GRIGNARD AND ORGANOLITHIUM REAGENTS DERIVED FROM DIHALOGEN COMPOUNDS

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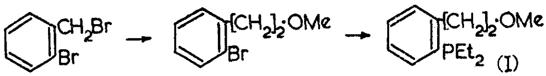
In this Review an attempt is made to outline the methods available for the preparation of Grignard and organolithium reagents from dihalogen compounds, and the uses which such compounds have found in synthesis. Many of these reagents are of organodimetallic type. Related compounds can often be prepared by adding lithium to a multiple linkage or by replacing hydrogen, linked to carbon, by lithium or by MgX, but the scope of such methods is clearly restricted, particularly in respect of control over the point of attachment of the metal.

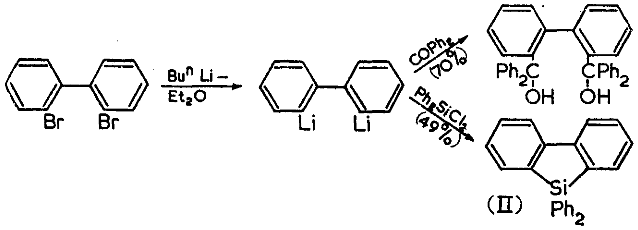
The reagents to be discussed are of value mainly in two ways. First, the two halogen atoms may be brought into reaction with metal selectively. For instance, in the synthesis of the tertiary phosphine (I) from *o*-bromobenzyl bromide,[1] the first step is effected by magnesium in ether, followed by chloromethyl methyl ether, and the second by magnesium and ethylmagnesium bromide in ether, followed by chlorodiethylphosphine, PEt_2Cl.



(I)

Of course this type of double synthesis is impossible if the functional group introduced in the first stage interferes with subsequent formation of a Grignard reagent ; but this limitation may be evaded in some cases by using an interconversion reaction with an alkyl-lithium, in place of magnesium, in the second stage, for formation of an organolithium reagent in this way is not inhibited by the presence of hydroxyl, carboxyl, amino-, or thiol groups ; and this method is often effective in replacing halogen which fails to react with magnesium or lithium.

Secondly, some dihalogen compounds give organodimetallic derivatives, of magnesium or lithium, in a single step. Such derivatives, when treated



(II)

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[1] Mann and Millar, *J.*, 1951, 2205.

with a monofunctional co-reactant, permit two functional groups to be introduced in one laboratory operation, or when treated with a difunctional co-reactant may give a cyclic product, *e.g.*, (II).[2]

Procedures of the latter type have been used particularly in the synthesis of a number of heterocyclic derivatives of Group IV and V elements, which are not easily made by other methods. Elegant syntheses of a number of novel hydrocarbons (*e.g.*, methylene*cyclo*propane, di- and tetraphenylene, and some macrocyclic types) utilise Grignard or lithium reagents derived from dihalogen compounds.

Choice of Reagent and Preparative Methods.—The types of reagent behave similarly in carbonyl addition or in elimination of metallic halide on treatment with typical co-reactants, although there are qualitative differences in reactivity (*e.g.*, towards olefins and azomethines), so that the two types are, in part, complementary. Whether one prepares a Grignard or an organolithium reagent from a given dihalogen compound therefore normally depends on the reactivity of the halogen compound, on yield and convenience, and on the need for bringing one or both of the halogen atoms into reaction.

The order of reactivity, $I > Br > Cl \gg F$, holds for reaction with metal and interconversion with organolithiums and for Wurtz-type coupling. Dibromides are generally chosen, in both the aliphatic and the aromatic series. Treatment in ethereal solution with magnesium is convenient and satisfactory for most aliphatic dihalides and the more reactive aromatic dihalides. Progressively more forcing reagents are: magnesium alloyed with copper; magnesium or an alloy previously heated with iodine; and magnesium used with a reactive halide such as ethyl bromide as an "entraining" agent. More forcing still is the use of tetrahydrofuran as solvent. Nevertheless, ease of reaction does not necessarily lead to a better final yield for a given reagent; particularly with aromatic dihalides, the reaction is best performed under nitrogen. Extensive surveys of the preparation and use of Grignard reagents are available.[3] A number of compounds which fail to react with magnesium can be brought into reaction with lithium. General methods for the formation of organolithium compounds, and the reactions of these compounds, have been reviewed by Braude[4] and by Wittig.[5]

As an alternative to the use of metallic lithium, an exchange reaction between a preformed alkyl- or aryl-lithium and the dihalogen compound may be used: $RLi + R'X \rightleftharpoons R'Li + RX$. The position of equilibrium

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[2] Gilman and Gorsich, *J. Amer. Chem. Soc.*, 1955, **77**, 6380.

[3] Kharasch and Reinmuth, "Grignard Reactions of Nonmetallic Substances", Prentice-Hall Inc., New York, 1954; Yoffe and Nesmeyanov, "A Handbook of Magnesium-Organic Compounds", Pergamon Press, London, 1956.

