Reaction of Some Heterocyclic Ketones with Lithium Dimethyl Copper

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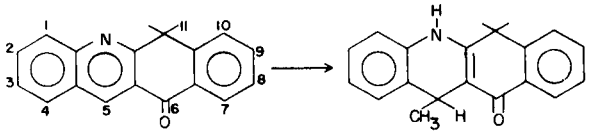
Reaction of lithium dimethyl copper with several heterocyclic ketones results in a 1,4-addition and introduction of a methyl group on the heterocyclic ring. In some cases, addition to the carbonyl also occurs.

As a result of recent studies aimed at the synthesis of selected potential carcinogenic compounds we became interested in the reaction of organometallic reagents with heterocyclic ketones. One of the first reports of a 1,4-addition in an activated heterocyclic system was the addition of *n*-propylmagnesium bromide to 3-cyanopyridine to give 4-*n*-propyl-3-pyridyl *n*-propyl ketone (1). Fuson and Miller, later found that phenyl magnesium bromide reacts with both 3-benzoylpyridine and 3-benzoylquinoline to give 1,4-addition products (2).

We chose as our model, 6-keto-11,11-dimethyl-6,11-dihydrobenz[*b*]acridine (**1**), (3) since it is structurally related to 3-benzoylquinoline and other compounds of interest to us.

Alkyl copper reagents are known to promote a wide variety of conjugate addition and alkylation reactions (4). Since, **1** can be viewed as an α,β-unsaturated ketone in which the double bond is contained in an aromatic ring, we viewed the possibility of a conjugate addition of an organocopper reagent as very likely. Indeed, when **1** was treated with a solution of lithium dimethylcopper at 0° there was obtained an 85% yield of a yellow crystalline product, **2**. That the



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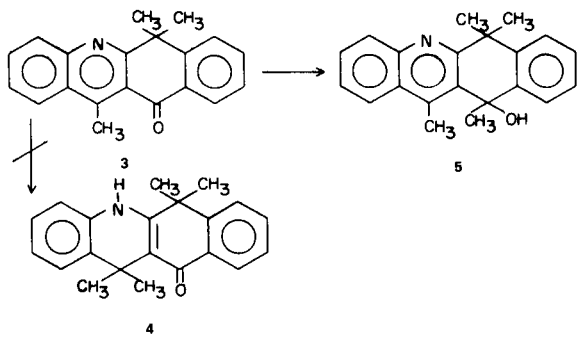
product was a 1,4-addition product was evident from the nmr spectrum which displayed two-three proton singlets, a three proton doublet and a one proton quartet. Further evidence for structure **2** was provided by the chloranil oxidation of the yellow product to 6-keto-5,11,11-trimethyl-6,11-dihydrobenz[*b*]acridine (**3**). A comparison of the nmr spectra of compounds **1** and **3** reveals the absence of a singlet at δ 9.13 for H_5 in the nmr spectrum of compound **3** and the presence of an additional methyl resonance at δ 3.19 establishes the position of the methyl group at C_5. No products due to 1,6- or 1,8-conjugate addition (attack at C_2 or C_4) were observed in the alkylation reaction of **1** (tlc and nmr).

Attempts at alkylating the nitrogen atom by the addition of methyl iodide to the organo-copper reaction mixture before hydrolysis led only to the formation of the normal 1,4-addition product **2**. A further observation, based on tlc data, is that the ketone **3** when subjected to the original conditions fails to undergo a second 1,4-addition reaction to yield an appreciable amount of a geminally alkylated product **4** but instead reacts to form the 1,2-addition product 6-hydroxy-5,6,11,11-tetramethyl-6,11-dihydrobenz[*b*]acridine (**5**).



