

Department of Chemistry, San Jose State College

II (1a). Acylation of the Pyrrole Grignard Reagent (1b)

Albert J. Castro, James R. Lowell, Jr., and John P. Marsh, Jr.

Alkylation of tridentate pyrrolylmagnesium chloride yields exclusively 2- and 3- monoalkylsubstitution (ratio 2-:3- :: 3.0-5.4:1) with different alkyl chlorides (2), following the general rule of carbon alkylation of a pyrrolylmagnesium halide in contrast with nitrogen alkylation of alkali metal salts of pyrrole (3, 4). Similar results have been recently described for the alkylation of pyrrolylmagnesium bromide (7). In contrast, the acylation of pyrrolylmagnesium bromide with acyl halides and esters has been reported to yield only 2-acetylpyrroles (7). In an apparently exceptional case pyrrolylmagnesium bromide and ethyl chloroformate have been described as yielding 1-ethoxycarbonylpyrrole, 2-ethoxycarbonylpyrrole and 1,2-diethoxycarbonylpyrrole (8). The latter results have been duplicated in our laboratory (9). However, we have also found that the reaction of pyrrolylmagnesium bromide with acetyl and propionyl chloride does in fact yield both 2- and 3-acyl derivatives, as in the alkylation reactions. The 3-acylpyrroles are higher boiling and formed in smaller amounts than the isomeric 2-acylpyrroles, which may explain why such isomers have escaped detection in earlier investigations. The ratio of 2- to 3-acylpyrrole observed by us with acetyl chloride is 7:1 (combined yield 41%); with propionyl chloride 5:1 (23%). The identity of the 2-acyl derivatives rests upon comparison of melting points with reported values. The constitution of the 3- isomers was established by elemental analyses, infrared and n.m.r. spectra. In addition, the melting point of the 3-acetylpyrrole obtained by us agrees with that reported for the compound synthesized through a ring closure method (10).

EXPERIMENTAL

Boiling points and melting points are uncorrected. The latter were determined with a Fisher-Johns apparatus. Infrared spectra were obtained as mineral oil mulls with a Beckmann IR-5 spectrophotometer; n.m.r. spectra, with a Varian A-60 spectrometer using tetramethylsilane as an internal standard in trifluoroacetic acid. Analyses are by the Berkeley Analytical Laboratory, P. O. Box 150, Berkeley, California, and by Dr. G. Weiler and Dr. F. B. Strauss, 164, Banbury Road, Oxford, England.

2- and 3-Acetylpyrrole.

A solution of pyrrolylmagnesium bromide was prepared from the careful addition of 333 ml. of 3 M (1 mole) methylmagnesium bromide (11) to 67 g. (1 mole) of pyrrole in 100 ml. of dry ether. The reaction mixture was cooled and stirred during this operation. Fifty milliliters of ether was added during the process to make up for that lost from the system and the mixture was refluxed for a short time after mixing the reactants. The resulting mixture was cooled and stirred, and 71 ml. (78.5 g., 1 mole) of acetyl chloride dissolved in 75 ml. of ether was added during a period of about 20 min. An additional 50 ml. of ether was added and the mixture was refluxed for a short period. The reaction mixture was hydrolyzed with saturated aqueous ammonium chloride solution, the ether layer was separated and the aqueous layer was extracted with ether. The ether layers were combined and the mixture was dried with magnesium sulfate. The desiccant was washed with acetone and after evaporating the ether and acetone the

residue was vacuum distilled yielding two fractions: (a) 38.73 g., b.p. 122-132°/24-25 mm. and (b) 8.85 g., b.p. 184-189°/24 mm. Fraction (a) solidified to crystalline 2-acetylpyrrole, m.p. 84.5-85.5° (lit. (12) 90°) (36%). Upon recrystallization from cyclohexane this compound was readily obtained as cream colored crystals, m.p. 88-89°. Fraction (b) solidified to a golden-brown, oily solid. Crystallization from ethyl alcohol gave 5.39 g. (5%) of cream colored, crystalline 3-acetylpyrrole, m.p. 113.5-115.0° (lit. (10) 115-116°). The infrared spectrum of this compound shows strong NH (2) and C=O (13) stretching vibrations at 3.16 and 6.14 μ , respectively. Its n.m.r. spectrum exhibits signals for ring H² at δ = 7.80 p.p.m., broad signal (relative intensity 1); ring H⁴ and H⁵, δ = 6.54, broad (2); methyl H, δ = 2.78, singlet (3). An analytical sample was prepared by sublimation at 130-135° (bath temp.)/21 mm., m.p. 113.6-114.0°.

