[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF MISSOURI]

Acylations with the Acid Chloride and Anhydride of 1-*n*-Butyl-2,5-dimethylpyrrole-3,4-dicarboxylic Acid

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The acylation of benzene, toluene, and the three xylenes with 1-*n*-butyl-2,5-dimethylpyrrole-3,4-dicarbonyl chloride (I) yielded cyclic diketones. The acylation of mesitylene yielded an open diketone.

The anhydride (II) of 1-*n*-butyl-2,5-dimethylpyrrole-3,4-dicarboxylic acid reacted with benzene in the presence of aluminum chloride to form a cyclic diketone. With toluene, the product was a mixture of cyclic diketone and keto acid.

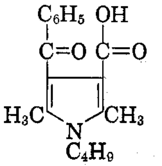
The reaction of II with phenyllithium yielded a phthalide type of compound, but with phenylmagnesium bromide and diphenylcadmium a keto acid was formed.

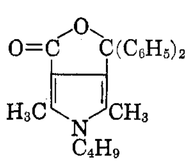
The fact that the acylation of some aromatic hydrocarbons with the acid chlorides of 2,5-dimethyl- and 2,5-diphenylfuran-3,4-dicarboxylic acids yielded mainly cyclic diketones rather than the phthalide type of compounds[2] led us to investigate acylations of these same hydrocarbons with the acid chloride I of 1-*n*-butyl-2,5-dimethylpyrrole-3,4-dicarboxylic acid and its anhydride II. This acid chloride and the anhydride had not previously been reported in the literature. The hydrogen in the 1-position was replaced by a *n*-butyl group to avoid any possible adverse effect of this hydrogen on the course of some of the reactions.

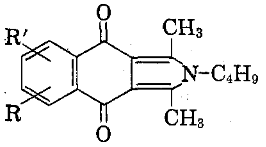
The acid chloride I was prepared from the acid by means of thionyl chloride. When the purification of I was attempted by recrystallization, the odor of hydrogen chloride was noted at each step and finally only II was obtained. After removal of traces of thionyl chloride during two crystallizations, I was sufficiently pure for use in the acylations.

The anhydride II could be obtained in two ways: cyclization of the acid by means of acetic anhydride in the presence of a trace of 85% phosphoric acid or by means of acetyl chloride. Cyclization by means of acetyl chloride was the most convenient procedure. For the acylation of benzene with I, three procedures were tried. The addition of I to the aluminum chloride in excess benzene gave the best yields. When the hydrocarbon was added to I and the aluminum chloride in nitrobenzene, only an intractable red oil was obtained. If the benzene was added to I and the aluminum chloride in carbon disulfide, the yield of IIIa was only 37% as compared with 88% in benzene solution. On the basis of these results, the first procedure was used for all of the acylations.

The acylation of benzene, toluene, and the three xylenes with I yielded only cyclic diketones III (9,10-dihydro-4,9-dioxo-1,3-dimethyl-4-*n*-butylnaphtho[2,3*c*]pyrroles). These compounds were yellow and fluoresced yellow in ultraviolet light. No ketoacid, no diaroyl compounds and no phthalide type of compounds were isolated from the reaction mixtures. Mesitylene formed 1-*n*-butyl-2,5-dimethyl-3,4-dimesitoylpyrrole.


IV


V


III

IIIa. R = R′ = H
IIIb. R = 6-CH_3; R′ = H
IIIc. R = 6-CH_3; R′ = 7-CH_3
IIId. R = 6-CH_3; R′ = 8-CH_3
IIIe. R = 5-CH_3; R′ = 8-CH_3

The products from the acylation of benzene and *p*-xylene were analyzed in the Grignard machine. Both compounds gave one active hydrogen and two carbonyl groups per molecule when the pot was heated in boiling water for fifteen minutes after the addition of the methylmagnesium iodide. If the mixture was not heated at this point but merely stirred for fifteen minutes at room temperature, only one carbonyl group reacted and there was no evolution of methane. Heating in boiling water for about 8 minutes gave about 0.6 mole of methane and about 1.5 carbonyl groups per molecule. 1-*n*-Butyl-2,5-dimethylpyrrole gave 0.017 mole of methane after heating for fifteen minutes.

