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The Acylation of Pyrrylmagnesium Bromide

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Several years ago we reported (1) that the reaction of pyrrylmagnesium bromide with alkyl halides results in the production of pyrrole, 2- and 3-alkylpyrroles and polyalkylpyrroles. It was also stated that acylation of pyrrylmagnesium bromide with acid halides and esters gave only 2-acylpyrroles, and that the reduction of the resulting 2-acylpyrroles is a convenient method of synthesizing the corresponding 2-alkylpyrroles. This statement was based primarily on the results of acylations with esters since it was observed in the only experiment using an acid chloride that the extremely vigorous reaction caused considerable splattering and tar formation, whereas the reaction with esters went smoothly and with no tar formation. However Castro (2) has recently reported that the acetylation of pyrrylmagnesium bromide with acetyl chloride gives both the 2- and 3-acetylpyrroles in a ratio of 4.4 to 1 as determined by the weight of the two products separated by distillation.

We have repeated the acetylation of pyrrylmagnesium bromide with acetyl chloride and following the procedure of Castro have confirmed the production of 3-acetylpyrrole as well as the 2-acetylpyrrole in a ratio of about 1 to 5 as determined by the weight of the two fractions. However, when ethyl acetate was used as the acylating agent, vacuum distillation of the product gave only a very small amount of 3-acetylpyrrole after the 2-acetylpyrrole had been distilled off. The ratio of the weights of the fractions in this case was about 1 to 100.

Since the results of such a separation by distillation are quite crude, a quantitative method using infrared spectrophotometry was developed to determine the amounts of 2- and 3-acetylpyrroles. With synthetic mixtures of the two isomers, 3-acetylpyrrole could be detected when present in a ratio of 1 to 35, and its concentration measured within 5 percent when present in at least a 1 to 10 ratio. By this method the ratio of 2- to 3-acetylpyrrole produced in the acetylation of a 1 *M* solution of pyrrylmagnesium bromide by acetyl chloride, diluted with an equal volume of ether, was 4.5 $\pm$ 0.2 to 1. Although the reaction with acetic anhydride was not quite as vigorous and less tar was produced, the ratio was 3.7 $\pm$ 0.2 to 1. Since when each drop of the solution of acetyl chloride was added to the pyrrylmagnesium bromide solution there was a loud hiss accompanied by considerable splattering, much of the reaction occurred in a region of much higher temperature than the boiling point of ether and where little ether remained as solvent. Large amounts of tar result from these extreme conditions and the observed ratio of 2- to 3-acetylation should not be compared with acetylations carried out under normal conditions. The acetylations with the acid chloride and anhydride were repeated at 100 fold dilution. With acetyl chloride only a small amount of tar was formed and the ratio of 2- and 3-acetylation was 3.6 $\pm$ 0.2 to 1; while with acetic anhydride, the ratio was 5.4 $\pm$ 0.3 to 1.

With ethyl acetate as the acylating agent, the reaction with 1 *M* pyrrylmagnesium bromide was much slower and no tar was produced. Since the concentration of the 3-acetylpyrrole produced was below the limit of the analytical method, the ratio must be greater than 35 to 1.

This marked change in orientation is obviously related to the reactivity of the acylating agent used. When the leaving group is a stronger base, such as the alkoxide ion in the case of esters, less positive charge is placed on the carbon atom of the incipient acylonium ion thus making it less reactive but more discriminating in its point of attack on the pyrryl anion and gives almost exclusively 2-acylation.

Thus acylation of pyrrylmagnesium bromide with esters may be considered as a useful synthetic method for preparing 2-acylpyrroles which can be reduced to the 2-alkylpyrroles. As an example, the Wolff-Kischner reduction of the 2-acetylpyrrole gave 2-ethylpyrrole in 65% yield.

EXPERIMENTAL

All reactions were carried out under a dry nitrogen atmosphere. The pyrrole (Matheson, Coleman and Bell) was distilled before use. The infrared spectra were obtained using a Beckman IR-8 instrument and the ultraviolet spectra were obtained with a Beckman DB instrument. The n.m.r. spectra were obtained on 10% solutions in dimethyl sulfoxide with tetramethylsilane as an internal reference using a Varian A-60 spectrometer.

Acetylation of Pyrrylmagnesium Bromide. A. Acetyl Chloride.

A solution of 39 g. (0.5 mole) of acetyl chloride in 35 ml. of absolute ether was added over 30 minutes to a solution of pyrrylmagnesium bromide prepared from 33 g. (0.5 mole) of pyrrole and 167 ml. of 3 *M* ethylmagnesium bromide in ether. After refluxing for 15 minutes, the reaction mixture was cooled and 200 ml. of a 15% solution of ammonium chloride was slowly added. After stirring the hydrolyzed mixture for 30 minutes, the ether layer and the aqueous layers were decanted from the insoluble yellow tar. The aqueous layer was separated and washed with 50 ml. of ether. The brown ether layer and extract were washed with 50 ml. of a 3% solution of sodium carbonate to give a light yellow solution which was washed with 50 ml. of water and dried over magnesium sulfate. The ether