[4] Braude in "Progress in Organic Chemistry", edited by J. W. Cook, Butterworths Scientific Publications, London, 1955, Vol. III, p. 172.

[5] Wittig in "Newer Methods of Preparative Organic Chemistry", Interscience Publications, New York, 1948; see, also, "Annotated Bibliography on the Use of Organolithium Compounds in Organic Synthesis", Lithium Corporation of America, Inc., Minneapolis, 1949 (and supplements).

in this reaction depends on the relative electronegativities of the groups R and R′, favouring the formation of the organolithium compound in which the metal is linked to the more electronegative of the organic radicals.[5a] The preferred compounds for use in this reaction are phenyl-lithium in ether, and *n*-butyl-lithium in ether or light petroleum. The properties of these compounds have been investigated especially by Wittig and by Gilman and their co-workers. Phenyl-lithium is in general less reactive than *n*-butyl-lithium, and is more prone to side reactions ; but it has proved valuable in bringing about intramolecular cyclisation with di(bromomethyl) compounds (see below). *n*-Butyl-lithium in ether effects replacement of halogen in some dihalogen compounds which are unaffected by magnesium or lithium and, acting in homogeneous solution, is more suitable than the metals for use in replacing one halogen atom only. Since ethers are slowly cleaved by alkyl-lithium compounds low temperatures and brief reaction times are desirable. Petroleum solutions do not suffer from this limitation, but interconversion is slower in this solvent. The halogen–metal interconversion with organolithium compounds has been reviewed.[6]

Mechanisms of Formation and Reaction.—Relatively little is known about the mechanism by which Grignard and organolithium reagents of any type are formed. Direct reaction of a halide with metal presumably involves a nucleophilic attack on halogen by the metal ; a " bimolecular " reaction at the metal surface has been postulated for organic halides and lithium, and the greater reactivity of this metal has been related to its smaller lattice energy and interatomic spacing.[4] Kharasch and Reinmuth [3] have put forward persuasive arguments for a scheme in which reaction with magnesium is initiated by radical-type unsaturated centres at the metal surface. The halogen–metal interconversion with organolithiums is thought to involve nucleophilic attack by the anion of the organolithium on positively polarised halogen ; [7] in reactions at low temperature configuration can be retained in compounds which have halogen linked to asymmetric carbon atoms or unsaturated centres.[4]

The reactions of lithium and magnesium compounds derived from dihalogen compounds are generally normal, except when the reactive groups are vicinal (as in the reagents from *o*-dihalogenobenzenes) or are separated by a conjugated carbon chain (as in *o*- and *p*-xylylene dihalides) : some specific cases of these structural effects are considered below. " Free " radical paths may well contribute to a greater extent in reactions of double Grignard reagents (*i.e.*, molecules containing two MgX groups) than in those of simple type.

Organolithium compounds are more reactive than the corresponding Grignard reagents in additions at multiple bonds and in reactions involving elimination of metal halide, probably because the C–Li bond is more polar than the C–MgX bond, and because the smaller lithium atom has less steric effect. Studies on mechanisms of reaction of Grignard reactions

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[5a] Rosenberg, *J. Amer. Chem. Soc.*, 1954, **76**, 4389.

[6] Jones and Gilman in " Organic Reactions ", John Wiley and Sons, Inc., New York, 1951, Vol. VI, p. 339.

[7] Sunthankar and Gilman, *J. Org. Chem.*, 1951, **16**, 8.

(which are complicated by the equilibrium $2R{\cdot}MgX \rightleftharpoons R_2Mg + MgX_2$) have been reviewed by Kharasch and Reinmuth,[3] and organolithium compounds by Braude.[4]

Limitations in the Use of Dihalogen Compounds.—The major difficulty is due to dehalogenation, which may be either intramolecular, leading to an unsaturated or cyclised product, or intermolecular, yielding, in the limit, polymeric material. However, if the reaction conditions are suitably chosen, yields of the organometallic reagent are satisfactory in many cases.

Some aromatic double Grignard reagents are only slightly soluble in ether, but their solubility is increased by addition of benzene, and they then usually react nicely with typical co-reactants such as carbon dioxide.

In the aromatic series, the reactivity of dihalogen compounds with magnesium is lower than that of corresponding monohalogen compounds. The difficulty of obtaining extensive reaction at a second halogen atom in one ring, which is also shown in interconversions, presumably arises because a carbanion or anionic complex resists attack by a nucleophile. However, some older claims of complete unreactivity to magnesium or lithium may require revision, since the early workers could not fractionate halogen compounds efficiently and did not have oxygen-free nitrogen, high-purity metals, or solvents such as tetrahydrofuran.