The acylation of benzene with II formed only the cyclic diketone IIIa in 12% yield. The acylation of toluene with II under the same experimental conditions formed IIIb and a ketoacid, each in 13% yield. In the furan series, no cyclic diketone was obtained from the corresponding anhydride.

The reaction of II with phenylmagnesium bromide and with diphenylcadmium yielded the keto acid IV. When this keto acid was recrystallized from ethanol, the compound, m.p. 135–

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[1] Abstracted from the Ph.D. dissertation of James A. Gallagher, June 1955.

[2] D. V. Nightingale and B. Sukornick, *J. Org. Chem.*, **24**, 497 (1959).

TABLE I

ACYLATIONS WITH 1-*n*-BUTYL-2,5-DIMETHYLPYRROLE-3,4-DICARBONYL CHLORIDE

Hydrocarbon	Yield, %, III	M.P., °C.	Formula	Calcd., % C	Calcd., % H	Found, % C	Found, % H
Benzene	88	129–130	$C_{18}H_{19}O_2N$	76.84	6.81	76.48	6.88
Toluene	34	135–136	$C_{19}H_{21}O_2N$	77.26	7.17	77.13	6.96
o-Xylene	82	216–217	$C_{20}H_{23}O_2N$	77.64	7.49	77.67	7.65
m-Xylene	83	125–126	$C_{20}H_{23}O_2N$	77.64	7.49	77.28	7.51
p-Xylene	33	102–103	$C_{20}H_{23}O_2N$	77.64	7.49	77.45	7.65
Mesitylene	57[a]	173–174	$C_{30}H_{37}O_2N$	81.22	8.41	81.07	8.38

[a] The open diketone.

136°, apparently crystallized with one molecule of alcohol of crystallization, $C_{18}H_{21}O_3N.C_2H_5OH$, which was not removed by heating in a drying pistol under reduced pressure. The percentages of carbon and hydrogen found agreed with the calculated values for a mono alcoholate. A determination of active hydrogen and carbonyl groups in the Grignard machine gave 1.89 active hydrogens and 2.26 carbonyl groups per molecule. These values are within experimental error for two active hydrogens and two carbonyl groups per molecule. If the crude product was recrystallized only from petroluem ether, the found values for carbon and hydrogen percentages of the compound, m.p. 133–134°, agreed with those calculated for $C_{18}H_{21}O_3N$. A mixture of the two compounds melted at 115–117°.

The reaction of II with phenyllithium formed a phthalide type of compound V as indicated by values from carbon and hydrogen analyses and determination of active hydrogen and carbonyl groups.

The ketoacid IV was reacted with thionyl chloride, but the resulting acid chloride could not be purified without decomposition, or kept for any length of time even in a vacuum desiccator. Immediately after removal of excess thionyl chloride, a toluene solution of the crude acid chloride was added to aluminum chloride in toluene. The The only product isolated from the reaction was the intra molecular acylation product, the cyclic diketone, IIIa rather than an open diketone.

The infrared absorption spectrum of IIIa has strong bands at 6.06 microns and 13.88 microns, the expected region for a carbonyl group conjugated with an unsaturated system and an *o*-disubstituted benzene ring which is part of a fused system.[3]

EXPERIMENTAL[4]

The melting points are uncorrected.

The preparation of 1-n-butyl-2,5-dimethyl-3,4-dicarboxylic acid. The procedure is an adaptation of Knorr's preparation of pyrrole.[5] Solid α,α'-diacetoethylsuccinate (25.8 g., 0.1 mole), 10.9 g. of *n*-butylamine and 300 ml. of water were mixed at room temperature and allowed to stand overnight with occasional stirring. The solution was acidified and extracted with ether, the ether extract was washed with 5% hydrochloric acid and finally with water. After removal of the solvent, the crude ester was recrystallized from ethanol and finally from petroleum ether (60–70°); yield, 21.6 g. (73%) m.p. 61–62°.

