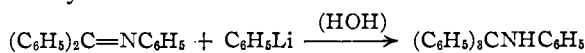


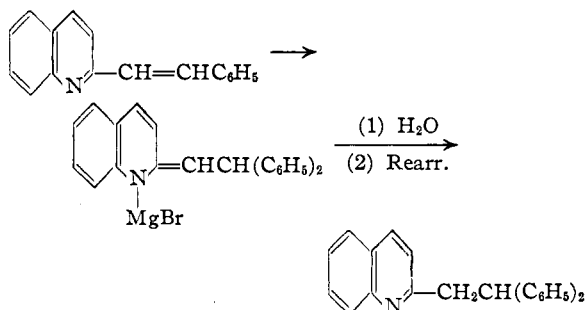
[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF IOWA STATE COLLEGE]

The Reaction of Phenyllithium and Phenylmagnesium Bromide with the Azomethine Linkage¹BY HENRY GILMAN AND GORDON C. GAINER²

One of the distinctly different types of reactions shown by phenylmagnesium bromide and phenyllithium is with the azomethine linkage. It has been shown³ that phenylmagnesium bromide does not react with benzophenone-anil in ether, but under forced conditions an unusual lateral-nuclear 1,4-addition occurs to give α -phenylbenzohydrilaniline. Phenyllithium, however, reacts with benzophenone-anil in ether to give a 1,2-addition product, namely, triphenylmethylamine.^{4a}



In connection with an examination of the mode of addition of organolithium compounds to some quinolines⁵ it was of interest to include benzalquinaldine. Fuson and co-workers⁶ have shown that there is a lateral-nuclear 1,4-addition of phenylmagnesium bromide to benzalquinaldine to give α -benzohydrilquinaldine.

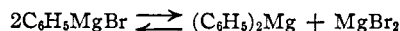


Inasmuch as benzalquinaldine and benzophenone-anil have lateral-nuclear conjugated systems (with the azomethine linkage lateral in the second case), there was a possibility that phenyllithium might show 1,2-addition to the azomethine linkage of benzalquinaldine. We have observed in this work that phenyllithium adds quite smoothly to benzalquinaldine to give an excellent yield of the same product obtained with phenylmagnesium bromide. The formation of this α -benzohydrilquinaldine is very probably due to 1,4-addition. It is unlikely that a lateral 1,2-addition occurred, for it is known that RLi compounds add much more rapidly to an isolated azomethine linkage

than to an olefinic linkage. Studies with lateral conjugated systems like those in chalcones have shown^{4b} that generally phenyllithium adds 1,2 and that phenylmagnesium bromide adds 1,4.

Another aspect of this problem was concerned with a so-called increase of reactivity of a phenylmagnesium type in order to determine whether such an increase would bring about a reaction or extent of reaction like that observed with the more reactive phenyllithium. It has long been known⁷ that phenylmagnesium bromide reacts very slowly with quinoline and that relatively drastic conditions are required to obtain 2-phenylquinoline, subsequent to hydrolysis and dehydrogenation. However, Bergmann and Rosenthal⁸ obtained 2-benzylquinoline and 2,4-dibenzylquinoline in a two-day reaction of quinoline with benzylmagnesium chloride in an ether-dioxane mixture. We have observed that under corresponding conditions, there results a 44% yield of 2-phenylquinoline from a room temperature reaction with phenylmagnesium bromide in an ether-dioxane medium.

This somewhat surprising result is reminiscent of the smooth addition of RLi compounds to quinoline.⁹ The reaction may be due to diphenylmagnesium as the active agent in the ether-dioxane equilibrium mixture.¹⁰



However, some earlier studies¹¹ have shown that diphenylmagnesium is actually less reactive than phenylmagnesium bromide toward *n*-valeronitrile. Reaction rates may vary significantly^{4a} with the reactant as well as with the RM compound. It is rather likely that the dioxane itself may contribute appreciably to the increased reaction rate. For example, in the *n*-valeronitrile reaction¹¹ the diphenylmagnesium was prepared from diphenylmercury and no dioxane was present. Also, it is well-known¹² that coordination compounds can markedly influence reaction

(7) Oddo, *Atti acad. Lincei*, [V] **16**, I, 538 (1907); Bergstrom and McAllister, *THIS JOURNAL*, **52**, 2847 (1930); see also, Bergstrom, *Chem. Revs.*, **35**, 178-179 (1944).