Characterisation of Reagents.—Early workers characterised their double Grignard reagents by hydrolysis. Isolation of the resulting hydrocarbon or halogenated hydrocarbon is inconvenient; and the yield of reagent indicated in this way, or by the amount of metal consumed or of ionic halide present after hydrolysis, is rarely approachable in terms of final product yield in typical syntheses. More useful is treatment with excess of carbon dioxide, best as a slurry of the solid and ether, which is convenient and gives yields of carboxylic acid more like those attainable in other syntheses. This method, or treatment with benzophenone to give a tertiary alcohol or diol, has also been commonly used with organolithium compounds. The side-reaction with carbon dioxide, giving a ketone, although troublesome with lithium compounds, is suppressed with Grignard reagents at low temperatures, which may however cause difficulty with double Grignard reagents owing to insolubility. Another difficulty with such compounds is illustrated by the behaviour of *o*-phenylenedi(magnesium halides), which on carboxylation give benzoic acid but no phthalic acid, probably as a result of chelation in the intermediate complex. Compounds of this type have been characterised by treatment with iododimethylarsine.[8]

Treatment with a mercuric halide to give an organomercurial has also been used for the estimation of organodimetallic reagents.[9, 10]

Types of Compound

The classification adopted below is based on the dihalogen compounds from which the reagents are derived. Interest in the latter resides largely

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[8] Heaney, Mann, and Millar, *J.*, 1956, 1, 4692, and unpublished results.

[9] Hilpert and Grüttner, *Ber.*, 1914, **47**, 177.

[10] Wittig and Herwig, *Chem. Ber.*, 1954, **87**, 1511.

in their value in synthesis, so yields are given in a number of typical cases.

Aliphatic Dihalides.—The reactions, with magnesium, of all the members of the series $Br\cdot[CH_2]_n\cdot Br$ from $n = 1$ to $n = 14$ have been investigated. Reactivity to magnesium (and to lithium) decreases with increasing chain length, and with $n = 16$ the compound does not react even with activated magnesium.[11] With excess of magnesium, the major primary product when $n \geqslant 4$ is the double Grignard reagent $BrMg\cdot[CH_2]_n\cdot MgBr$; these reagents are more soluble in ether the longer the chain length, and at $n = 10$ complete miscibility is attained.[12] The principal side-reaction is the intermolecular condensation summarised as:

$$m Br\cdot[CH_2]_n\cdot Br + (m - 1)Mg \longrightarrow Br\cdot[CH_2]_{nm}\cdot Br + (m - 1)MgBr_2$$

where the compounds for which $m = 2, 3 \ldots$ etc. are formed in progressively diminishing yields. In the presence of excess of metal these higher dibromides also form double Grignard reagents,[13] the higher members probably as a result of the entraining action of the simpler compounds. The compounds having $n = 1$—3 give derivatives of no value in synthesis. Methylene dibromide gives a reagent which fails to react with typical Grignard co-reactants other than hydrolysing agents, possibly because it is too insoluble; [14] di- and tri-methylene dibromide undergo both intra- and intermolecular elimination of magnesium bromide, the former giving ethylene and the latter, after carboxylation, *cyclo*propane, propylene, and suberic acid.[3] With higher compounds intramolecular condensation diminishes, not being observable with pentamethylene dibromide,[13] and the reagents derived from the compounds having $n = 4$—10 have all been used in synthesis. The most satisfactory techniques for reducing "coupling" have been the use of (*a*) activated magnesium and high dilution,[15] and (*b*) ordinary magnesium and wet (0·1% aqueous) ether.[9, 16] In this way yields of final products have been raised from 30—50% to 50—70%, though the advantage of using "wet" ether in the preparation of $BrMg\cdot[CH_2]_5\cdot MgBr$ has been contested.[12]

By reaction with suitable chloro-compounds, tetra- and penta-methylenedi(magnesium bromide) have been used to prepare five- and six-membered heterocyclic derivatives of arsenic,[17] phosphorus,[3] antimony,[17] bismuth,[17] lead,[17] and silicon; [3, 18] organotin halides give distannanes.[19] With cadmium chloride an organocadmium compound (probably a linear polymer) is formed which reacts with half-ester acid chlorides to give good yields of diketo-diesters.[12] These reagents have also been used in syntheses involving other purely organic co-reactants.[3, 16] The inaccessibility until recently

[11] Chuit, *Helv. Chim. Acta*, 1926, **9**, 264.
[12] Kreuchunas, *J. Amer. Chem. Soc.*, 1953, **75**, 3339.
[13] von Braun and Sobecki, *Ber.*, 1911, **44**, 1918.
[14] Fidler, Jones, Clark, and Stange, *J. Amer. Chem. Soc.*, 1955, **77**, 6634.
[15] Lukeš and Bláha, *Chem. Listy*, 1952, **46**, 683.
[16] Brown and Jones, *J.*, 1946, 781.
[17] Grüttner and Krause, *Ber.*, 1916, **49**, 437, 2666.
[18] West, *J. Amer. Chem. Soc.*, 1954, **76**, 6012.
[19] Zimmer and Moslé, *Chem. Ber.*, 1954, **87**, 1255.