Anal. Calcd. for $C_{16}H_{25}O_4N$: C, 65.06; H, 8.53. Found: C, 65.10; H, 8.58.

In a 100-ml. round bottom flask was placed 10 g. of 1-*n*-butyl-2,5-dimethyl-3,4-dicarbethoxypyrrole, 10 g. of potassium hydroxide, 10 ml. of water, and 30 ml. of ethylene glycol. The solution was refluxed overnight, cooled to room temperature, and acidified with 50% acetic acid. After cooling in an ice-salt bath for about an hour, crystals of the desired acid separated and were collected on a filter. The filtrate was acidified with hydrochloric acid to precipitate the remaining acid, which was redissolved in a minimum amount of 10% sodium hydroxide to remove a small amount of hydrochloric acid from the crystals, and the solution acidified with 50% acetic acid. The combined solids were recrystallized from ethyl acetate to yield 7 g. (87%) of 1-*n*-butyl-2,5-dimethylpyrrole-3,4-dicarboxylic acid, m.p. 178–180°.

Anal. Calcd. for $C_{12}H_{17}O_4N$: C, 60.24; H, 7.16. Found: C, 60.12; H, 7.36.

Preparation of the acid chloride of 1-n-butyl-2,5-dimethylpyrrole-3,4-dicarboxylic acid. To 2.28 g. (0.01 mole) of the acid was added 32 g. of thionyl chloride. The reaction began immediately and after it had subsided, the mixture was heated on a steam bath for 30 min. The excess thionyl chloride was removed with an aspirator, the residue was dissolved in dry ether and the solution decolorized with Norite. The solution was filtered and the ether removed with the aspirator. After two recrystallizations, the acid chloride was satisfactory for use in the acylations, but efforts to obtain an analytical sample lead finally to the anhydride. Yields of twice recrystallized acid chloride ranged from 76% to 91%.

Preparation of the anhydride of 1-n-butyl-2,5-dimethylpyrrole 3,5-dicarboxylic acid. Procedure A. In a 100-ml. round bottom flask fitted with a reflux condenser were placed 5 g. (0.021 mole) of the acid and 40 ml. of acetyl chloride. The solution was refluxed for 2 hr. or less on a steam bath and then connected to the aspirator to remove part of the acetyl chloride. The flask was then placed in an acetone dry ice bath and cooled for about 15 min. The precipitated anhydride was collected on a Buchner funnel, then stirred in a beaker with a small amount of ether and with 20 ml. of 5% sodium bicarbonate solution. After standing about 20 minutes, the anhydride was collected on a Buchner funnel and washed with water. Recrystallization from petroleum ether (60–70°) yielded 2.8 g. (61%) of colorless anhydride, m.p. 127–128°.

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(3) L. F. Bellamy, *The Infrared Spectra of Complex Molecules*, Methuen and Co., Ltd., London, 1954, pp. 119, 129, 54.

(4) The carbon and hydrogen analyses were performed by Mr. Y. C. Lee and Mr. R. Elliot at the University of Missouri.

(5) L. Knorr, *Ber.*, **18**, 299 (1885).

Anal. Calcd. for $C_{12}H_{15}O_3N$: C, 65.14; H, 6.83. Found: C, 65.43; H, 6.88.

Procedure B. In a 50-ml. round bottom flask fitted with a six inch column packed with glass helices were placed 8 g. (0.033 mole) of 1-*n*-butyl-2,5-dimethylpyrrole-3,4-dicarboxylic acid, one drop of 85% phosphoric acid, and 20 ml. of acetic anhydride. The flask was heated to 140° and held at this temperature until the head of the column reached 118°, the boiling point of acetic acid. These temperatures were maintained for an hour and then the acetic acid and acetic anhydride were removed with an aspirator. The residue was recrystallized from petroleum ether (60–70°) to yield 4.4 g. (60%) of II, m.p. 127–128°.

