[CONTRIBUTION NO. 1045 FROM THE DEPARTMENT OF CHEMISTRY UNIVERSITY OF PITTSBURGH]

Reaction of 1-Alkynes with Organometallic Compounds. VIII.[1] Rate of Reaction of Grignard Reagents with Hexyne-1 in the Presence of Tertiary Amines and Magnesium Bromide[2]

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The rate of reaction of hexyne-1 with ethylmagnesium bromide and iodide in the presence of aliphatic amines is a function of the structure of the amine and the amount of magnesium halide. An increase in reactivity was observed with increasing branching in the α-carbon atom on the amine until steric effects make the coordination of the amine with the Grignard reagent difficult. Aromatic amines and pyridine produced only minor increase in the rate of reaction. The addition of magnesium bromide to ethylmagnesium bromide in the presence of dimethylethylamine produced significant increases in the rate of reaction with hexyne-1. Possible mechanisms of reaction are presented.

Recently we reported that the rate of reaction of ethylmagnesium bromide with hexyne-1 can be affected by the addition of magnesium bromide[5] or by the presence of triethyl amine.[1] This paper deals with the effect of tertiary amines (other than triethylamine), in the presence of variable amounts of magnesium bromide, on the rate of reaction of Grignard reagents with hexyne-1. It was hoped to gain additional insight into the constitution of the Grignard reagent.[6]

EXPERIMENTAL

Hexyne-1 was prepared by the alkylation of sodium acetylide with *n*-butyl bromide in liquid ammonia.[7] It was distilled through a fractionating column, sealed under dry nitrogen in ampoules, and stored for not more than two months at 0°. B.p. 70.5° at 735 mm., n_D^{25} 1.3968, d_4^{26} 0.714.

Ethylmagnesium bromide was prepared and stored as previously described.[8] A quantitative determination of the amount of active organomagnesium compound in the ether solution was obtained by measuring the amount of ethane when an aliquot was treated with an excess of hexyne-1. The concentration was $2.14N \pm 1.5\%$. It had a bromine to basic magnesium ratio of 1.08. The calculated[9] bromine to total magnesium ratio was 1.04. As an independent check the total magnesium content was obtained using 8-hydroxyquinoline; this gave a bromine to total magnesium ratio 1.01.

Ethylmagnesium iodide solution was $2.04N$. The iodide to basic magnesium ratio was 1.15. The calculated iodine to total magnesium ratio was 1.07.

Magnesium bromide was prepared as previously described[5] and was found to contain 0.455 g. of $MgBr_2$ per ml. of ether solution.

Tertiary amines. The amines were secured from commercial sources or prepared (except for ethydiisopropylamine) from the appropriate primary or secondary amines by the reductive methylation using formaldehyde and formic acid.[10] All of the liquid amines except dimethylethylamine were purified by adding them to an ether solution of methylmagnesium bromide. The precipitate formed was removed by filtration, an additional amount of methylmagnesium bromide was added to the filtrate, and the solution was distilled through an efficient fractionating column. Because dimethylethylamine has a boiling point near that of ethyl ether, it was purified by distilling from ethylmagnesium bromide in triethylamine solvent. The tertiary amines were stored under refrigeration in ampoules for not longer than two months.

Triethylamine (Eastman Kodak Co.) b.p. 89°, n_D^{26} 1.3980, d_4^{20} 0.73.

Methyldiethylamine (from diethylamine), b.p. 63° at 728 mm., n_D^{25} 1.3879, d_4^{23} 0.703.

Dimethylisopropylamine (from isopropylamine, courtesy of Sharples Chemical Co.) b.p. 63° at 733 mm., n_D^{26} 1.3887, d_4^{25} 0.695.

Dimethyl-n-butylamine (from *n*-butylamine, courtesy of Union Carbide Chemicals Co.), b.p. 90° at 726 mm., n_D^{25} 1.3951, d_4^{28} 0.721.

Methyldiisopropylamine (from diisopropylamine, courtesy of Union Carbide Chemicals Co.), b.p. 112° at 739 mm., n_D^{25} 1.4092, d_4^{27} 0.758.

Anal. Calcd. for $C_7H_{17}N$: N, 12.2. Found: N, 11.9.

Dimethylethylamine (from ethylamine) b.p. 37° at 736 mm., n_D^{25} 1.3697, d_4^{23} 0.698.

Dimethyl-t-butylamine (from t-butylamine, courtesy of Rohm & Haas Co.), b.p. 90° at 735 mm., n_D^{25} 1.4020, d_4^{22} 0.750.

Anal. Calcd. for $C_6H_{15}N$: N, 13.8. Found: N, 13.6.

