. 150°, 0.1 mm) yielded 3.1 g. (42%) of IV as a pale yellow oil; ir (neat): 5.9 μ (C=O, ketone) 5.95 μ (C=O, lactam); nmr δ 2.0-2.5 (m, 4H), δ 3.65-4.2 (t, 1H), δ 4.8-5.5 (ABq, 2H), δ 7.1-8.2 (m, 10H).

Anal. Calcd. for C₁₈H₁₇NO₂: C, 77.4; H, 6.13; N, 5.01; M.W. 279. Found: C, 77.0; H, 6.26; N, 4.8; M⁺ 279.

The 2,4-dinitrophenylhydrazone of IV was prepared, m.p. 206.5-207°.

Anal. Calcd. for C₂₄H₂₁N₅O₅: C, 62.74; H, 4.61; N, 15.24; M.W. 459. Found: C, 62.72; H, 4.75; N, 15.30; M⁺ 459.

Upon acidification of the combined hydrochloric acid and sodium hydroxide aqueous portions, subsequent extraction with methylene chloride, and removal of the methylene chloride under reduced pressure, 3.2 g. (53%) unreacted III was recovered.

In an experiment identical to the previous one, 2 moles of phenyllithium replaced phenylmagnesium bromide. Upon work-up, 44% of IV and 0.2 g. (~2%) of V were isolated.

N-Benzyl-5-(hydroxydiphenylmethyl)-2-pyrrolidone (V).

A sample of 0.38 g. (1.35 mmoles) IV was dissolved in 25 ml. of ether, cooled to 0°, and 3.0 mmoles phenylmagnesium bromide (Alpha Products) was added. A white precipitate formed immediately. The reaction was stirred at room temperature for 23 hours, then acidified with 2*N* hydrochloric acid and extracted with ether (2 x 15 ml.). The ether solution was dried over magnesium sulfate and upon evaporation of the ether gave 0.45 g. (93%) of V, m.p. 192-194° (methanol/water); ir (potassium bromide): 3.0 μ (OH), 6.0 μ (C=O, lactam); nmr δ 1.82-2.30 (m, 4H), δ 4.39-4.50 (t, 2H), δ 4.56-5.1 (ABq, 2H), δ 6.87 (s, broad, 1H), δ 7.05-7.45 (m, 15H).

Anal. Calcd. for C₂₄H₂₃NO₂: C, 80.64; H, 6.48; N, 3.92; M.W. 357. Found: C, 80.4; H, 6.43; N, 3.7; M⁺ 357.

In an experiment similar to the above, 6*N* hydrochloric acid was used to quench the reaction. Work-up of the reaction gave 75% of V and 21% of VI. When phenyllithium was used instead of phenylmagnesium bromide and the reaction was quenched with 6*N* hydrochloric acid, 60% of V and 25% of VI were obtained.

N-Benzyl-5-diphenylmethylidene-2-pyrrolidone (VI).

A mixture of 0.34 g. (0.95 mmole) of V and approximately 50 ml. PPA were mixed in a small round-bottomed flask equipped with a drying tube. The mixture was warmed to 110-120° for one hour. Shorter times or lower temperatures resulted in an incomplete dehydration according to tlc. The mixture was allowed to cool and then poured over 5 g. of ice. Extraction with ether, drying of the ether extract with anhydrous magnesium sulfate, and evaporation of the ether gave 0.5 g. of a pale brown oil. This oil was placed under vacuum overnight and approximately 0.32 g. (100%) VI were obtained as pale white crystals, m.p. 110-113° dec.; ir (potassium bromide): 5.95 μ (C=O, lactam); nmr δ 2.12, 2.16 (overlapping triplets, 4H, *J* = 7 Hz), δ 4.46-4.82 (ABq, 2H), δ 6.8-7.2 (m, 15H); ms: M⁺ 339.

Exact mass. Calcd. for C₂₁H₂₁NO: 339.1616. Found: 339.1624; the other computed possibilities were chemically impossible.

REFERENCES

- (1) Contribution No. 2547 from these laboratories. This work was supported in part by Grant GM-10366, of the U.S. Public Health Services, to Indiana University.
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