Acylations with 1-n-butyl-2,5-dimethylpyrrole-3,4-dicarbonyl chloride.[6] The general procedure is as follows: In a 200-ml. three necked round bottom flask was placed 1.0 mole of the hydrocarbon and 3.04 g. (0.023 mole) of aluminum chloride. The flask was fitted with the usual equipment and cooled in an ice bath. The acid chloride (2.93 g.) (0.01 mole) was added slowly to the cooled hydrocarbon solution, then the ice bath was removed and the mixture was stirred overnight at room temperature. The complex was decomposed in the usual manner with iced hydrochloric acid, the hydrocarbon layer was separated, the aqueous layer was washed with ether, and the ether washings were added to the hydrocarbon layer. The solvents were removed by steam distillation, the organic residue was dissolved in ether, and the solution extracted with sodium hydroxide. The separated ether layer was evaporated at room temperature and the solid residue was recrystallized from ethanol and finally from petroleum ether (60–70°). Yields, physical constants, and analytical data are summarized in Table I.

Acylations with 1-n-butyl-2,5-dimethylpyrrole-3,4-dicarboxylic acid anhydride. In a 500-ml. flask was placed 100 ml. of benzene and 3.20 g. (0.024 mole) of aluminum chloride. The flask was cooled in ice and 2.21 g. (0.01 mole) of the anhydride II was added slowly with stirring. The material in the flask became gummy but after standing overnight, most of the gum had dissolved, and the solution was stirred for 4 hr. at room temperature.

The complex was decomposed with iced hydrochloric acid. The separated solid was collected on a filter and proved to be 1-*n*-butyl-2,5-dimethylpyrrole-3,4-dicarboxylic acid. The hydrocarbon layer was separated, the aqueous layer was extracted with ether, and the ether extract added to the hydrocarbon layer. The ether-benzene solution was extracted with 10% sodium hydroxide, separated, and the solvents steam distilled. The residue was recrystallized from petroleum ether (60–70°) to yield 0.32 g. (12%) of yellow needles, m.p. 126–127°, which were identified as the cyclic diketone IIIa.

Acidification of the sodium hydroxide extract yielded a small amount of the dicarboxylic acid but no ketoacid IV.

The acylation of toluene with 2.20 g. (0.01 mole) of anhydride and 3.20 g. (0.024 mole) of aluminum chloride in the same manner yielded 0.35 g. (13%) of cyclic diketone IIIb, m.p. 134–135°, and 0.50 g. of 1-*n*-butyl-2,5-dimethyl-4-toluoylpyrrole-3-carboxylic acid, m.p. 129–130°.

Anal. Calcd. for $C_{19}H_{23}O_3N$: C, 72.83; H, 7.40. Found: C, 72.93; H, 7.59.

Reaction of II with phenylmagnesium bromide. A solution of phenylmagnesium bromide prepared from 6.28 g. (0.04 mole) of bromobenzene in about 150 ml. of ether was added to 8.70 g. (0.04 mole) of II suspended in 100 ml. of dry ether in a 500-ml. three necked round bottom flask fitted with the usual equipment. After the slightly exothermic reaction, the solution was stirred for about 2 hr.

The complex was decomposed by pouring onto iced hydrochloric acid. The solid which separated contained magnesium and was warmed briefly with hydrochloric acid on the steam bath to complete decomposition. Ether was added, the solution filtered, and the ether layer added to the ether layer initially obtained from the partial decomposition of the complex.

The combined ether solutions were washed with water, sodium bicarbonate, sodium carbonate, and finally with sodium hydroxide.