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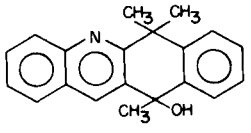
The reaction of **1** with methyl magnesium iodide was found to form a mixture (3:1) of 1,2- (**6**) and 1,4-addition (**2**) products in contrast to the behaviour reported earlier



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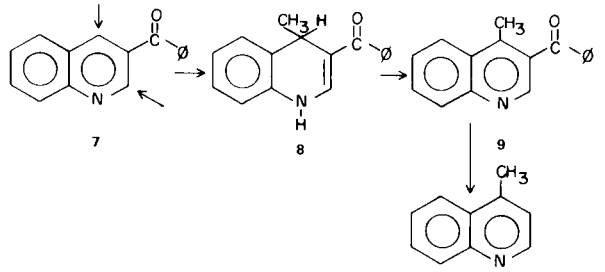
(3). Since we believe this to be the first reported example of the addition of an organocopper reagent to a heterocyclic system of this nature, the reactivities of several other related

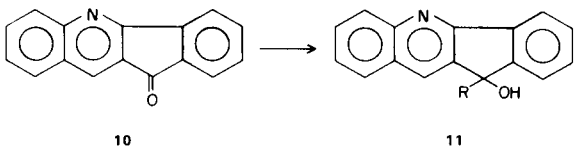
systems were examined.

In the case of 3-benzoylquinoline **7** (2), there exists in principle the possibility of a trivial 1,2-addition to the carbonyl or two different modes of 1,4-conjugate addition, namely a 1,2- or 1,4-addition to the quinoline nucleus. When the reaction was carried out in the normal manner (see Experimental) only a yellow solid **8** was isolated. Spectral data (3-proton doublet and 1 proton quartet) indicate that it is a conjugate addition product. Oxidation of **8** with chloranil gave an aromatized ketone **9** which was different than authentic 2-methyl-3-benzoylquinoline (5), inferring the site of substitution to be C_4. The position



of the methyl group was established unequivocally by degrading a sample with molten potassium hydroxide to yield a sample of 4-methylquinoline.

The reaction of 6-keto-5,5-dimethyl-5,6-dihydrobenz-[c]acridine with the organocopper reagent also afforded a conjugate addition product (6). However, the reagent afforded only a 1,2-addition product when permitted to react with 11*H*-indeno[1,2-*b*]quinolin-11-one (**10**) (7). The failure of the indenoquinoline to undergo this 1,4-addition can be attributed to the general reluctance of these ring systems to undergo 1,4-addition reactions. For example, the reaction of phenyl magnesium bromide with related systems frequently (2,3,8,9) yields a 1,4-addition product. However, in this ring system (**10**) even phenyl magnesium bromide reacts in a 1,2-fashion to give **11** where R = C_6H_5 (7).



The importance of the carbonyl function in promoting the addition reaction was demonstrated by subjecting 11,11-dimethyl-6,11-dihydrobenz[*b*]acridine to the reaction conditions. Although decomposition of the reagent was apparent, the starting acridine was recovered unchanged in 98% yield. From this observation it appears that the above described reaction is a conjugate 1,4-addition to the unsaturated carbonyl system, however, there is little doubt that the nitrogen does play a significant role in determining the course of the reaction. In the reaction of benz[*b*]-acridine ketone **1** where substitution could occur in the benzene or quinoline nucleus, exclusive addition occurs in the heterocyclic ring.

Further studies are continuing in order to delineate the scope and utility of this reaction.

EXPERIMENTAL

6-Keto-5,11,11-trimethyl-5,6,11,12-tetrahydrobenz[*b*]acridine (**2**).

This material was prepared in a manner similar to that described below for the synthesis of the dihydroquinoline **8**. Thus, from ketone **1** (819 mg., 3 mmoles), cuprous iodide (760 mg., 4.0 mmoles) and methyl lithium, there was obtained a good yield of the pure product (771 mg., 89%, m.p. 255-256°); nmr (deuteriochloroform): δ 1.30 (d, 3H, CH_3-5, J = 7.0 Hz), 1.64 (s, 3H, CH_3), 1.73 (s, 3H, CH_3), 4.55 (q, 1H, H-5, J = 7.0 Hz), 6.90-7.70 (m, 7H, arom), 8.28 (m, 1H, H-10).

Anal. Calcd. for $C_{19}H_{15}NO$: C, 83.01; H, 6.62; N, 4.84. Found: C, 83.29; H, 6.54; N, 4.78.

6-Keto-5,11,11-trimethyl-6,11-dihydrobenz[*b*]acridine (**3**).

