

Novel Synthesis of 2,4-Diarylbenzo[*h*]quinazolines

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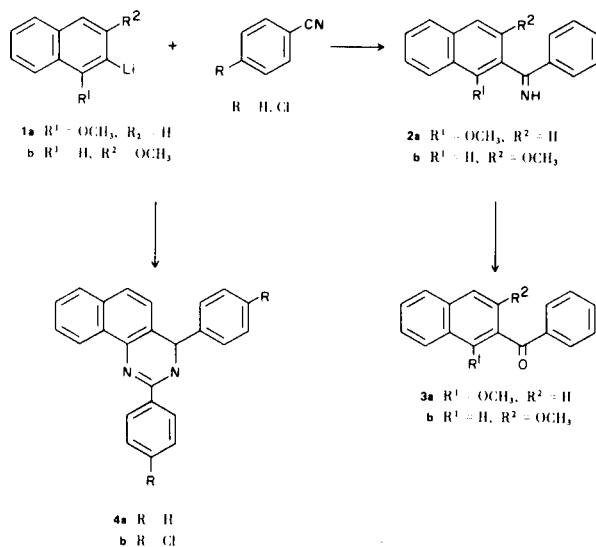
Received March 23, 1973

As part of our program directed toward the synthesis of compounds with potential biological interest we had need of 2-benzoyl-1-methoxy- and 2-benzoyl-3-methoxynaphthalene (**3a** and **3b**). To obtain these we decided to allow the known (1,2) lithium reagents from 1- and 2-methoxynaphthalene (**1a** and **1b**) to react with benzonitrile and then hydrolyze the expected imines **2a** and **2b** to the desired ketones.

When the procedure was attempted with the lithium reagent from 2-methoxynaphthalene (**1b**) and benzonitrile a 90% yield of the imine **2b** was isolated as a hydrochloride salt. Hydrolysis of **2b** with refluxing aqueous sodium hydroxide or hydrochloric acid gave the ketone **3b** in 85% or 55% yields respectively.

Reaction of the lithium reagent from 1-methoxynaphthalene (**1a**) with benzonitrile under similar conditions did not give any of the expected imine **2a** or the ketone **3a**. Instead, there was isolated a solid analyzing for $C_{24}H_{14}N_2$ (m/e 332) which gave ir, uv and nmr spectra in agreement with the known (3) 2,4-diphenylbenzo[*h*]quinazoline (**4a**). Preparation of **4a** by the published procedure and comparison with our substance revealed that the two compounds were identical. Reaction of 4-chlorobenzonitrile with **1a** gave a 31% yield of 2,4-di-(*p*-chlorophenyl)benzo[*h*]quinazoline (**4b**).

Although this reaction was not studied further these

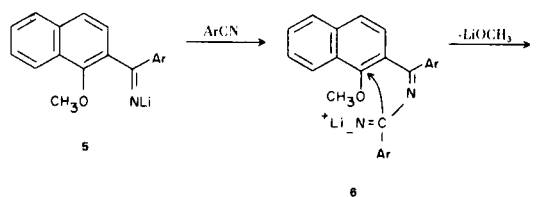


results suggest that it can be used to prepare a variety of 2,4-diarylbenzo[*h*]quinazolines under mild conditions.

A possible pathway to the formation of **4a** is given in Scheme 1. The lithium reagent **5** obtained from **1a** and a benzonitrile could react with a second molecule of benzonitrile to give the lithium reagent **6**. Intramolecular nucleophilic displacement of the methoxy group by the terminal imine nitrogen would then result in **4**.

A similar mechanism has recently been proposed by Berry and Wakefield (4) to account for the formation of 2,4-diaryl-5,6,7,8-tetrachloroquinazolines from pentachlorophenyllithium and a benzonitrile.

SCHEME 1



EXPERIMENTAL

Melting points were determined on a Thomas-Hoover capillary melting point apparatus and have not been corrected. Ir spectra were taken on a Perkin-Elmer "Infracord" Spectrophotometer. Uv spectra were obtained on a Cary Model 14 spectrometer. Proton nmr were measured on a Varian Associates A-60 spectrometer using TMS as an internal reference. The mass spectra were obtained on a LKB 900 mass spectrometer.

Elemental analysis were determined by Mr. W. Bonkowski and his associates in our laboratories.

Lithiated 1-Methoxynaphthalene Reactions.

A. With Benzonitrile.

A stirred solution of 39.5 g. (0.25 mole) of 1-methoxynaphthalene in 200 ml. of tetrahydrofuran maintained under a nitrogen atmosphere was treated dropwise with 155 ml. (0.25 mole) of 1.6 *M* *n*-butyllithium in hexane (Foote Mineral Co.). The solution after being stirred an additional 2.5 hours at room temperature was cooled to an internal temperature of -20° and then a solution of 51.6 g. (0.50 mole) of benzonitrile in 100 ml. of tetrahydrofuran was added over a 0.5 hour period. The cooling was removed and the solution allowed to stand *ca.* 15 hours at room temperature. The mixture was then treated with 50 ml. of saturated ammonium chloride solution, filtered, dried with an-

hydrous magnesium sulfate and the solvent removed *in vacuo*. The semi-solid residue was crystallized from chloroform/pentane (1:1) to give 29.1 g. (35%) of 2,4-diphenylbenzo[*h*]quinazoline (**4a**), m.p. 159-160° (lit. (3) m.p. 160°); ir (potassium bromide): no C=O band in 5.8-6.1 μ region; nmr (chloroform): δ 7.45-8.14 (m, 13H, 2C₆H₅, H-7,8,9), 8.93 (m, 2H, H-5, H-6), 9.63 (m, 1H, H-10); uv, λ max (95% ethanol): 240 m μ (ϵ 33,890) 266 (38,935), 315 (18,025), 350 (6,490), 368 (6,490); mass spectrum, molecular ion peak at *m/e* 332, 255 (M-C₆H₅), 166.

