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N-BUTYLLITHIUM IN AMINOLYSIS AND AMMONOLYSIS OF ESTERS[1]

Kim-Wenn Yang[2], Joseph G. Cannon[3], and John G. Rose

Division of Medicinal Chemistry, College of Pharmacy, University of Iowa,

Iowa City, Iowa 52240, U. S. A.

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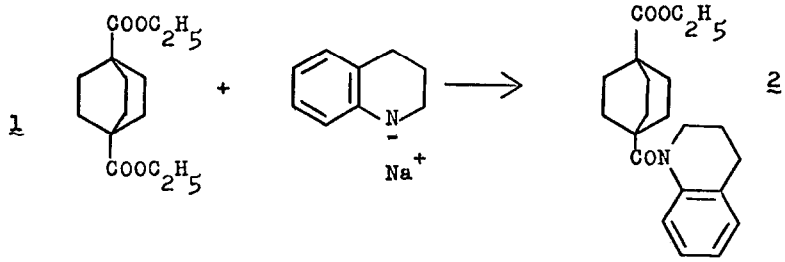
In 1954, Bassett and Thomas[4] described the reaction of primary or secondary amines with a Grignard reagent to form aminomagnesium halides which promote aminolysis of methyl benzoate. Stern[5] reported that sodioaryl amines of the type Ar-NHNa, prepared by treatment of the amine with sodium amide or with metallic sodium, react with esters to provide good yields of amides.

This paper describes the use of other strong bases as mediators of aminolysis reactions on esters. When 1, 2, 3, 4-tetrahydroquinoline was heated with an equimolar portion of sodium hydride in ethylene glycol dimethyl ether, the soluble sodio-amine derivative which was formed reacted with one equivalent of diethyl bicyclo[2. 2. 2]octane-1, 4-dicarboxylate (1), to form the half ester-half amide (2).



1 2

However, this technique failed in the case of treatment of 1 with dimethylamine or with 1, 2, 3, 4-tetrahydroisoquinoline and sodium hydride; no aminolysis product could be isolated.

n-Butyllithium was found to be superior to sodium hydride; it mediated reactions with

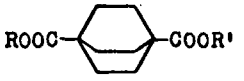
aliphatic as well as aromatic amines, to form half ester-half amides or unsymmetrical diamides derived from 1 or 2. The lithium derivative of dibenzylamine reacted with ethyl benzoate and with ethyl pivalate to afford excellent yields of amides. An ethyl ester which was resistant to more conventional methods of ammonolysis was converted into the primary amide utilizing liquid ammonia and n-butyllithium in tetrahydrofuran-n-hexane. (See Table II).

The aminolysis of carboxylic esters with a lithium-amine derivative represents a new method of preparation of amides, especially adaptable to polyfunctional esters and to systems otherwise resistant to aminolysis. The following procedures illustrate the method:

Aminolysis of Ethyl Benzoate. - To a stirred mixture of 0.03 mole of n-butyllithium in n-hexane (Alpha Inorganics, Inc.), 6 g. (0.03 mole) of dibenzylamine, and 40 ml. of purified tetrahydrofuran was added dropwise 4.5 g. (0.03 mole) of ethyl benzoate. The resulting mixture was poured into a slurry of 80 ml. of ice and 20 ml. of 10% HCl; the solid which separated was recrystallized. (See Table II).

Ammonolysis of Ethyl trans-2-(2-tetrahydropyranyloxy)cyclopropanecarboxylate. - To a stirred mixture of 75 ml. of liquid NH_3 and 25 ml. of purified tetrahydrofuran was added in a slow stream 0.1 mole of n-butyllithium in n-hexane; a copious white precipitate formed. Ethyl trans-2-(2-tetrahydropyranyloxy)cyclopropanecarboxylate (20.8 g., 0.097 mole) in an equal volume of tetrahydrofuran was added dropwise with stirring; the white precipitate dissolved. After stirring for 4 hr., the excess NH_3 was evaporated at room temperature, the reaction mixture was poured into an ice-water slush, and the resulting solution was extracted repeatedly with ether. Evaporation of the ether from the combined extracts left a light yellow gum which was chromatographed in benzene on neutral alumina and eluted with ether-methanol (9:1) to afford trans-2-(2-tetrahydropyranyloxy)cyclopropanecarboxamide. (See Table II).

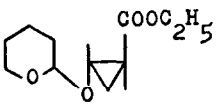
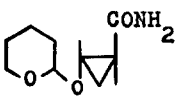
Table I. Aminolysis of Ester Derivatives of Bicyclo[2.2.2]octane Utilizing n-Butyllithium.



Ester	Amine	Product[a]	Yield, %	B.p., °C. (mm.) or m.p., °C.
R=R'=C_2H_5	1, 2, 3, 4-tetrahydro-isoquinoline	R=C_2H_5; R'=1, 2, 3, 4-tetrahydro isoquinolino	48	115-116[b]
R=R'=C_2H_5	dibenzylamine	R=C_2H_5; R'=N, N-dibenzylamino	36	200-210 (10^{-3})
R=C_2H_5; R'=1, 2, 3, 4-tetrahydro-isoquinolino	dimethylamine	R=R'=N, N-dimethylamino	48	161-162[b]
R=C_2H_5; R'=N, N-dibenzylamino	dimethylamine	R=N, N-dimethylamino; R'=N, N-dibenzylamino	56	195-196[b]

(a) Satisfactory spectral and elemental analytical data were obtained for all products.
(b) from ethanol.

Table II. Aminolysis of Miscellaneous Esters Utilizing n-Butyllithium.

Ester	Amine	Product[a]	Yield, %	M.p., °C.
ethyl benzoate	dibenzylamine	N, N-dibenzyl-benzamide	88	112-113[b, c]
ethyl pivalate	dibenzylamine	N, N-dibenzyl-pivalamide	85	63-64[c]
	NH_3		26	118-120[d]

(a) Satisfactory spectral and elemental analytical data were obtained for all reactants and products unreported in the literature. (b) ref. 6 lists m.p. 112 . (c) from ethanol. (d) from ethyl acetate.

References

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2. Abstracted in part from a portion of a Ph. D. thesis (K. W. Y.), University of Iowa, 1969.

3. To whom all correspondence should be addressed.

4. H. Ll. Bassett and C. R. Thomas, J. Chem. Soc., 1188 (1954).

5. E. S. Stern, Chem. Ind. (London), 277 (1956).

6. R. L. Shriner, R. C. Fuson, and D. Y. Curtin, "The Systematic Identification of Organic Compounds," 5th ed., John Wiley & Sons, Inc., New York, London, Sydney, 1964, p. 333.