(8) Bergmann and Rosenthal, *J. prakt. Chem.*, [2] **135**, 274 (1932).

(9) An interesting illustration [see, Gilman and Spatz, *THIS JOURNAL*, **63**, 1553 (1941)] of the ready addition reactions of RLi compounds is the 93.5% yield of 2-*n*-butylquinoline in a 15-minute reaction at -35° of *n*-butyllithium with quinoline.

(10) Schlenk and Schlenk, *Ber.*, **62**, 920 (1929).

(11) Gilman and Brown, *THIS JOURNAL*, **52**, 1181 (1930). See, also, ref. 4a of the present paper, and Bachmann, *ibid.*, **52**, 4412 (1930).

(12) Gilman and Jones, *ibid.*, **62**, 1243 (1940). The dioxane may function not only by forming coordination compounds with the RM types, but also by partially setting free the quinoline from a less reactive coordination compound.

(1) Paper LXV in the series: "Relative Reactivities of Organometallic Compounds." The preceding paper with Woods is in *THIS JOURNAL*, **70**, 550 (1948).

(2) Present address: The Westinghouse Co., Pittsburgh, Penna.

(3) Gilman, J. E. Kirby and Kinney, *THIS JOURNAL*, **51**, 2252 (1929).

(4) (a) Gilman and R. H. Kirby, *ibid.*, **55**, 1265 (1933); (b) **63**, 2046 (1941).

(5) Gilman and Gainer, *ibid.*, **69**, 877 (1947).

(6) Hoffman, Farlow and Fuson, *ibid.*, **55**, 2000 (1933).

velocities of organometallic reactions, and dioxane may function significantly in this manner.

It should be stated that even in the absence of dioxane, phenylmagnesium bromide in ether adds to quinoline at room temperature to give a 7.5% yield of 2-phenylquinoline at the end of two days. Accordingly, forced conditions⁷ are not required to effect addition of RMgX compounds to quinoline.

Finally, a combination of phenylmagnesium bromide and phenyllithium was used in a reaction with quinoline. The purpose of this experiment was to determine whether the onium-complex¹³ with the RMgBr compound and quinoline might affect the course of addition of phenyllithium to give phenylquinolines other than 2-phenylquinoline.¹⁴ However, the only product isolated when phenyllithium was added to the quinoline-phenylmagnesium bromide complex was 2-phenylquinoline.

Experimental

Benzalquinaldine and Phenyllithium.—The benzalquinaldine was prepared in almost quantitative yield in essential accordance with the procedure of Skraup and Bothm.¹⁵ However, instead of crystallizing the crude product from ethanol, any residual benzaldehyde and quinaldine were removed by washing the powdered crude crystalline product with boiling petroleum ether (b. p., 60–68°) in which the benzalquinaldine is essentially insoluble.

To a stirred solution of 23.1 g. (0.1 mole) of benzalquinaldine dissolved in a minimum of dry benzene to which was then added an equal volume of anhydrous ether, was added (dropwise) 0.1 mole of phenyllithium in ether. The solution immediately assumed a blood-red color; refluxing occurred; and after stirring for one hour hydrolysis was effected by pouring into water. Evaporation of the dried ether extract gave a quantitative yield of α -benzohydrilquinaldine melting over the range 115–119°. A mixed melting point determination of a recryst-

(13) Sachs and Sachs, *Ber.*, **37**, 3091 (1904); **38**, 1087 (1905).