The sodium bicarbonate and sodium carbonate extracts were acidified dropwise with 10% hydrochloric acid. The first material to separate was a gummy product which was dried in a vacuum desiccator and melted at 118–125°. The gum was completely precipitated at *p*H 7. After removal of the gum, continued acidification to about *p*H 5 yielded a white solid which melted at 124–128°. After removal of this material by filtration, further acidification yielded a small amount of dicarboxylic acid.

The crude solids were recrystallized first from ethanol and finally from aqueous ethanol. Yield, 2.55 g. (21%), m.p. 135–136°. The values from the carbon and hydrogen analyses indicated that this compound was an alcoholate.

Anal. Calcd. for $C_{18}H_{21}O_3N.C_2H_5OH$: C, 69.54; H, 7.88. Found: C, 69.54; H, 7.52.

Tschugaeff-Zerwitinoff determination: 1.89 active hydrogens and 2.26 carbonyl groups per molecule.

The reaction was repeated, but the product was recrystallized only from petroleum ether (60–70°). The yield was 2.86 g. (24%) of white crystals, m.p. 133–134°.

Anal. Calcd. for $C_{18}H_{21}O_3N$: C, 72.21; H, 7.07. Found: C, 71.88; H, 7.37.

A mixture of this product and that recrystallized from alcohol (above) melted at 115–117°.

Reaction of II with diphenylcadmium. To a toluene solution of diphenylcadmium prepared from 10.6 g. of bromobenzene was added 6 g. of II. The reaction flask was heated to 70° and stirred at this temperature for about 2 hr. The complex was decomposed with iced concentrated hydrochloric acid and filtered.

The separated solid (2.55 g.) was unchanged II.

The toluene layer was separated from the aqueous layer, the aqueous layer was washed with ether and these washings combined with the toluene layer. The combined solvents were extracted with 5% sodium carbonate solution and then the alkaline solution was acidified with 50% acetic acid. The product separated as a gummy mass and was removed. It was redissolved in 5% sodium carbonate and 10% acetic acid was added dropwise. The keto acid precipitated and was recrystallized from ethanol. Yield, 0.81 g. (10%), m.p. 135–136°, mixture m.p. with the product (alcoholate) m.p. 135–136° from the reaction with phenylmagnesium bromide 135–136°.

Reaction of II with phenyllithium. A solution of phenyllithium prepared from 3.14 g. of bromobenzene in 100 ml. of dry ether was added to a slurry of 4.42 g. (0.02 mole) of II in 100 ml. of dry ether in a 500-ml. flask fitted with the usual equipment. When the addition was complete, the mixture was allowed to stand overnight. The complex was decomposed with 150 ml. of water, and the solution was filtered to remove 0.3 g. of dicarboxylic acid. The ether layer was separated, the aqueous layer was washed three times with ether and the ether washings added to the original ether layer. This solution was then extracted three times with 1% sodium hydroxide solution and these alkaline washings added to the original aqueous layer. A yellow oil was obtained by evaporation of the ether solution which crystallized on standing.

The aqueous layer was acidified dropwise with 10% hydrochloric acid to about *p*H 8. A solid separated and was collected on a filter. Further acidification yielded 0.4 g. of dicarboxylic acid.

The solid from the ether solution and the solid which separated from the aqueous layer at *p*H 8 were warmed on a steam bath with 5% sodium hydroxide for about 20 min. The insoluble white solid was collected on a filter, and acidification of the filtrate yielded 0.7 g. of dicarboxylic acid.

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(6) R. Fuson, S. Speck, and W. Hatchard, *J. Org. Chem.*, **10**, 55 (1945).

The white solids (2.4 g., 33%) were recrystallized from aqueous ethanol to yield crystals which melted at 167–167.5°.

Anal. Calcd. for $C_{24}H_{25}O_2N$: C, 80.19; H, 7.01. Found: C, 79.79; H, 7.15.

Tschugaeff-Zerewitinoff determination: 0.12 mole of active hydrogen and 0.85 carbonyl group per molecule.

