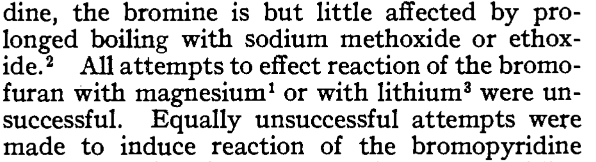
[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF IOWA STATE COLLEGE]

2,4,5-Triphenyl-3-furyllithium and 3,4,6-Triphenyl-2-pyridyllithium

BY HENRY GILMAN AND DONALD S. MELSTROM

The bromine atoms in 2,4,5-triphenyl-3-bromofuran and 3,4,6-triphenyl-2-bromopyridine are relatively unreactive. In the bromofuran, the bromine is unaffected after heating with alcoholic potash for twenty hours[1]; and in the bromopyridine, the bromine is but little affected by prolonged boiling with sodium methoxide or ethoxide.[2] All attempts to effect reaction of the bromofuran with magnesium[1] or with lithium[3] were unsuccessful. Equally unsuccessful attempts were made to induce reaction of the bromopyridine with magnesium.[3] However, the bromopyridine did undergo reaction slowly with lithium to give a suspension which appeared not to react with carbon dioxide, aldehydes or ketones, and yet gave a 20–25% yield of 2,4,5-triphenylpyridine subsequent to hydrolysis and high vacuum distillation.[3]

It appeared particularly appropriate to determine whether the more recently developed halogen–metal interconversion reaction might be successful in preparing RLi compounds from these relatively unreactive bromo-heterocycles. We have now found that 2,4,5-triphenyl-3-bromofuran reacts smoothly with *n*-butyllithium to give an RLi compound from which, after carbonation, a 66% yield of pure 2,4,5-triphenylfuran-3-carboxylic acid is obtained.



The structure of the carboxylic acid was established by decarboxylation to the known 2,3,5-triphenylfuran. It is quite probable that the corresponding 2,4,5-triphenyl-3-furylmagnesium iodide will form readily from the RLi compound in accordance with the following metal-metal interconversion reaction[4]

$$\mathrm{RLi} + \mathrm{MgI_2} \longrightarrow \mathrm{RMgI} + \mathrm{LiI}$$

and that this Grignard reagent will also react with carbon dioxide as well as with other carbonyl compounds.

By a corresponding sequence of reactions, the RLi compound was formed from 3,4,6-triphenyl-2-bromopyridine, and this reacted with carbon dioxide to give a 67% yield of 3,4,6-triphenylpyridine-2-carboxylic acid. The structure of this acid was also established by decarboxylation to the known 2,4,5-triphenylpyridine. The satisfactory yield of RLi compound is another illustration of the possibility of selecting experimental conditions so that a halogen–metal interconversion reaction rather than addition to the azomethine linkage in pyridine[5a] and in quinoline[5b] takes place.

The successful halogen–metal interconversion reaction with 2,4,5-triphenyl-3-bromofuran suggested a related experiment with the corresponding chlorofuran. It was observed that the same type of reaction occurred, but at an appreciably lower rate as evidenced by the recovery of a significant quantity of the 2,4,5-triphenyl-3-chlorofuran. This halogen–metal interconversion is apparently the first case of a reaction of this kind with a nuclear chlorine type. It was shown recently that benzyl chloride reacts with *n*-butyllithium to give an extremely small quantity of benzyllithium,[6a] and that phenylethynyl chloride gives an appreciable amount of phenylethynyllithium.[6b] Compounds like the chloroanisoles,[6c] chlorobenzene and α-chloronaphthalene appear not to undergo halogen–metal interconversion reactions. This is in marked contrast with the corresponding bromo and iodo compounds.

Acknowledgments.—The authors are grateful to Dr. C. F. H. Allen and Dr. R. E. Lutz for providing samples of some of the compounds.

Experimental

2,4,5-Triphenyl-3-bromofuran and *n*-Butyllithium.—A solution of 3.75 g. (0.01 mole) of 2,4,6-triphenyl-3-bromofuran[7] in 50 cc. of ether was added rapidly to a solution of 0.02 mole of *n*-butyllithium in 50 cc. of ether. The mixture was stirred for thirty minutes and then carbonated by pouring on crushed Dry Ice. The yield of crude acid melting at 241–244° was 2.67 g. (78%). Recrystallization from glacial acetic acid gave 2.23 g. (66%) of pure 2,4,5-triphenylfuran-3-carboxylic acid which melted at 257–258° and began to sublime at 210°.