of the higher dibromides ($n = 6$—14) limited their use,[11, 16, 18] although yields of the double Grignard reagents improve with increasing chain length, at least up to the decamethylene compound.[12, 15] Very restricted use has been made of the single Grignard reagents, the probable intermediates in the coupling reaction. An excess of hexamethylene dibromide when heated with magnesium gives dodecamethylene dibromide by the route :

$$\mathrm{Br{\cdot}[CH_2]_6{\cdot}MgBr + Br{\cdot}[CH_2]_6{\cdot}Br \longrightarrow Br{\cdot}[CH_2]_{12}{\cdot}Br} \qquad (30\%)$$

and heptamethylene dibromide similarly yields tetradecamethylene dibromide.[20]

Dilithium compounds prepared from aliphatic dihalides have been investigated only in recent years. The restriction in the series $\mathrm{Br{\cdot}[CH_2]_n{\cdot}Br}$ that $n \geqslant 4$ for the satisfactory preparation of a dimetallic compound again holds, and yields of the higher compounds are similar to those obtainable from double Grignard reagents.[21] Methylenedilithium is obtainable only in very poor yield by the action of the metal on methylene dibromide at a low temperature ; [21] it is of interest that this compound may be prepared by the pyrolysis of methyl-lithium.[22] Ethylenedilithium could not be prepared from ethylene dibromide either by the action of the metal [21] or by the use of phenyl-lithium.[23] The higher compounds have been used in high-yield syntheses of disilanes,[21] *spiro*silanes such as $\mathrm{[CH_2]_4{>}Si{<}[CH_2]_4}$,[18] and cyclic derivatives of boron.[23a]

Unsaturated dihalides tend to undergo dehalogenation with magnesium ; thus 1 : 4-dibromobut-2-ene gives butadiene in nearly quantitative yield.[24] The highly strained hydrocarbon methylene*cyclo*propane has been prepared [25] in this way from 3-chloro-2-chloromethylpropene by using tetrahydrofuran as solvent : $\mathrm{(Cl{\cdot}CH_2)_2C{:}CH_2 \longrightarrow [CH_2]_2 > C{:}CH_2}$ (17%).

Dihalogenobenzenes.—Although a number of dihalogenobenzenes (*e.g.*, *o*-, *m*-, and *p*-di-iodo- and *m*- and *p*-dibromo-benzene) have been shown to react with substantially more than one equivalent of magnesium, the double Grignard reagents can be obtained only in poor yield and have been little used. Such reagents from *p*-dibromo- [26] and *p*-dibromodeuterobenzene [27] have been employed, but more valuable than the former is *p*-phenylenedilithium, obtained by means of *n*-butyl-lithium.[19, 28] It has recently been shown that 3-bromo-4-iodotoluene with an excess of magnesium yields a double Grignard reagent.[29]

Much wider use has been made of single Grignard reagents. *p*-Bromo-

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[20] Müller and Schütz, *Ber.*, 1938, **71**, 689.

[21] West and Rochow, *J. Org. Chem.*, 1953, **18**, 1739.

[22] Ziegler, Nagel, and Patheiger, *Z. anorg. Chem.*, 1955, **282**, 345.

[23] Wittig and Harborth, *Ber.*, 1944, **77**, 306.

[23a] Torssell, *Acta Chem. Scand.*, 1954, **8**, 1779.

[24] Khitrik, *J. Gen. Chem.* (*U.S.S.R.*), 1940, **10**, 2098.

[25] Gragson, Greenlee, Derfer, and Boord, *J. Amer. Chem. Soc.*, 1953, **75**, 3344.

[26] von Braun, Irmisch, and Nelles, *Ber.*, 1933, **66**, 1471.

[27] Best and Wilson, *J.*, 1946, 239.

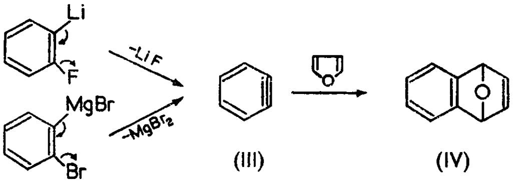
[28] Gilman, Langham, and Moore, *J. Amer. Chem. Soc.*, 1940, **62**, 2327.