Acylation of toluene with 1-n-butyl-2,5-dimethyl-3-benzoyl-4-carbonyl chloride. Because this acid chloride could not be purified without extensive decomposition, the crude product from the reaction of 1.40 g. of keto acid and thionyl chloride was dissolved in dry toluene and added dropwise to a mixture of 1.5 g. of aluminum chloride and 50 ml. of toluene in the conventional equipment. From this reaction there was isolated by the procedures previously described 0.40 g. (29%) of cyclic diketone IIIa, m.p. and mixed m.p. with IIIa from the acylation of benzene with I, 129–130°.

Preparation of 1-n-butyl-2,5-dimethylpyrrole. Acetonylacetone (57 g., 0.5 mole) and 36 g. (0.5 mole) of *n*-butylamine were placed in a flask fitted with a reflux condenser. The exothermic reaction began immediately. The mixture stood overnight and was then distilled. The product boiled at 98–100° (20 mm.), yield 64 g. (85%), n_D^{20} 1.4828.

Anal. Calcd. for $C_{10}H_{17}N$: C, 79.40; H, 11.34. Found: C, 79.08; H, 11.27.

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A Study of the Entrainment Method for Making Grignard Reagents

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Modifications of the entrainment method used in this work were: (1) introduction of all of the "inert" halide at the start of the reaction, (2) use of ethylene bromide rather than ethyl bromide as the entrainment reagent, (3) a slow rate of addition (*ca.* 12 hr.) of the entrainment reagent. In this manner, α-chloronaphthalene was converted to α-naphthoic acid in 56% yield and to naphthalene in 66% yield, *p*-bromodimethylaniline to *p*-dimethylaminobenzoic acid in 48% yield and to dimethylaniline in 71% yield, hexachlorobenzene to pentachlorobenzoic acid in 71% yield and pentachloroacetophenone in 31% yield, and *p*-bromoacetophenone azine to *p*-carboxyacetophenone in 34% yield and to phenyl-*p*-acetophenylcarbinol in 9% yield. The yields for the specific compounds are superior to any obtained heretofore by means of the entrainment method and demonstrate the utility of ethylene bromide as an entrainment agent.

A number of "inert" halogen compounds, such, for example, as α-chloronaphthalene, fail to give Grignard reagents under ordinary conditions. Four methods are available for application under these circumstances: the lithium, the reactive solvent, the activated metal, and the entrainment methods. The lithium method[1-3] has been applied occasionally for conversion of "inert" halides to organic lithium compounds, but its main use, stemming from the high reactivity of organic lithium compounds, has been to accomplish additions in a more effective way than with Grignard reagents. In one of the few papers devoted to a comparison of conversion of "inert" halides,[4] Gilman and coworkers state that chlorobenzene, *p*-chlorotoluene, α-chloronaphthalene, and *p*-bromodimethylaniline give better yields of organolithium compounds than of Grignard reagents but that the reverse is true for conversion of dihalides to organometallic compounds. An example of the former conversion is the preparation of *p*-dimethylaminobenzoic acid in 41–56% yields from the *p*-dimethylaminophenyllithium.[5] Braude and Evans have been successful recently in preparing vinyllithium compounds.[6] Examples of conversion of "inert" halides to organolithium compounds are not numerous, however. Perhaps additional factors contributing to this neglect are the possibilities of the organolithium compound being insoluble or of the lithium halide coating the surface of the lithium.

The second method of application, the reactive solvent method, is comparatively recent. Indeed, the most promising results of this method have been published after the work in this laboratory on the entrainment method had been well advanced. The reactive solvent is one which complexes with the Grignard reagent more effectively and in this manner brings about reaction or completion of reaction between magnesium and "inert" halides. Tetrahydrofuran seems to be the solvent of choice although other cyclic ethers are also effective.[7-9] The method is particularly well adapted to synthesis of vinyl Grignard reagents. We must keep in mind, however, that tetrahydro-

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