N-methylpiperidine (from piperidine) b.p. 107° at 735 mm., n_D^{25} 1.4348, d_4^{25} 0.821.

N-ethylpiperidine (Eastman Kodak Co.) b.p. 130° at 734 mm., n_D^{25} 1.4413, d_4^{24} 0.830.

Ethyldiisopropylamine (from diisopropylamine, courtesy of Union Carbide Chemicals Co., by reaction with ethyl

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[1] Part VII. J. H. Wotiz, C. A. Hollingsworth, R. E. Dessy, and L. C. Lin, *J. Org. Chem.*, **23**, 228 (1958).

[2] Presented before the 133rd National Meeting of the American Chemical Society, San Francisco, April 1958.

[3] Present address: Research Center, Diamond Alkali Co., Painesville, Ohio.

[4] Abstracted from the thesis of A. W. S. presented in partial fulfillment of the requirement for the degree of Master of Science, 1957. (Present address: Mellon Institute, Pittsburgh, Pa.).

[5] J. H. Wotiz, C. A. Hollingsworth, and R. E. Dessy, *J. Org. Chem.*, **21**, 1063 (1956).

[6] R. E. Dessy, G. S. Handler, J. H. Wotiz, and C. A. Hollingsworth, *J. Am. Chem. Soc.*, **79**, 3476 (1957).

[7] A. Henne and K. W. Greenlee, *J. Am. Chem. Soc.* **67**, 484 (1945).

[8] J. H. Wotiz, C. A. Hollingsworth, and R. E. Dessy, *J. Org. Chem.*, **20**, 1545 (1955).

[9] The basic-magnesium determination (H_2SO_4 titration) does not measure the magnesium as $MgBr_2$. By using the bromine analysis (Volhard titration), the amount of magnesium as $MgBr_2$ can be calculated. This value added to the amount of basic magnesium, gives the calculated total magnesium.

[10] T. Clarke, B. Gillespie, and Z. Weisshous, *J. Am. Chem. Soc.*, **55**, 4571 (1933).

bromine in ethylene glycol)[11] b.p. 119° at 731 mm., n_D^{25} 1.4112, d_4^{27} 0.751.

Anal. Calcd. for $C_8H_{19}N$: N, 10.8. Found: N, 10.7.

Tripropylamine (courtesy of Sharples Chemical Co.), b.p. 155° at 727 mm., n_D^{25} 1.4142, d_4^{27} 0.746.

N,N-dimethylaniline (Baker and Adamson), b.p. 102° at 40 mm., n_D^{25} 1.5557, d_4^{30} 0.948.

N,N-diethylaniline (Paragan Testing Laboratories), b.p. 124° at 40 mm., n_D^{25} 1.5391, d_4^{30} 0.924.

Pyridine (courtesy of the United States Steel Corp.), b.p. 114° at 727 mm., n_D^{25} 1.5067, d_4^{30} 0.974.

Tribenzylamine (Eastman Kodak Co.) m.p. 92–93°.

The apparatus for the rate determinations was the same as previously described.[8] Attempts were made to hold the reaction mixtures at a constant temperature by keeping the solutions at reflux temperatures (about 35°), and by using a high heat input. Increases in the initial reflux temperatures of up to 1.8° were caused by the differences in boiling points of added amines. In all of the reactions there was a drop in the temperature of from 0.2 to 1.5° as the reaction proceeded to half-life. In general, the temperature drop was greatest in the more rapid reactions.

Rates. (a) The determinations were made at a $1M$ concentration of the ethylmagnesium halide (0.0235 mole) and and $0.25M$ concentration (0.0059 mole) of the tertiary amine. The Grignard reagent was diluted with ether and amine to a total volume of 23.5 ml. Then 1.0 equivalent of hexyne-1 (0.0235 mole) was added to the refluxing mixture and the volume of evolved gas was measured at certain time intervals.

(b) The determinations in the presence of magnesium bromide were made at 1.0 molar concentration of ethylmagnesium bromide (0.0235 mole) and 1.0 molar dimethylethylamine (0.0235 mole). Various amounts of an ether solution of magnesium bromide (0.455 g./ml.) and ethyl ether were added to bring the total volume to 23.5 ml. The $MgBr_2$ solution was added to ethylmagnesium bromide and refluxed for 30 min. Afterward, the dimethylethylamine was introduced, the solution refluxed for 15 min., and the reaction started by the addition of 1.0 equivalent (0.0235 mole) of hexyne-1.