(14) Ziegler and Zeiser, *Ann.*, **485**, 182 (1931); see, also, ref. 5 in this paper.

(15) Skraup and Bothm, *Ber.*, **59**, 1013 (1927).

tallized sample and an authentic specimen⁶ showed no depression.

Quinoline and Phenylmagnesium Bromide.—On the addition of 20 cc. of dry, freshly distilled dioxane to an ether solution of 0.166 mole of phenylmagnesium bromide, a pure white precipitate formed immediately. To the stirred suspension was added 21.5 g. (0.166 mole) of quinoline in an equal volume of ether, and a tan-colored precipitate formed. The suspension was stirred, without refluxing, for forty-eight hours. Subsequent to hydrolysis by saturated ammonium chloride solution, evaporation of the ether extract, oxidation of the dihydro intermediate by nitrobenzene, and distillation there was obtained 15 g. (44%) of 2-phenylquinoline (mixed m. p.).

When the above procedure was repeated without the use of dioxane, there was obtained from a 0.1 mole run 4 g. (20%) of a crude product (b. p., 145–160° (0.3 mm.)) which yielded after crystallization from benzene-petroleum ether (b. p., 60–68°) 1 g. (5%) of pure 2-phenylquinoline. A small quantity of the picrate of 2-phenylquinoline (corresponding to 0.5 g. or 2.5% of 2-phenylquinoline) was obtained from the picrates of the mother liquor.

Quinoline, Phenylmagnesium Bromide and Phenyllithium.—To 0.2 mole of the tan-colored ether-insoluble quinoline-phenylmagnesium bromide complex was added 0.2 mole of phenyllithium in ether. The mixture was stirred without refluxing for twelve hours, and during this time the complex dissolved completely. Hydrolysis by water and subsequent working up by customary procedures (including the nitrobenzene oxidation) gave 24 g. (58.5%) of 2-phenylquinoline (mixed m. p.).

Acknowledgment.—The authors are grateful to Dr. R. G. Jones for assistance.

Summary

1. Phenyllithium adds to benzalquinaldine to give α -benzohydrilquinaldine. This reaction very probably takes place by a 1,4-addition.

2. Phenylmagnesium bromide adds, in ether and at room temperature, to quinoline to give 2-phenylquinoline. The rate of addition under these mild conditions is markedly accelerated in an ether-dioxane medium, possibly because of the intermediate formation of coordination complexes.

AMES, IOWA

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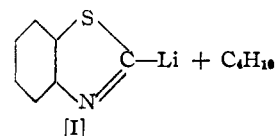
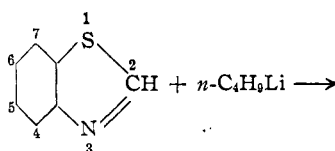
[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF IOWA STATE COLLEGE]

Reactions of Organometallic Compounds with Benzothiazoles

BY HENRY GILMAN AND JOHN A. BEEL

Since it has been shown that certain benzothiazole derivatives are physiologically active,¹ some compounds containing this nucleus were considered to be of interest in the chemotherapy of tuberculosis. Feasible methods of preparing the desired compounds seemed to be through the addition of the proper organometallic compound to the azomethine grouping in benzothiazole and through the preparation of an organometallic compound of benzothiazole itself.

(1) (a) Bogert and Hess, *Rec. trav. chim.*, **48**, 904 (1929); (b) Newberry and Viaud, British Patent 517,272 (January 25, 1940) [*C. A.*, **35**, 6741 (1941)]; (c) Rose, Shonle and Chen, *Pharm. Arch.*, **11**, 81 (1940); (d) Ballowitz, *Arch. exptl. Path. Pharmacol.*, **168**, 687 (1931).



Courtot² had previously prepared 2-benzothiazolylmagnesium bromide (in yields not stated)

(2) Courtot and Tchelitcheff, *Compt. rend.*, **217**, 231 (1943).