was removed under vacuum and the residue (17.2 g.) vacuum distilled to give two fractions which solidified on cooling; (a) 12.5 g., b.p. 121-133°/25 mm. and (b) 2.3 g., b.p. 170-185°/25 mm. Fraction (a) was recrystallized from cyclohexane to give 2-acetylpyrrole; m.p. 88.6-90° (lit. (3) 90°), λ max mμ (log ε) in 95% ethanol; 288 (4.16), 250 infl. (3.58) (lit. (4) 290 (4.21), 251 (3.61), ν (NH) 3265 (very broad), ν (C=O) 1626 cm^{-1} (KBr). In the n.m.r. spectrum, the methyl protons gave a single peak at 7.63 τ (area 3) while the H^4 proton gave a multiplet (area 1) at 3.78 τ and the $H^{3,5}$ protons gave a broad multiplet (area 2) at 2.95 τ (lit. (5) H^{CH_3}, 7.76 τ; H^4, 3.81 τ; $H^{3,5}$, 3.04 τ in dioxane). Recrystallization of fraction (b) from benzene gave 3-acetylpyrrole; m.p. 112.5-113.5° (lit. (6) 115-116°); λ max mμ (log ε) in 95% ethanol; 270 infl. (3.76), 243 (3.94); ν (NH) 3200 (very broad), ν (C-O) 1628 cm^{-1} (KBr) (lit. (2) ν (NH) 3165, ν (C=O) 1630 cm^{-1} (Nujol)). The n.m.r. spectrum had the single methyl peak at 7.51 τ (area 3) and three multiplets (each of area 1); H^2, 2.40 τ; H^4, 3.14 τ; and H^5 3.49 (lit. (2) H^{CH_3}, 7.22 τ; H^2, 2.20 τ; and $H^{4,5}$ 3.46 τ in trifluoroacetic acid).

B. Ethyl Acetate.

A solution of 44 g. (0.5 mole) of ethyl acetate in 45 ml. of absolute ether was added over 30 min. to 150 ml. of a 3.3 *M* solution of pyrrylmagnesium bromide in absolute ether. The solution was refluxed for 30 minutes and worked up as above. Vacuum distillation of the residue (11.6 g.) gave 10.6 g. of 2-acetylpyrrole and 0.1 g. of 3-acetylpyrrole.

2-Ethylpyrrole.

Following the procedure of Cornforth and Firth (7), 5.5 g. (0.05 mole) of 2-acetylpyrrole, prepared in Part B, was refluxed for 15 minutes with 10 g. of potassium hydroxide and 8 ml. of 85% hydrazine hydrate in 100 ml. of diethylene glycol. The condenser was arranged for distillation and the reaction mixture heated so that the 2-ethylpyrrole slowly distilled over. After 4 hours, an equal volume of water was added to the distillate (10 ml.) and was saturated with sodium chloride. Both layers were extracted four times with 10 ml. of ether. The combined ether extracts were dried over magnesium sulfate and the ether removed under reduced pressure. The residue was vacuum distilled to give 2.5 g. (65%) of 2-ethylpyrrole; b.p. 69-72°/20 mm.; n_D^{25} 1.4967 (lit. (8) b.p. 67°/20 mm., n_D^{24} 1.4962).

Quantitative Acetylation of Pyrrylmagnesium Bromide.

Solutions of the 2- and 3-acetylpyrroles obtained in Part A and synthetic mixtures of the two isomers in varying proportions were dissolved in spectrograde acetonitrile to give a total concentration of 100 mg./ml. The infrared bands chosen for the analysis were at 968 and 659 cm^{-1} for the 2- and 3-acetylpyrroles respectively. The optical densities of the solutions were measured at the two wavelengths in a 0.1 mm. NaCl cell against an identical cell containing the solvent. From these data a set of simultaneous equations were derived for the calculation of the concentration of the isomers in a mixture.

One tenth of a mole of the acetylating agent dissolved in 10 ml. of absolute ether was added over 20 minutes to 100 ml. of a 1.0 *M* solution of pyrrylmagnesium bromide. Except for the reaction with ethyl acetate which was refluxed for 2 hours, the mixtures were refluxed for 20 minutes before hydrolyzing with 100 ml. of 15% ammonium chloride solution. The aqueous layers were extracted three times with 50 ml. of ether and the combined ether layers were washed with 50 ml. of 3% sodium carbonate and then with 50 ml. of water before being dried over magnesium sulfate. The ether and any unreacted pyrrole were removed under a vacuum of 5 mm. at 30°. A portion of the residue was dissolved in spectrograde acetonitrile to give a solution containing 100 mg./ml. for the infrared spectra. The concentration of the 2- and 3-acetylpyrroles were calculated from the optical densities. The results of two separate sets of experiments were averaged.

The acetylations with acetyl chloride and acetic anhydride were repeated at a 100 fold more dilute concentration by adding 0.05 mole of the acetylating agent dissolved in 100 ml. of ether to 250 ml. of 0.2 *M* pyrrylmagnesium bromide. The reactions were worked up and analyzed as before.

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REFERENCES

(1) P. S. Skell and G. P. Bean, *J. Am. Chem. Soc.*, 84, 4655 (1962).
(2) A. Castro, J. Lowell and J. Marsh, *J. Heterocyclic Chem.*, 1, 207 (1964).
(3) B. Oddo, *Ber.*, 43, 1012 (1910).
(4) V. Eisner and P. Gore, *J. Chem. Soc.*, 922 (1958).
(5) S. Gronowitz, A. Hornfeldt, B. Gestlom and R. Hoffman, *Arkiv Kemi*, 18, 133 (1961).
(6) I. Rinkes, *Rec. trav. chim.*, 57, 423 (1938).
(7) J. W. Cornforth and M. E. Firth, *J. Chem. Soc.*, 1091 (1958).
(8) W. Hertz and C. F. Courtney, *J. Am. Chem. Soc.*, 76, 576 (1954).

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