This material was prepared in an analogous fashion to that described for the manner of formation of 4-methyl-3-benzoylquinoline (**9**) (see below). On a small scale (0.5 mmole) a fair yield of the desired material was obtained (45%, m.p. 144-145°); nmr (deuteriochloroform): δ 1.87 (s, 6H, CH_3), 3.19 (s, 3H, CH_3), 7.20-8.49 (m, 8H, arom.); nmr of compound **1** (deuteriochloroform): δ 1.90 (s, 6H, CH_3), 7.30-8.55 (m, 8H, arom), 9.13 (s, 1H, H-5).

Anal. Calcd. for $C_{20}H_{17}N$: C, 83.59; H, 5.67; N, 4.87. Found: C, 83.64; H, 5.71; N, 4.49.

3-Benzoyl-4-methyl-1,4-dihydroquinoline (**8**).

A sample of 3-benzoylquinoline (3) (1.9 g., 8.2 mmoles) in ether (75 ml.) was added to a solution of lithium dimethyl copper (from 4.75 g. of cuprous iodide and methyl lithium) in ether (100 ml.) at 0° over a period of one hour. After stirring at room temperature for two hours, wet ether (100 ml.), followed by water (100 ml.) was added. After the hydrolysis was complete the ether layer was separated. The aqueous layer was extracted with additional ether (3 x 100 ml.). The combined ether extracts were washed with water, saturated sodium chloride solution; and dried over anhydrous magnesium sulfate. The crude product (1.8 g.) was recrystallized from benzene-heptane to give a pure yellow powder (1.6 g., 79%, m.p. 187-188°); nmr (deuteriochloroform): δ 1.28 (d, 3H, CH_3, J = 7.0 Hz), 4.28 (q, 1H, H-4, J = 7.0 Hz), 6.62-7.60 (m, 10H, arom.).

Anal. Calcd. for $C_{17}H_{15}NO$: C, 81.24; H, 6.82; N, 5.57. Found: C, 81.51; H, 6.68; N, 5.48.

3-Benzoyl-4-methylquinoline (**9**).

A chloroform solution (50 ml.) containing a sample of the dihydro compound **8** (400 mg., 1.6 mmoles) and chloranil (500 mg., 2.3 mmoles) was heated under reflux for four hours. The cooled chloroform solution was extracted with sodium hydroxide solution (10%, 4 x 25 ml.) and water (2 x 20 ml.). The chloroform layer was separated and dried over anhydrous magnesium sulfate and evaporated to dryness. The residue was recrystallized from petroleum ether (38-41°) to afford white crystals of product (270 mg., 69%, m.p. 94-96°); nmr (deuteriochloroform): δ 2.68 (s, 3H, CH_3), 7.4-8.3 (m, 9H, arom.), 8.85 (s, 1H, H-2); nmr of 2-methyl-

3-benzoylquinoline (5) (deuteriochloroform): δ 2.74 (s, 3H, CH_3), 7.40-8.25 (m, 9H, arom.), 8.12 (s, 1H, H-4).

Anal. Calcd. for $C_{17}H_{15}NO$: C, 81.90; H, 6.06; N, 5.62. Found: C, 82.10; H, 6.26; N, 5.42.

A sample of compound **9** was mixed with powdered potassium hydroxide and fused over a free flame. Water was added to the cooled mixture and the product was steam-distilled. After extraction, drying, and evaporation there was obtained a pure sample of 4-methylquinoline.

Reaction of Compound **1** with Methyl Magnesium Iodide.

The reaction was carried out as previously described by Cromwell and David (3). Examination of the crude reaction product by tlc (silica gel; benzene) indicated the presence of two compounds. These were separated by column chromatography on silica gel with benzene, benzene-chloroform and chloroform as eluents. The major component was the 1,2-addition product **6** previously described and the minor product was the 1,4-addition product **2**. Integration of the nmr spectrum of the crude reaction mixture indicated the relative amounts of the two products as 75:25.

Reaction of 11*H*-Indeno[1,2-*b*]quinolin-11-one (**10**) with Lithium Dimethylcopper.

A sample of ketone **10** when treated with a solution of copper reagent as described for quinoline **7** afforded only the 11-hydroxy-11*H*-inden[1,2-*b*]quinoline (**11**) (where R = CH_3) which was identical in all respects to that obtained by Cromwell and Mitsch (7).

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