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The Reaction of *N*-Substituted Carbonimidic Dihalides with Grignard Reagents. The Generation of Alkyl or Aryl Halides from Grignard Reagents

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The reaction of *N*-alkyl- or *N*-aryl-carbonimidic dihalides with Grignard reagents afforded α-elimination products, isocyanides, rather than substitution ones. Two kinds of alkyl or aryl halides were produced concomitantly in this reaction: one kind consisted of halides generated from the Grignard reagents used, and the other, of halides the halogens of which had been derived from the dihalides. The ease of formation of these halides was found to decrease in the order: iodide> bromide> chloride, regardless of which substrate served as the source of a halogen atom. A probable reaction mechanism is proposed.

The Grignard reactions of various carbonate derivatives (*e.g.*, phosgene,[1] chloroformates, and carbonates), as well as acyl chlorides and esters, which involve the replacement of one or two chlorine or alkoxy groups by alkyl or aryl groups of Grignard reagents have been well-established.[2] A very similar replacement has been reported for iminocarbonates,[3a] imidoyl chlorides,[3b] and imidates;[3a] and we have also observed that a chloroformimidate behaved similarly.[4] In contrast to these results, we found that *N*-alkyl- or *N*-aryl-carbonimidic dihalides reacted with Grignard reagents to afford α-elimination products, isocyanides, and that two kinds of alkyl or aryl halides were formed concomitantly. One of the latter products consisted of halides generated from the Grignard reagents used. A closely related observation has been reported for (dichloroiodo)-benzene by Melnikov.[6] This compound reacted with phenylmagnesium bromide to afford diphenyliodonium chloride (a substitution product), iodobenzene, chlorobenzene, bromobenzene (products corresponding to the present elimination), and biphenyl. The formations of all these products, except for that of bromobenzene, may be explained by either an ionic or radical mechanism; the pathway to afford bromobenzene has not yet been explored. The present paper will describe our results regarding the Grignard reaction of carbonimidic dihalides, which involves a novel generation of alkyl or aryl halides from the Grignard reagents.

Results and Discussion

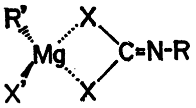
When *N*-alkyl- or *N*-aryl-carbonimidic dihalides were treated in ether with Grignard reagents with a different halogen atom, the reaction occurred exothermally to afford isocyanides (**1**), two kinds of alkyl or aryl halides (**2** and **3**), magnesium halides, and a tarry product. Since the reaction of **1** with Grignard reagents is known, we adopted an inverse addition procedure (*i.e.*, the addition of a Grignard reagent to the dihalide) for the present reaction. Some typical data are shown in Table 1. Though the recorded yields of **1**, **2**, and **3** were not always those obtained under the optimum conditions for each reaction, their yields appeared to depend on the structures of both substrates.

$$\mathrm{R\text{-}N{=}CX_2 + R'MgX' \rightarrow \underset{\mathbf{1}}{R\text{-}N{\equiv}C} + \underset{\mathbf{2}}{R'X'} + \underset{\mathbf{3}}{R'X}}$$

No liberation of isocyanides from *N*-substituted carbonimidic dihalides was observed, at least under the reaction conditions without Grignard reagents; therefore, it is obvious that the elimination reaction is promoted by the use of Grignard reagents. The halides **2** are produced only by the present reaction, since the absence of the remaining halides in the Grignard reagents was confirmed in each case before their use.

The preference for elimination over substitution in the present reaction appears to arise from the structual characteristics of *N*-substituted carbonimidic dihalides. It is well-known that the Grignard reactions of carboxylic acid derivatives, such as acid chlorides and esters, proceed by means of an addition-elimination mechanism, in which the initial coordination of the carbonyl O with the Mg atom of the Grignard reagent is involved. Thus, in the present reaction, the failure of the substitution of X in the dihalides may be attributed to a considerable decrease in the electron density on the imino N, which is caused by the presence of two electron-withdrawing groups (X) on the carbonimidoyl C. Further, it may be considered that the formation of stabilized products, isocyanides, may favor the elimination process.