Anal. Calcd. for C₈H₇NO: C, 66.03; H, 6.47; N, 12.84. Found: C, 66.04; H, 6.52; N, 12.69.

2- and 3-Propionylpyrrole.

The procedure was like that described above, except that the reverse order of mixing the reagents was used in the synthesis of pyrrolylmagnesium bromide. The pyrrole Grignard reagent was prepared from 250 g. (3.7 moles) of pyrrole and 1165 ml. of 3.11 M (3.6 moles) methylmagnesium bromide diluted with 2 l. of ether. Three hundred and forty-six grams (3.7 moles) of propionyl chloride was used. Three fractions were obtained from the distillation of the reaction mixture: (a) 65-95°/0.45-3.4 mm., (b) 95-100°/1.2-1.3 mm., and (c) 100-155°/0.70-1.05 mm. Fractions (a) and (b) were combined and after crystallization from cyclohexane there was recovered 83.4 g. (19%) of white crystalline 2-propionylpyrrole, m.p. 49-50° (lit. (12) 52.5°). Crystallization of fraction (c) from benzene yielded 16.2 g. (4%) of white needles of 3-propionylpyrrole, m.p. 113.5-114.9°. The infrared spectrum of this compound has strong bands for NH and C=O stretching vibrations at 3.15 and 6.12 μ , respectively. Its n.m.r. spectrum shows signals for ring H² at δ = 7.74, broad simpler (1); ring H⁴ and H⁵, δ = 6.78, broad (2); methylene H, δ = 3.00, quartet (2, J = 5 c.p.s.); methyl H, δ = 1.39, triplet (3, J = 5 c.p.s.).

Anal. Calcd. for C₇H₉NO: C, 68.27; H, 7.36; N, 11.37. Found: C, 67.75; H, 7.29; N, 11.17.

REFERENCES

- (1) (a) For paper I in this series see ref. 2. (b) This investigation was supported by a Public Health Service Research Grant, C-6255, from the National Cancer Institute.
- (2) A. J. Castro, J. F. Deck, N. C. Ling, J. P. Marsh, Jr. and G. E. Means, submitted for publication, *J. Org. Chem.*
- (3) P. A. Cantor and C. A. VanderWerf, *J. Am. Chem. Soc.*, **80**, 970 (1958).
- (4) Exceptions are known. Thus, allyl bromide is described as yielding 2-allylpyrrole upon reaction with pyrrolylmagnesium bromide and a mixture of 1- and 2-allylpyrrole, with the latter the major product (1-:2- :: 1:6), from the reaction with pyrrolylpotassium (3). Since this report, the ratio of substitution at the 1- and 2- positions in the reactions of allyl type halides with alkali metal and dimethylanilinium salts of pyrrole has been shown to be influenced by the medium and the cation (5). Both pyrrolylmagnesium iodide and pyrrolylithium are described as yielding 1-trimethylsilylpyrrole upon reaction with trimethylchlorosilane (6).
- (5) C. F. Hobbs, C. K. McMillin, E. P. Papadopoulos and C. A. VanderWerf, *J. Am. Chem. Soc.*, **84**, 43 (1962).
- (6) R. Fessenden and D. Crowe, *J. Org. Chem.*, **25**, 598 (1960).
- (7) P. S. Skell and G. P. Bean, *J. Am. Chem. Soc.*, **84**, 4655 (1962).
- (8) F. K. Signagio and H. Adkins, *ibid.*, **58**, 1122 (1936).
- (9) B. T. Nakata, private communication.
- (10) I. J. Rinkes, *Rec. trav. chim.*, **57**, 423 (1938).
- (11) Arapahoe Chemicals, Inc., Boulder, Colorado.
- (12) B. Oddo, *Ber.*, **43**, 1012 (1910).
- (13) W. Herz and J. Brasch, *J. Org. Chem.*, **25**, 1513 (1958).

Received July 8, 1964

San Jose, California