Anal. Calcd. for $C_{23}H_{20}O_3$: neut. equiv., 340. Found: neut. equiv., 333 and 347.

A 0.5-g. portion of the acid was mixed intimately with 1 g. of soda-lime, and from this mixture after strong heating there was obtained (subsequent to crystallization from ethanol) 0.13 g. (30%) of pure 2,3,5-triphenylfuran melting at 93–94°.[8] Identification was completed by a mixed melting point determination with an authentic specimen.[9]

The **methyl 2,4,5-triphenylfuran-3-carboxylate** was obtained by reaction of the acid in ether with diazomethane, in an 85% yield, as colorless needles melting at 123.5–124° after crystallization from alcohol.

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[1] Allen and Rosener, THIS JOURNAL, **49**, 2110 (1927).

[2] Kohler and Allen, *ibid.*, **46**, 1522 (1924). Sodium butoxide does effect replacement of the bromine by butoxyl.

[3] Allen and Frame, *ibid.*, **62**, 1301 (1940).

[4] Gilman and Kirby, *ibid.*, **63**, 2046 (1941); see also Gilman and Swiss, *ibid.*, **62**, 1847 (1940).

[5] (a) Gilman and Spatz, *ibid.*, **62**, 446 (1940); (b) **63**, 1553 (1941).

[6] (a) Gilman and Haubein, *ibid.*, **66**, 1515 (1944); (b) *ibid.*, **67**, 1420 (1945); (c) Wittig, Pieper and Fuhrmann, *Ber.*, **73**, 1193 (1940).

[7] Kindly provided by Dr. C. F. H. Allen.

[8] Japp and Klingemann, *J. Chem. Soc.*, **57**, 674 (1890).

[9] Kindly provided by Dr. R. E. Lutz.

Anal. Calcd. for $C_{24}H_{18}O_2$: methoxyl, 8.76. Found: methoxyl, 8.84.

2,4,5-Triphenyl-3-chlorofuran and *n*-Butyllithium.—A solution of 1 g. (0.003 mole) of 2,4,5-triphenyl-3-chlorofuran[9] in 15 cc. of ether was added rapidly to a solution of 0.005 mole of *n*-butyllithium in 15 cc. of ether. The mixture was stirred for one hour and then carbonated in the usual manner to give 0.14 g. (14%) of crude acid melting at 240–245°. After crystallization from glacial acetic acid, the weight of pure acid melting at 257–258° was 0.1 g. (10%). The acid was shown to be identical with that obtained from 2,4,5-triphenyl-3-bromofuran by mixed melting points of the acids and their methyl esters. From the neutral fraction, 0.58 g. (58%) of unchanged 2,4,5-triphenyl-3-chlorofuran was recovered. The high recovery of initial reactant indicates that the yield of halogen-metal interconversion product might be increased appreciably by a longer period of reaction.

3,4,6-Triphenyl-2-bromopyridine and *n*-Butyllithium.—A solution of 3 g. (0.008 mole) of 3,4,6-triphenyl-2-bromopyridine (prepared in accordance with the directions of Kohler and Allen[2]) in 25 cc. of ether was added during five minutes to a solution of 0.017 mole of *n*-butyllithium in 60 cc. of ether, cooled to −35° in a Dry Ice–acetone bath. The solution turned orange-red during the addition and deposited a precipitate about one minute after addition of the halide was complete. Subsequent to stirring for ten minutes at −35°, the mixture was carbonated and worked up in the usual manner. A considerable quantity of white solid (probably the lithium salt of the organic acid), insoluble in dilute potassium hydroxide, was obtained; this was dissolved in hot water and added to the alkaline extract. Acidification of the alkaline extract precipitated 1.82 g. (67%) of acid melting at 166–168° with decomposition. The melting point was not changed after crystallizing a portion from a mixture of benzene and petroleum ether (b. p. 60–68°). The 3,4,6-triphenylpyridine-2-carboxylic acid is readily soluble in ethanol and benzene but only slightly soluble in ether and petroleum ether.

Anal. Calcd. for $C_{24}H_{17}O_2N$: neut. equiv., 351; N, 3.99. Found: neut. equiv., 348 and 349; N, 4.18.