It is worthwhile to present some information regarding the formation of **2** from Grignard reagents, because only one such transformation has been known.[6] The reactions of *N*-alkyl- or *N*-aryl-carbonimidic dichlorides with aryl magnesium bromides or iodides gave only **2**, while reactions with alkylmagnesium bromides or iodides yielded both **2** and **3**, the former being predominant. When *N*-phenylcarbonimidic dibromide was used as the substrate,[7] both halides were generally formed; **2** predominated over **3** when the halogen atom in the Grignard reagents was iodine, and the reverse was true when the halogen was chlorine. Further, the yields of **1** were roughly equal to the combined yields of **2** and **3** in general, except for some cases in which alkyl- or aryl-magnesium iodides were used.[8] To explain all these results, we tentatively proposed a mechanism involving the formation of a coordinated complex, **4**, followed by its synchronous decomposition to give **1** and either **2** or **3**.



4

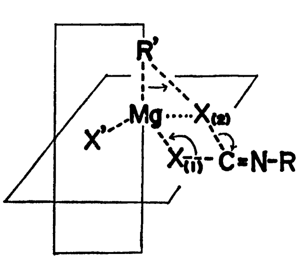
The effect of R in carbonimidic dichlorides on the

TABLE 1. RESULTS OF THE REACTION OF CARBONIMIDIC DIHALIDES WITH ORGANOMETALLIC REAGENTS
(Solvent; Ether, 50 ml)

$R\text{-}N{=}CX_2$ 0.05 mol	$R'MgX'$ 0.05 mol	Temp. °C	Time hr	Reaction products, Yield (%)[a]			
				R-NC **1**	R'X' **2**	R'X **3**	Unreacted dihalide
$c\text{-}C_6H_{11}N{=}CCl_2$	C_6H_5MgBr	35	0.5	40	46	0	16
$c\text{-}C_6H_{11}N{=}CCl_2$	$p\text{-}CH_3C_6H_4MgBr$	35	0.5	37	40	0	17
$c\text{-}C_6H_{11}N{=}CCl_2$	C_6H_5MgI	35	0.5	24	66	0	trace
$c\text{-}C_6H_{11}N{=}CCl_2$	C_2H_5MgBr	25	3	31	—[b]	—[b]	6
$c\text{-}C_6H_{11}N{=}CCl_2$	$n\text{-}C_6H_{13}MgBr$	25	3	66	46	7	trace
$c\text{-}C_6H_{11}N{=}CCl_2$	$n\text{-}C_6H_{13}MgI$	25	0.5	22	34	1	43
$n\text{-}C_4H_9N{=}CCl_2$	C_6H_5MgBr	35	0.5	6	18	0	34
$C_6H_5N{=}CCl_2$	C_6H_5MgBr	35	0.5	trace	12	0	37
$C_6H_5N{=}CBr_2$[c]	C_6H_5MgI[c]	0	0.5	59	27	9	—[b]
$C_6H_5N{=}CBr_2$[c]	C_6H_5MgCl[c,d]	15	0.5	34	3	51	—[b]
$C_6H_5N{=}CBr_2$[c]	$n\text{-}C_6H_{13}MgCl$[c]	0	0.5	79	7	50	—[b]
$C_6H_5N{=}CBr_2$[c]	$n\text{-}C_6H_{13}MgI$[c]	0	0.5	32	37	26	—[b]
$c\text{-}C_6H_{11}N{=}CCl_2$	C_6H_5ZnBr	35	0.5	24	30	0	10
$c\text{-}C_6H_{11}N{=}CCl_2$	C_6H_5HgBr[e]	80	6	0	0	0	100
$c\text{-}C_6H_{11}N{=}CCl_2$	C_6H_5Li	0	0.5	40	0	35	30

a) Based on carbonimidic dihalide charged (determined by glc). b) Not determined. c) Both substrates, 0.02 mol each; solvent, 30 ml. d) THF was used as solvent. e) Benzene (10 ml) was used as solvent.