[29] Hart and Mann, *Chem. and Ind.*, 1956, 574.

phenylmagnesium bromide with a variety of co-reactants gives the expected products, generally in yields of 40—50%. All the chlorophenylmagnesium bromides and iodides have also been used, as have the *m*- and *p*-fluorophenylmagnesium bromide.[3]

n-Butyl-lithium in ether appears to be particularly effective for replacement of a single halogen atom by lithium in dihalogenobenzenes. *p*-Dibromobenzene gives *p*-bromophenyl-lithium in 50—70% yield,[28, 30] and *m*- and *p*-chlorophenyl-lithium can similarly be prepared from the bromochlorobenzenes. Fluorine is not susceptible to interconversion, and *m*-difluorobenzene is metallated at a C–H bond by methyl- or phenyl-lithium.[6] A study of the effect of hydroxyl and methoxyl substituents in dibromobenzenes and -naphthalenes has shown that such substituents activate halogen in interconversions in the order $o > p > m$.[7]

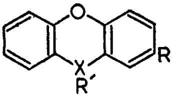
Studies on *o*-halogenophenyl-lithiums are of particular interest, having contributed to the recognition of the " benzyne " (*cyclo*hexadienyne) intermediate. Treatment of *o*-bromofluorobenzene in furan with lithium amalgam gives 1 : 4-epoxy-1 : 4-dihydronaphthalene (IV) in good yield, and it was suggested that this arose by elimination of lithium fluoride from *o*-fluorophenyl-lithium followed by Diels–Alder addition to furan of the resulting reactive " benzyne " intermediate [represented by (III)],[31] the structure of which presumably involves an electronically excited acetylenic state together, possibly, with dipolar canonical forms.



o-Fluoro-, *o*-chloro-, and *o*-bromo-phenyl-lithium have been prepared [32] by treating the corresponding *o*-bromohalogenobenzenes with ethereal *n*-butyl-lithium at temperatures below – 50°. All are highly labile (*o*-$Br{\cdot}C_6H_4Li$ > *o*-$Cl{\cdot}C_6H_4Li$ > *o*-$F{\cdot}C_6H_4Li$) and their coupling reactions and addition to furan have been interpreted as involving the intermediate (III).[32, 33] The *o*-halogenophenylmagnesium bromides can also yield this intermediate.[33] The above *o*-halogenophenylmetallic compounds may be prepared in good yield, except the *o*-bromo-compounds (which are available in 20—30% yield by treatment of *o*-dibromobenzene with *n*-butyl-lithium,[32] or with magnesium in ether or tetrahydrofuran [8, 33]) and *o*-fluorophenylmagnesium bromide; all react in " normal " fashion with typical co-reactants under suitable conditions. The formation and reactions of the " benzyne " intermediate have recently been reviewed by Wittig.[33a]

[30] Gilman and Melvin, *J. Amer. Chem. Soc.*, 1950, **72,** 995.
[31] Wittig and Pohmer, *Angew. Chem.*, 1955, **67,** 348.
[32] Gilman and Gorsich, *J. Amer. Chem. Soc.*, 1956, **78,** 2217.
[33] Wittig and Pohmer, *Chem. Ber.*, 1956, **89,** 1334.
[33a] Wittig, *Suomen Kem.*, 1956, **29,** *A*, 283.

Dihalogen Derivatives of Diaryl Ethers, Diphenylamine, and Dibenzyl.—*o*-Bromophenyl 2-bromo-4-methylphenyl ether reacts slowly with magnesium, to give ultimately a high yield of the double Grignard reagent, which has been treated with various aryldihalogenostibines, thus affording a series of 10-aryl-2-methylphenoxstibines. A compound of this type, 10-*p*-carboxyphenyl-2-methylphenoxstibine (V ; X = Sb, R = Me, R′ = *p*-$HO_2C{\cdot}C_6H_4$), has been resolved ; it probably owes its asymmetry to folding of the tricyclic system about the O–Sb axis.[34]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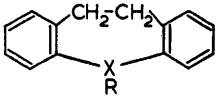
(VI)

Di-*o*-bromophenyl ether gives a dilithium compound with *n*-butyl-lithium, which with phenyldichlorophosphine gives 10-phenylphenoxphosphine (V ; X = P, R = H, R′ = Ph).[35] One or both halogen atoms in di-*p*-bromophenyl ether may be replaced by metal if ethereal *n*-butyl-lithium is used in appropriate amount,[28] and the same would certainly be true for all these compounds, in which interconversion is assisted by the *o*- or *p*-ether linkage. *oo′*-Dibromodiphenylamine similarly gives a dilithium compound, which on carboxylation gives the 2 : 2′-dicarboxylic acid (84%).[36]

2 : 2′-Dibromodibenzyl with *n*-butyl-lithium gives 2 : 2′-dilithiodibenzyl, which with dichlorophenyl-arsine or -phosphine gives, in 20—25% yield, the cyclic arsine or phosphine (VI ; X = As or P, R = Ph), these being isodimorphous.[37] This organodilithium compound has also been used to prepare the first cyclic derivatives of boron having carbon–boron bonds within the ring, by reaction with *n*-butyl borate.[38]

Dihalogenodiphenyls.—As in the preceding series, the members which have proved the most useful are the 2: 2′-compounds, yielding organodimetallic derivatives of value in the synthesis of several elusive cyclic structures.