DISCUSSION

The effect of amines. The equation for the reaction under investigation can be written schematically as

$$C_2H_5MgX + C_4H_9C{\equiv}C{-}H \xrightarrow[\text{reflux}]{R_3N} C_2H_6 + C_4H_9C{\equiv}CMgX$$

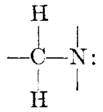
The rate of this reaction of an ether solution of ethylmagnesium bromide and the iodide with hexyne-1, in the presence of tertiary amines, was ascertained. Relative reactivities were calculated from half-lives by assigning a value of 100 to the reaction of hexyne-1 with ethylmagnesium bromide, each at one molar concentration and in the absence of amine. The relative reactivities in the presence of 15 tertiary amines are listed in Table I. They ranged from 124 to 606 for ethylmagnesium bromide and from 152 to 1400 in the case of the iodide.

TABLE I

Relative Reactivities of Ethyl Grignards with Hexyne-1 in the Presence of Tertiary Amines

$R_1-N(R_3)-R_2$			No.	Relative Reactivity	
R_1	R_2	R_3	α-H's	C_2H_5MgBr	C_2H_5MgI
				100[a]	91[b]
CH_3	CH_3	C_2H_5	8	144	269
CH_3	CH_3	n-C_4H_9	8	164	276
CH_3	$-(CH_2)_5-$		7	257	519
CH_3	C_2H_5	C_2H_5	7	316	659
CH_3	CH_3	i-C_3H_7	7	457	938
n-C_3H_7	n-C_3H_3	n-C_3H_7	6	243	[c]
C_2H_5	$-(CH_2)_5-$		6	460	901
C_2H_5	C_2H_5	C_2H_5	6	493	1010
CH_3	CH_3	t-C_4H_9	6	606	1400
CH_3	i-C_3H_7	i-C_3H_7	5	314	466
C_2H_5	i-C_3H_7	i-C_3H_7	4	145	152
CH_3	CH_3	C_6H_5	[d]	124	[c]
C_2H_5	C_2H_5	C_6H_5	[d]	125	[c]
$C_6H_5CH_2$	$C_6H_5CH_2$	$C_6H_5CH_2$	[d]	127	[c]
	Pyridine		[d]	126[e]	[c]

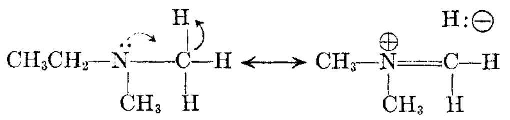
[a] Half-life 685 sec. [b] The relative reactivity of 71 was previously reported (ref. 18). The higher value in the present investigation is attributed to experimentally found differences in the magnesium halide contents. [c] Not determined. [d] Aromatic. [e] Heterogeneous.



$$-\overset{\text{H}}{\underset{\text{H}}{\overset{|}{\underset{|}{\text{C}}}}}-\overset{|}{\underset{|}{\text{N}}}:$$

An examination of the data reveals that the relative reactivity increases as the number of α-hydrogens, in the amine decreases. The maximum reactivity is reached with six α-hydrogens, dimethyl-t-butylamine. However, a further reduction in the number of α-hydrogens, for example, to five as in methyldiisopropylamine, decreases the reactivity. This decrease can be attributed to steric effects resulting from increased substitution of the α-carbon atom.

The increase in reactivity brought about by changing the structure of an amine with eight α-hydrogens to an amine with six α-hydrogens may be attributed to an increase in the inductive effect (electron release) resulting from the substitution of alkyl groups on the α-carbon atom. Another possible explanation is that it may be caused by anionic hyperconjugation,[12] "hydridization," *e.g.*,



$$CH_3CH_2-\underset{CH_3}{\underset{|}{\ddot{N}}}-\overset{H}{\underset{H}{C}}-H \longleftrightarrow CH_3-\underset{CH_3}{\underset{|}{\overset{\oplus}{N}}}{=}\underset{H}{\underset{|}{C}}-H \quad H{:}\ominus$$

When applied to tertiary amines,[13] as the number of α-hydrogens decreases in a series of amines, the number of hydridization possibilities would decrease and the electron pair on the nitrogen would become more available for reaction or coordination. The reactivity toward a Lewis acid, magnesium in a Grignard reagent, would therefore increase until the alkyl groups introduce a steric factor.

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(11) S. Caspe, *J. Am. Chem. Soc.*, **54**, 4457 (1932).

(12) R. E. Dessy, J. H. Wotiz, and C. A. Hollingsworth, *J. Am. Chem. Soc.* **79**, 358 (1957).

(13) F. H. Seubold, *J. Org. Chem.*, **21**, 156 (1950).