yields of the reaction products shows that their reactivity toward a fixed Grignard reagent decreases in this order: cyclohexyl>*n*-butyl>phenyl. We also observed a similar substituent effect on the reaction of the dichlorides with SCN^- in ethanol,[9] suggesting an S_N 1 character for the fission of the C–Cl bond. Thus, it may be anticipated that the decomposition of **4** will be started by the loosening of the $C\text{–}X_{(1)}$ bond and that this will result in bond formation between $X_{(1)}$ and Mg atoms. If the induced nucleophilic attack of the R′ group on $X_{(2)}$ or X′ and the subsequent electron-transfer from the $C\text{–}X_{(2)}$ bond to the C atom (when the attack of R′ occurred on X′, an additional electron-transfer from Mg–X′ to $Mg\text{–}X_{(2)}$ should be involved) take place before the complete fission of the $C\text{–}X_{(1)}$ bond, the transition state affording **1** and **3**, and that affording **1** and **2**, can be pictured as **5** and **6** respectively. Here the assumption that a geometrically and electronically approximate equivalence can be attained in the transition states appears not unreasonable. The reason will be given below. If this is true, the relative ease of the halide formation can be expected to decrease in this order: iodide>bromide>chloride, whichever participates X or X′, because the susceptibilities of X and X′ toward R′ are considered to correlate with their electronegativities. The selectivity data in the halide formation from the reactions with *N*-phenylcarbonimidic dibromide were in qualitative agreement with this expectation. In the reaction with *N*-cyclohexylcarbonimidic dichloride, aromatic Grignard reagents showed a higher selectivity for the halide formation (*i.e.*, only **2** is formed), than that from aliphatic Grignard reagents. This may be because aryl carbanions are generally less reactive than alkyl ones.



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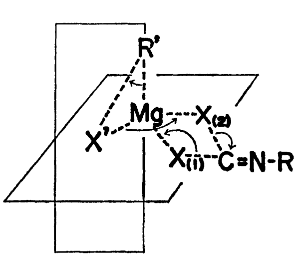

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An extension of this reaction to other organometallic reagents was also attempted. When phenylzinc bromide was treated with *N*-cyclohexylcarbonimidic dichloride, a similar reaction occurred, though the yields of the products were unsatisfactory as expected. The reaction with much less reactive phenylmercuric bromide, however, did not afford any products; rather, most of the starting materials were recovered. Phenyllithium reacted with the dichloride to give the corresponding isocyanide and chlorobenzene.

Experimental

Materials. All the carbonimidic dihalides were prepared by the method of Kühle *et al.*[10] $R{=}cyclo\text{-}C_6H_{11}$ in $RN{=}CCl_2$, bp 88—91 °C/23 mmHg (lit,[10] 79—82 °C/13 mmHg); $R{=}n\text{-}C_4H_9$, bp 40—42 °C/11 mmHg (lit,[10] 45—45.5 °C/14 mmHg); $R{=}C_6H_5$, bp 79—80 °C/8 mmHg (lit,[10] 83—85 °C/11 mmHg); $R{=}C_6H_5$ in $RN{=}CBr_2$, bp 104 °C/10 mmHg (lit,[10] 76.5—77.5 °C/0.15 mmHg). In the preparation of Grignard reagents, the complete conversion of the halides was confirmed by glc analyses. Phenylzinc bromide was prepared *in situ* by the exchange reaction[11] of phenylmagnesium bromide with zink chloride in ether. Phenylmercuric bromide was prepared from tetraphenyltin and mercuric bromide as has been described by Seyferth *et al.*[12] (mp 274—280 °C, lit,[12] 280 °C).

Reaction of Carbonimidic Dihalides with Grignard Reagents. Several examples are given below.

a) Reaction of Cyclohexylcarbonimidic Dichloride with Phenylmagnesium Bromide. An ethereal solution of the Grignard reagent, prepared from 7.9 g (0.05 mol) of bromobenzene and 1.2 g (0.05 mol) of magnesium turnings in 50 ml of ether in the usual way[13] except that the solution was refluxed for an additional 30 min after the addition of all the bromobenzene, was gradually added to 9.0 g (0.05 mol) of cyclohexylcarbonimidic dichloride, the temperature being kept below 10 °C. After the mixture had then been allowed to stand at room temperature, the reaction started spontaneously and a white precipitate began to come out; then the mixture was refluxed for 30 min. The brown reaction mixture, with a characteristic odor of isocyanide, was poured into ice-water; the ethereal layer was separated, and then it was combined with a chloroform extract of the aqueous phase. The organic layer was dried, and the solvents were removed. The subsequent distillation of the residue gave 7.9 g of the distillate (bp 40—78 °C/23 mmHg), which was revealed to contain bromobenzene (46% yield), cyclohexyl isocyanide (40%), and the recovered dichloride (16%), leaving 2.1 g of a tarry product. No chlorobenzene was formed in this reaction.