With magnesium, 2 : 2′-dibromodiphenyl is slowly and partially converted into a slightly soluble double Grignard reagent ; when heated with cupric chloride in ether (Krizewski–Turner reaction) this yields diphenylene (4%) and tetraphenylene (*s*-tetrabenzo*cyclo*octatetraene ; 16%).[39] The dibromo-compound reacts smoothly with *n*-butyl-lithium in appropriate amount to give either the mono- or the di-lithium compound ; the latter with dichlorodiphenylsilane gives the cyclic silane (II).[2, 32] With phenyl-lithium, the dibromo-compound gives triphenylene in low yield (apparently *via* 2-bromoterphenyl) and diphenyl, but no diphenylene.[40] An alternative route to 2 : 2′-dilithiodiphenyl is afforded by direct reaction between 2 : 2′-

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[34] Campbell, *J.*, 1947, 4.

[35] Mann and Millar, *J.*, 1953, 3746.

[36] Jones and Mann, *J.*, 1956, 786.

[37] Mann, Millar, and Smith, *J.*, 1953, 1130.

[38] Letsinger and Skoog, *J. Amer. Chem. Soc.*, 1955, **77**, 5176.

[39] Rapson, Shuttleworth, and van Niekerk, *J.*, 1943, 326.

[40] Barton and McOmie, *J.*, 1956, 796.

di-iododiphenyl and lithium. This procedure gives an excellent yield, and has been employed both in the synthesis of *P*-phenyl-9-phosphafluorene (by reaction of the product with phenyldichlorophosphine)[41] and in a more recent synthesis of diphenylene. The dilithium compound with mercuric chloride gives a nearly quantitative yield of diphenylmercury, which on being heated with silver powder gives diphenylene (54%).[10]

3 : 3′-Dibromodiphenyl reacts with magnesium only with the aid of an entraining agent, giving the double Grignard reagent. However, 3 : 3′-dilithiodiphenyl is readily obtained by the use of *n*-butyl-lithium ; the metal fails to react.[42]

4 : 4′-Dibromo- and 4 : 4′-di-iodo-diphenyl yield double Grignard reagents with magnesium,[43, 44] but these are less useful in synthesis than 4 : 4′-dilithiodiphenyl, obtainable by the action of *n*-butyl-lithium on the dibromo-compound.[19, 28] In the same way, partial replacement of bromine may be effected in satisfactory yield.[28]

The reactions with magnesium of four of the six homonuclear dibromodiphenyls have been very fully investigated by Case.[45] The most satisfactory results were obtained with a magnesium–copper alloy, and the extent of reaction is given as 2 : 4 $>$ 2 : 5 $>$ 3 : 5 $>$ 3 : 4. The last compound failed to react. Coupling with the remaining compounds was not extensive ; double Grignard reagents were formed in poor yields, but failed to be carboxylated normally. It is clear that these reagents have little value in synthesis, and as with dihalogenobenzenes it is hard to cause a second homonuclear halogen atom to react with metal.

Dihalogenonaphthalenes.—1 : 2-Dibromonaphthalene reacts with magnesium only in the presence of an entraining agent, and yields mainly a double Grignard reagent, as adduced by the formation of naphthalene on hydrolysis. However, this reagent gives only a trace of dicarboxylic acid on carboxylation. Reaction of 1 : 4-dibromonaphthalene with magnesium does not require an entraining agent, and with one equivalent of metal a single Grignard reagent is formed which is carboxylated normally in good yield ; excess of metal leads to partial formation of a double Grignard reagent which fails to react with carbon dioxide.

1 : 5-Dibromonaphthalene gives a double Grignard reagent with all proportions of magnesium, and after reaction with an excess of metal affords, on carboxylation, an almost quantitative yield of the 1 : 5-dicarboxylic acid. Similarly, both halogens are reactive in 1 : 6- and 1 : 7-dibromonaphthalene, the former compound also giving 5-bromo-2-naphthyl magnesium bromide in satisfactory yield, which reacts normally with carbon dioxide and with cyanides.[46] With " mixed " dihalogenonaphthalenes, there is no difficulty in bringing one halogen only into reaction with magnesium.[3]

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[41] Wittig and Geissler, *Annalen*. 1953, **580,** 44.

[42] Snyder, Weaver, and Marshall, *J. Amer. Chem. Soc.*, 1949, **71,** 289.

[43] Malinovskiĭ and Pokrovskiĭ, *Trudy Gor'kov. Gosudarst. Pedagog. Inst.*, 1940, No. 5, 51 ; *Chem. Abs.*, 1943, **37,** 3077.

[44] Kern, Gehm, and Seibel, *Makromol. Chem.*, 1955, **15,** 170.

[45] Case, *J. Amer. Chem. Soc.*, 1936, **58,** 1246.

[46] Zalkind, *Ber.*, 1934, **67,** 1031.