A 0.2-g. portion of the pure acid was heated in an oil-bath at 170–175° until evolution of carbon dioxide ceased and finally for a short time at 185°. The product on crystallization from ethanol gave 0.15 g. (86%) of pure 2,4,5-triphenylpyridine, melting at 111–112°, and identified by a mixed melting point determination with an authentic specimen.[7]

The **methyl 3,4,6-triphenylpyridine-2-carboxylate** was prepared by reaction of a benzene solution of the acid with an ether solution of diazomethane. The ester, which melted at 117–118° after crystallization from dilute methanol, was, like the acid from which it was derived, not appreciably soluble in ether.

Anal. Calcd. for $C_{25}H_{19}O_2N$: N, 3.84. Found: N, 3.98.

Summary

It has been shown that satisfactory yields of RLi compounds are obtainable by the halogen–metal interconversion reaction with 2,4,5-triphenyl-3-bromofuran (which does not react directly with lithium or magnesium) and with 3,4,6-triphenyl-2-bromopyridine (which does not react directly with magnesium).

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[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, INDIANA UNIVERSITY]

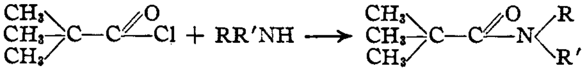
N-Substituted Tri-alkyl Acetamides

BY W. M. DEGNAN[1] AND C. J. SHOEMAKER[2,3]

Fourneau and Florence[4] have shown that the amides of highly branched acids are more effective as sedatives than the amide of the corresponding normal acid. It has also been demonstrated by Whitmore and Homeyer[5] that sedative and hypnotic activity of an amide can be increased if the nitrogen atom is highly substituted. Results of work by Bass[6] showed that *t*-butyl acetamide is inactive; whereas Whitmore and Homeyer[5] have patented certain *t*-butyl acetamides as possible sedative and hypnotic compounds, providing the nitrogen atom carries appropriate groups such as the diethyl or dimethyl groups.

Trimethylacetamide is inactive as a sedative or hypnotic,[7] but as in the case of the *t*-butyl acetamide it was hoped that sedative action would appear if the nitrogen atom were highly substituted. To that end a series of N-substituted trimethylacetamides and N-substituted dimethylethylacetamides were prepared, identified and submitted to pharmacological assay.

The amides were prepared by the familiar Schotten–Baumann reaction. Thus



$$\left.\begin{matrix}\mathrm{CH_3}\\\mathrm{CH_3}\\\mathrm{CH_3}\end{matrix}\right>\mathrm{C{-}C}\begin{matrix}\diagup\!\!\diagup\mathrm{O}\\\diagdown\mathrm{Cl}\end{matrix} + \mathrm{RR'NH} \longrightarrow \left.\begin{matrix}\mathrm{CH_3}\\\mathrm{CH_3}\\\mathrm{CH_3}\end{matrix}\right>\mathrm{C{-}C}\begin{matrix}\diagup\!\!\diagup\mathrm{O}\\\diagdown\mathrm{N}\left<\begin{matrix}\mathrm{R}\\\mathrm{R'}\end{matrix}\right.\end{matrix}$$

The hydrogen chloride was removed by several methods. Potassium hydroxide was not completely satisfactory, especially when the amounts involved were small. Better results were obtained by using either potassium carbonate or an excess of the amine. Yields of the amide in most cases were high.

Twelve of the amides were submitted to pharmacological assay by administering them, by mouth, to white rats in amounts varying from 100 to 1500 mg. per kilogram weight of the rat. No sedative action or hypnotic properties were observed in any of the compounds. The N-diethyltrimethylacetamide and trimethylacetyl morpholine caused convulsions.

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[1] Dr. Degnan's death occurred on September 30, 1943.

[2] Abstracted from the thesis submitted by Clarence J. Shoemaker to the faculty of the Graduate School of Indiana University in partial fulfillment of the requirements for the degree, Doctor of Philosophy.

[3] Now on active duty with the U. S. Navy.

[4] Fourneau and Florence, *Bull. soc. chim.*, **43**, 211 (1928).

[5] Whitmore and Homeyer, U. S. Patent 2,060,154.

[6] Bass, *J. Pharmacol.*, **64**, 50 (1938).

[7] Weil and Rosenthal, *Roczniki Chem.*, **8**, 44 (1928).