Although tripropylamine has the same number of α-hydrogens as triethylamine, its relative reactivity is only half as large. This decrease in reactivity could be attributed to angular structures of the alkyl chain.[14] Since the alkyl groups project in front of the nitrogen atom they produce F-strain.[15]

The relative reactivities of the four nonaliphatic tertiary amines were about 125. Because of the relatively weakly basic properties of dimethylaniline, diethylaniline, and pyridine, the low reactivities are not unexpected. Steric effects may account for the low activity of tribenzylamine. Pyridine was the only amine to produce a heterogeneous reaction mixture. However, the theoretical amount of ethane was evolved.

It is interesting to compare the effect of the tertiary aliphatic amines on the rate of reaction of hexyne-1 with ethylmagnesium bromide and with ethylmagnesium iodide. The distribution of reactivities is of comparable order and the iodide reactions are about twice as fast. The maximum reactivity in both cases was observed in the presence of dimethyl-*t*-butylamine. A possible explanation for the similarity in the distribution of the reactivities may be found in a consideration of β-strain in the amine since β-strain is independent of the reference acid.

Effect of magnesium bromide in the presence of dimethylethylamine. The rate of evolution of ethane was determined in several experiments in which various amounts of magnesium bromide were added to 1.0*N* solutions of ethylmagnesium bromide and reacted with an equivalent amount of hexyne-1 in the presence of an equimolar quantity of dimethylethylamine. This amine was selected because, in the presence of low concentration of $MgBr_2$, it produces only a relatively moderate increase in the rate of reaction, making possible more accurate determinations of half-life. A plot of the relative reactivity against ratio of $MgBr_2$ to Et_2Mg concentrations is in Fig. 1. and is a straight line for the concentrations studied. Ratios greater than 1.78 were not studied because the reactions would have been too rapid to measure accurately. The relative reactivity was 1370 when 0.75 equivalent of $MgBr_2$ was added to the Grignard solution bringing the $MgBr_2$ to Et_2Mg ratio to 1.78. By correcting for the magnesium bromide content in the original ethylmagnesium bromide solution, a point is obtained which also falls on the line in Fig. 1.

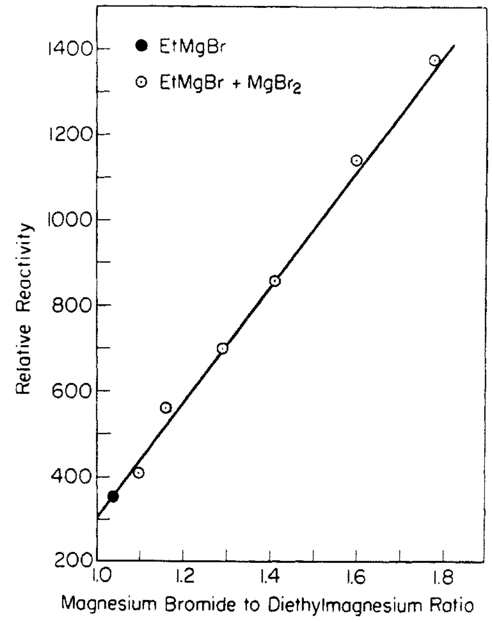


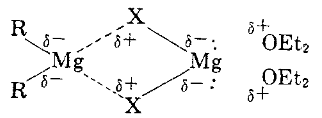
Fig. 1. Effect of added magnesium bromide on the rate of reaction of ethylmagnesinm bromide with hexyne-1 in the presence of dimethylethylamine

The rate-increasing effect of added magnesium bromide in the presence of amine is just the opposite of the effect found for added magnesium bromide in the absence of amine.[5] Such information coupled with the knowledge that triethylamine has no effect on the rate of reaction of magnesium bromide-free-diethylmagnesium with hexyne-1,[1] may provide useful insight as to the manner in which the amine effects the reaction. These facts strongly indicate that the action of the amine is related to the magnesium bromide present in a Grignard solution.

By means of radioactive magnesium the nonexistence of one portion of Schlenk's equilibrium[16] was recently demonstrated:[6]

$$2C_2H_5MgBr \not\rightleftharpoons (C_2H_5)_2Mg + MgBr_2 \rightleftharpoons (C_2H_5)_2Mg{\cdot}MgBr_2 \quad (1)$$

It has been proposed[17] that $R_2Mg.MgX_2$ can be represented as a bridged halogen structure:



It is possible that the tertiary amine, since it is a relatively stronger base, replaces some of the coordinated ether molecules. The coordinated amine would then supply electrons to the aggregate to make the release of the alkyl groups as R^- easier and the Grignard reagent more reactive.