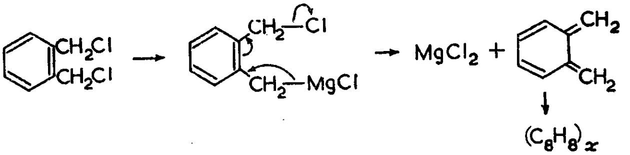
The reactions of the above dibromonaphthalenes with lithium and *n*-butyl-lithium have not been recorded, although the exchange reaction with some dibromonaphthols has been studied.[7] Vicinally substituted naphthalenes would be expected to yield a " naphthyne " intermediate, the existence of which has been postulated.

Dihalogen Derivatives of Anthracene and Naphthacene.—9 : 10-Dibromoanthracene undergoes replacement of one or both halogens on treatment with lithium or *n*-butyl- or phenyl-lithium, depending on the ratio of reactants used. The products react satisfactorily with carbon dioxide, alkyl halides, and ethylene oxide, although yields from the dilithium compound are poor. The 2-methyl compound behaves similarly, bromine at the 10-position being replaced preferentially. The bromine of 9-bromo-10-chloroanthracene is also replaceable, best by phenyl-lithium.[47]

6 : 11-Dibromo-1 : 2 : 3 : 4-tetrahydronaphthacene resembles 9 : 10-dibromoanthracene in its behaviour on halogen–metal interconversion.[48] 9 : 10-Di-*p*-bromophenylanthracene and 5 : 11-di-*p*-bromophenyl-6 : 12-diphenylnaphthacene both yield double Grignard reagents by the entrainment procedure ; the reagent from the second compound (a substituted rubrene) has the distinction of giving a black solution in ether.[49]

Halogen-substituted Benzyl Halides.—The high reactivity of benzyl halides leads to the predominant formation of a coupled product on treatment of such halides with lithium or its simple alkyl and aryl derivatives ; thus 2-bromobenzyl bromide with phenyl-lithium gives 2 : 2′-dibromodibenzyl, providing the most satisfactory route to this compound.[38] A similar reaction has been observed with 1-bromo-2-bromomethylnaphthalene.[50] However, reaction with magnesium enables halogenobenzylmagnesium halides to be prepared in good yields.[1, 3]

Di(halogenomethyl)aryl Compounds.—The xylylene dihalides all fail to give derivatives of value in synthesis. Mann and Stewart have shown [51] that *o*-xylylene dichloride with magnesium in ether gives a poly-*o*-xylylene, probably *via* the highly reactive *o*-quinodimethane (VII) :



(VII)

Similar mechanisms have been offered for a number of related cases in which an MgX residue is separated from a group capable of forming a stable anion by a suitable conjugated system.[51] *p*-Xylylene dibromide also gives a polymer with magnesium ; [52] this reaction presumably pro-

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[47] Mikhaĭlov and Bronovitskaya, *Zhur. obschchei Khim.*, 1952, **22**, 157 ; 1953, **23**, 130.

[48] Mikhaĭlov and Chinaeva, *ibid.*, 1952, **22**, 1887.

[49] Dufraisse and Morgoulis-Molho, *Bull. Soc. chim. France*, 1940, **7**, 930.

[50] Hall and Turner, *J.*, 1955, 1242.

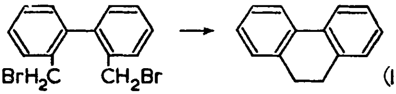
[51] Mann and Stewart, *J.*, 1954, 2826.

[52] Carothers, *Chem. Rev.*, 1931, **8**, 373.

ceeds by an analogous mechanism involving *p*-quinodimethane. It is of interest that this dihalide with sodium in ether gives tri-*p*-xylylene, and *m*-xylylene dibromide similarly yields di-*m*-xylylene, which could not be obtained by the action of lithium or phenyl-lithium.[53] The above mechanism of polymer formation is not, of course, available for *m*-xylylene dihalides.

Hall, Lesslie, and Turner [54] observed that 2 : 2′-di(bromomethyl)-diphenyl (VIII) reacts with magnesium or phenyl-lithium in ether to give 9 : 10-dihydrophenanthrene (IX), presumably *via* an intermediate organo-monometallic compound :

(VIII)

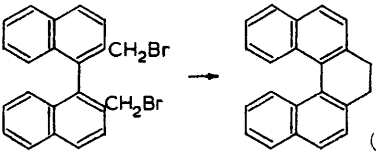


(IX)

This procedure affords a general method for the synthesis of 9 : 10-dihydrophenanthrenes, from which, if desired, phenanthrenes may be obtained by dehydrogenation. The preferred reagent is ethereal phenyl-lithium, the necessary di(bromomethyl) compounds being prepared either by bromination of the appropriate dimethyl compound with *N*-bromosuccinimide, or from dicarboxylic esters by reduction to diols with lithium aluminium hydride, followed by treatment with hydrogen bromide.[55] A poor yield is obtained in the synthesis of 9 : 10-dihydro-4 : 5-dimethoxyphenanthrene, probably as a result of steric interference between the methoxyl groups inhibiting the close approach of the CH_2Br and CH_2Li groups in the diphenyl intermediate.[56]