b) *Reaction of Cyclohexylcarbonimidic Dichloride with* n-*Hexylmagnesium Bromide.* The Grignard reagent prepared from 8.3 g (0.05 mol) of *n*-hexyl bromide and 1.2 g (0.05 mol) of Mg in 50 ml ether was added to 9.0 g (0.05 mol) of the dichloride, after which the mixture was treated as has been described above. Distillation afforded 7.9 g of the distillate (bp 57—82 °C/55 mmHg) and left a tarry residue (2.7 g). The yields of the products were as follows: *n*-hexyl chloride, 7%; *n*-hexyl bromide, 46%; cyclohexyl isocyanide, 66%; and a trace amount of recovered dichloride.

c) *Reaction of Phenylcarbonimidic Dibromide with Phenylmagnesium Iodide.* A solution of the Grignard reagent obtained from 4.1 g (0.02 mol) of iodobenzene and 0.5 g (0.02 mol) of Mg in 20 ml of ether was slowly added to 5.3 g (0.02 mol) of the dibromide in 10 ml of ether at 0 °C. During the addition, the reaction occurred spontaneously and the temperature of the reaction mixture rose to *ca.* 30 °C, even under external cooling with an ice-salt mixture. After the reaction had subsided, the brown reaction mixture was refluxed for 15 min and then worked-up as has been described above. Distillation gave 2.6 g of the distillate (bp 40—74 °C/23.5 mmHg), leaving a tarry residue (1.5 g). The yields of the products were as follows: bromobenzene, 9%; iodobenzene, 27%; and phenyl isocyanide, 59%. Neither benzophenone anil nor benzanilide (the expected substitution products) could be detected in the tarry residue.

Reaction of Cyclohexylcarbonimidic Dichloride with Phenyllithium. An ethereal solution of phenyllithium, prepared from 7.9 g (0.05 mol) of bromobenzene and 0.8 g (0.12 mol) of lithium, was treated with 9.0 g (0.05 mol) of the dichloride at 0 °C. Glc analysis showed that the reaction products were chlorobenzene (35% yield) and cyclohexyl isocyanide (40%).

Authentic Samples for Glc. All the isocyanides were prepared from the corresponding formamides by the method of Ugi *et al.*[14]

Glc Analysis. The analysis was carried out on a Shimadzu GC-5A apparatus, using Apiezon L (25%)-Shimalite (3 m) and PEG 6000 (25%)-Chromosorb W (3 m) columns (carrier gas, N_2).

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4) In the reaction of ethyl *N*-phenylchloroformimidate (prepared by the method of Kühle[5]) with phenylmagnesium bromide (in ether at 35 °C for 0.5 hr), ethyl *N*-phenylbenzimidate was obtained as the main product (over a 50% yield). Lesser amounts of benzanilide and *N*-(diphenylmethylene)aniline were also formed, neither phenyl isocyanide nor bromobenzene were found in the products (unpublished data).

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7) The aromatic dibromides are generally isolable, while the less stable aliphatic ones are not. Therefore, the reaction with the aliphatic dibromides could not be undertaken.

8) In view of the comparatively high reactivity of these Grignard reagents, their consumption as a result of the reaction with alkyl or aryl halides may be considered.

9) The consumption of SCN^- at 20 °C was found to be as follows. For R=cyclohexyl, 58% after 5 min, and for R=phenyl, 44% after 45 min (unpublished data).

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11) For general procedure, see "Jikken Kagaku Koza," ed. by M. Kotake and others, Vol. 20, Part II, Maruzen, Tokyo (1956), p. 93.

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