Another possible explanation for the increased reactivity considers the attack of the amine on the positive halogen in a bridged structure:

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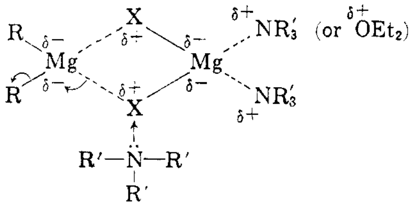
(14) O. L. Brady and F. R. Cropper, *J. Chem. Soc.*, 507 (1950).

(15) H. C. Brown, *Record Chem. Prog.*, **14,** 83 (1953).

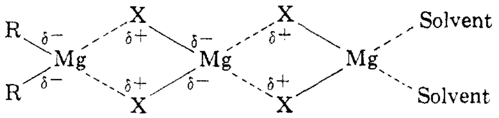
(16) W. Schlenk and W. Schlenk, Jr., *Ber.* **62,** 920 (1929).

(17) E. G. Rochow, D. T. Hurd, and R. N. Lewis, The Chemistry of Organometallic Compounds, John Wiley and Sons, Inc., New York (1957), pp. 79–94, 97.



Through a concerted action the carbon in R⁻ would be released more readily. Since triethylamine was found to be without affect on the reactivity of halogen-free diethylmagnesium,[1] the mechanism involving the halogen is favored inspite of an apparent weakness. The attack of the amine on the halogen should be a function of the steric factor on the amine and the size of the halogen (reference acid). Thus, when changing the halogen from bromine to iodine, one would expect differences in the order of reactivities with the change in the structure of the amine (Table I). However none were observed, and the maximum reactivity occurred in both cases in the presence of dimethyl-*t*-butylamine.

The addition of magnesium bromide to ethylmagnesium bromide would shift the position of equilibrium in equation (1) to the right. Further coordination is possible by forming bridged chains or polymers:[17]



The amine presumably could coordinate with the magnesium, but whether electronic effects would be transmitted through the "bridged" halogens to the alkyl group is uncertain.

The sharp increase in reactivity of ethylmagnesium bromide in the presence of a mixture of tertiary amine and magnesium bromide may explain in part why the triethylamine reversed the order of reactivity of methyl- and ethylmagnesium halides.[1] In the absence of amine the order of reactivity was[18] Cl>>Br>I while in the presence of "catalytic" amounts of triethylamine the order of reactivity was I>Br>Cl.[1] In the preparation of Grignard reagents, the alkyl iodides lead to side reactions, Wurtz-type of coupling. The alkyl chlorides have the least tendency to undergo Wurtz-type coupling.

$$RI + Mg \longrightarrow RMgI \xrightarrow{RI} R{-}R + MgI_2$$

This was evident from the determinations of halogen to basic-magnesium ratios of the three ethyl-magnesium halides used in the present study; iodide 1.15, bromide 1.08, and chloride 0.67.[19] Thus the iodide containing the highest magnesium halide content was effected to the greatest extent by the addition of tertiary amine.

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(18) J. H. Wotiz, C. A. Hollingsworth, and R. E. Dessy, *J. Am. Chem. Soc.* 77, 103 (1955).

(19) The much lower value is caused in part by the low solubility of the $MgCl_2$ in ether.

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Cyclization of Certain Heterocyclic Azides

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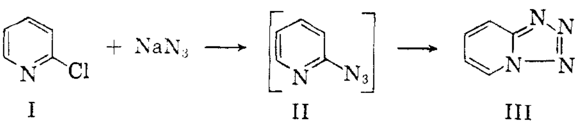
The synthesis and properties of certain heterocyclic azides are described. A theory is proposed to account for the isomerization of azides to tetrazoles.

Introduction. In view of the discrepancies in the literature regarding the structure of certain azides, a number of these compounds were synthesized. In many cases, the azide function is adjacent to a ring nitrogen atom and cyclization to form the isomeric bicyclic tetrazole may take place, as in the well known example of 1,2,3,3a-tetrazaindene (III).



I II III

The proximity of the azide group to a ring nitrogen does not necessarily result in cyclization. In fact, it has been pointed out that there are no known examples of the cyclization of an azide group attached to a five-membered heterocyclic ring.[1] This statement was proved to be no longer true since at least three examples of ring closure into a five-membered ring were found; these will be discussed in a later section.

The azides and isomeric tetrazoles described in this paper were prepared by two methods: (1) treatment of a hydrazine with nitrous acid, and (2) reaction of a halide with sodium azide in aqueous alcohol. The course of the reaction (azide formation of cyclization) appeared to be independ-

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(1) J. H. Boyer and F. C. Canter, *Chem. Revs.*, **54**, 22 (1954).