Comparison of the ir, uv and mixture m.p. (159-160°) of **5a** with material prepared by the procedure given in reference 3 revealed them to be identical.

Anal. Calcd. for C₂₄H₁₆N₂: C, 87.0; H, 4.8; N, 8.4. Found: C, 87.0; H, 4.9; N, 8.3.

B. With 4-Chlorobenzonitrile.

The lithium reagent obtained from 39.5 g. (0.25 mole) of 1-methoxynaphthalene and 155 ml. (0.25 mole) of 1.6 *M* *n*-butyllithium in hexane was allowed to react with a solution of 68.8 g. (0.50 mole) of 4-chlorobenzonitrile in 100 ml. of tetrahydrofuran and processed as in A. There was obtained 30.9 g. (31%) of 2,4-di(*p*-chlorophenyl)benzo[*h*]quinazoline, m.p. 220-221.5° (chloroform/hexane); ir (potassium bromide): no C=O band in 5.8-6 μ region; uv, λ max (95% ethanol) 243 m μ (ϵ 29,590), 278 (43,130), 319 (18,054), 353 (5,515), 371 (5,515).

Anal. Calcd. for C₂₄H₁₄Cl₂N₂: C, 71.8; H, 3.5; Cl, 17.7; N, 7.0. Found: C, 71.9; H, 3.7, Cl, 17.9; N, 6.9.

Reaction of Lithiated 2-Methoxynaphthalene with Benzonitrile.

A stirred solution of 39.5 g. (0.25 mole) of 2-methoxynaphthalene in 200 ml. of tetrahydrofuran maintained under a nitrogen blanket was treated with 155 ml. (0.25 mole) of 1.6 *M* *n*-butyllithium in hexane. The solution after being stirred an additional 2.5 hours at room temperature was cooled to an internal temperature of -20° and then a solution of 25.8 g. (0.25 mole) of benzonitrile in 50 ml. of tetrahydrofuran was added over a 0.5 hour period. The cooling was removed and the solution allowed to stand *ca.* 16 hours at room temperature. The mixture was then treated with 50 ml. of saturated ammonium chloride, filtered, dried with anhydrous magnesium sulfate and the solvent

removed *in vacuo*. The residual solids treated with 500 ml. of cold 2 *N* HCl and stirred for about 2 hours at room temperature. The resultant solid was filtered off, washed with 100 ml. of benzene, 100 ml. of ether and then dried *in vacuo* to give 66.5 g. (90%) of the crude hydrochloride of 2-benzoyl-3-methoxynaphthalene imine (**2b**) m.p. 280-290°; ir (potassium bromide): 3.15-4.05 (=NH₂⁺), 6.08 and 6.12 μ (C=NH₂⁺); nmr (DMSO-d₆): δ 3.83 (3H, s, OCH₃), 7.40-8.35 (11H, m, C₆H₅, C₁₀H₆). *Anal.* Calcd. for C₁₈H₁₆ClNO: C, 72.6, H, 5.4; Cl, 11.9; N, 4.7. Found: C, 72.8; H, 5.7; Cl, 11.7; N, 4.5.

A suspension of 5.0 g. of **2b** in 50 ml. of 2 *N* sodium hydroxide was stirred and refluxed for *ca.* 16 hours. The mixture was then cooled to room temperature and extracted with chloroform. The organic layer was dried with anhydrous magnesium sulfate, filtered and concentrated *in vacuo*. There was obtained 3.8 g. (85%) of 2-benzoyl-3-methoxynaphthalene, m.p. 87-88°; (*i*-C₃H₇OH/H₂O); ir (dichloromethane): 5.98 μ (C=O); nmr (deuteriochloroform): δ 3.93 (3H, s, OCH₃), 7.38-8.21 (11H, m, C₆H₅, C₁₀H₆).

When 5.0 g. of **2b** was hydrolyzed with 2 *N* hydrochloric acid under the same conditions 2.5 g. (55%) of **3b** was obtained.

Anal. Calcd. for C₁₈H₁₄O₂: C, 82.4; H, 5.4. Found: C, 82.2; H, 5.4.

Acknowledgment.

We gratefully acknowledge the efforts of Dr. Sandor Barcza and his associates in obtaining the instrumental data used in this work.

REFERENCES

- (1) R. Huisgen and H. Rist, *Ann.*, **594**, 137 (1955).
- (2) B. M. Graybill and D. A. Shirley, *J. Org. Chem.*, **31**, 1221 (1966).
- (3) H. Meerwein, P. Laasch, R. Mersch and J. Nentwig, *Chem. Ber.*, **89**, 224 (1956).
- (4) D. J. Berry and B. J. Wakefield, *J. Chem. Soc. (C)* **1971**, 642.