A particularly interesting case is the conversion of 2 : 2′-di(bromomethyl)-1 : 1′-dinaphthyl (X) into 9 : 10-dihydro-3 : 4-5 : 6-dibenzophenanthrene (XI) ; use of an optically active dibromide results in the formation of an active product of opposite rotation, activity in both compounds being dependent on the non-coplanarity of the two naphthyl systems.[50] 1 : 8-Di(bromomethyl)naphthalenes undergo a similar reaction, yielding acenaphthenes.[57]

(X)



(XI)

Where intramolecular cyclisation is impossible or difficult, a similar reaction leads to intermolecular coupling, giving rise in suitable cases to

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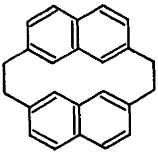
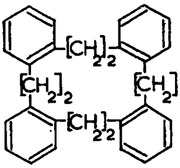
[53] Baker, McOmie, and Norman, *J.*, 1951, 1114.
[54] *J.*, 1950, 711.
[55] Beaven, Hall, Lesslie, Turner, and Bird, *J.*, 1954, 131 ; Bergmann and Pelchowicz, *J. Org. Chem.*, 1954, **19**, 1387 ; Badger, Jefferies, and Kimber, *J.*, 1957, 1837.
[56] Hall and Turner, *J.*, 1951, 3072.
[57] Bergmann and Szmuszkovicz, *J. Amer. Chem. Soc.*, 1953, **75**, 2760.

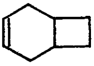
some interesting large-ring compounds. Thus 2 : 7-di(bromomethyl)naphthalene yields di(naphthalene-2 : 7-dimethylene) (XII) ; [58] and 2 : 2′-di(bromomethyl)dibenzyl gives 1 : 2-5 : 6-9 : 10-13 : 14-tetrabenzo*cyclo*hexadeca-1 : 5 : 9 : 13-tetraene (XIII).[59] These strainless non-planar structures are obtainable in yields of 20—60%.



(XII)



(XIII)



(XIV)

Although not strictly within the purview of the present section, it is of interest that *cis*-1 : 2 : 3 : 6-tetrahydro-*o*-xylylene di-iodide with phenyl-lithium gives *bicyclo*[4 : 2 : 0]oct-3-ene (XIV) (75%), from which *cyclo*octa-1 : 3 : 5-triene may be prepared.[60]

Dihalogen Derivatives of Heterocyclic Compounds.—Few results have been reported with dihalogenofurans. Single Grignard reagents have been prepared from 2 : 5-di-iodofuran [3] and 3 : 4-di-iodo-2 : 5-dimethylfuran.[61]

In the thiophen series, halogen in the 2-position is notably reactive, and all the 2 : 3-dihalogenothiophens yield single Grignard reagents ; that from the dibromo-compound, when subjected to the Krizewski–Turner reaction, yields 3 : 3′-dibromo-2 : 2′-dithienyl (36%). The 3 : 4-di-iodo-compound also gives a single Grignard reagent.[62] 2 : 5-Di-iodothiophen gives a double Grignard reagent, and affords 2 : 5-dilithiothiophen in good yield with ethereal phenyl-lithium.[6]

3 : 5-Dibromopyridine, which fails to react with magnesium, gives 3-bromo-5-lithiopyridine with *n*-butyl-lithium, but the second halogen resists replacement.[63] 2 : 6-Dibromopyridine behaves similarly with *n*-butyl-lithium,[63] but, surprisingly, gives a double Grignard reagent.[64]

Several symmetrical dibromodibenzofurans have been converted into dilithium derivatives by the action of *n*-butyl-lithium ; such derivatives, obtainable in good yields, are of potential value in synthesis.[6] 2 : 8-Dihalogeno-9-ethylcarbazoles behave similarly.[6] Treatment with an equimolecular quantity of *n*-butyl-lithium would almost certainly give the monolithium compounds in these cases.

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[58] Baker, McOmie, and Warburton, *J.*, 1952, 2991.
[59] Bergmann and Pelchowicz, *J. Amer. Chem. Soc.*, 1953, **75,** 4281.
[60] Alder and Dortmann, *Chem. Ber.*, 1954, **87,** 1492.
[61] Hurd and Wilkinson, *J. Amer. Chem. Soc.*, 1948, **70,** 739.
[62] Steinkopf and Kohler, *Annalen*, 1937, **532,** 250.
[63] Gilman and Spatz, *J. Org. Chem.*, 1951, **16,** 1485.
[64] Proost and Wibaut, *Rec. Trav. chim.*, 1940, **59,** 971.