This is to certify that the

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PREPARATION AND APPLICATION OF
DI-GRIGNARD REAGENTS

presented by

Ching-Hahn Suh

has been accepted towards fulfillment
of the requirements for

Masters degree in Science

Harold Hart
Major professor

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PREPARATION AND APPLICATION OF DI-GRIGNARD REAGENTS

By

Ching-Hahn Suh

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in partial fulfillment of the requirements
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ABSTRACT

PREPARATION AND APPLICATION OF DI-GRIGNARD REAGENTS

By

Ching-Hahn Suh

The following three types of di-Grignard reagents are prepared:

1. di-Grignard reagents from di-haloarenes;
2. di-Grignard reagents from 1,2,4,5-tetrahalobenzenes;
3. 1,4-di-Grignard reagents from hexahalogenobenzenes.

Three conventional methods (direct preparation, exchange and entrainment) have been reviewed. Two new methods have been studied:

1. a combination of the direct, exchange and entrainment methods;
2. a combination of the exchange and entrainment methods.

They both show better results than conventional methods. Some limited applications of these di-Grignard reagents to synthesis have been carried out.

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INTRODUCTION

The history of di-Grignard reagents is long. In 1934, Grignard prepared the first two di-Grignard reagents by the entrainment method:[1]

$$4\text{-BrC}_6\text{H}_4\text{MgBr} + \text{C}_2\text{H}_5\text{Br} + \text{Mg} \longrightarrow 1,4\text{-(BrMg)}_2\text{C}_6\text{H}_4 \longrightarrow \text{C}_6\text{H}_6$$

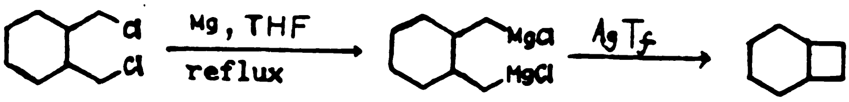
Molar Ratio: 1 : 2 excess 40%

$$4\text{-BrC}_6\text{H}_4\text{CH}_2\text{MgBr} + \text{C}_2\text{H}_5\text{Br} + \text{Mg} \longrightarrow 4\text{-BrMgC}_6\text{H}_4\text{CH}_2\text{MgBr} \longrightarrow \text{CH}_3\text{C}_6\text{H}_5 \text{ } 35\%$$

Molar Ratio: 1 : 2 excess

In 1971, Tamborski et. al. prepared the di-Grignard 2,3,5,6-tetrabromo-1,4-bis (magnesium bromide)benzene by exchange of CH_3CH_2MgBr or C_6H_5MgBr with hexabromobenzene.[2] The yields were 51% and 2% respectively.

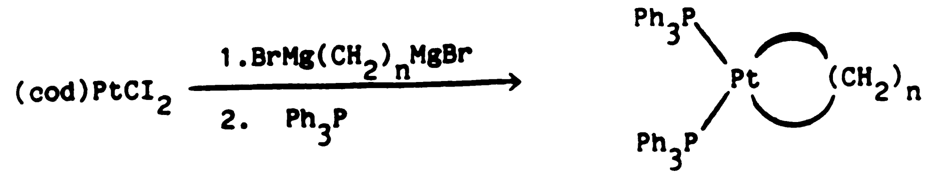
In 1976, Whitesides and Gutowski prepared several α,ω-alkane di-Grignard reagents by the direct method. They used silver triflate ($AgOSO_2CF_3$) to oxidize the di-Grignard, thus providing a practical synthesis for four-, five- and six-membered carbocyclic rings.[3] For example,



(61%)

Figure 1. Cyclization from α,ω-Alkane Di-Grignards

They also used α,w-alkane di-Grignard reagents to synthesize metallocyclic complexes.[4] For example,



cod=cyclo-octa-1,5-diene n=4,5,6

Figure 2. Metallocyclic Complexes from α,ω-Alkane Di-Grignards

In 1978, Clark and O'Reilly prepared p-bis-(Magnesium bromide)benzene by the direct method, and used it in a reaction with ethylene oxide, and a 50% yield of 1,4-bis (2-hydroxyethyl)benzene was obtained.[5]

In 1982, Raston, et. al. prepared the di-Grignard reagent o-$C_6H_4(CH_2MgCl)_2$ from o-bis(chloromethyl)benzene by the direct method, and they used the di-Grignard in synthesis of a metallocyclic complex.[6]

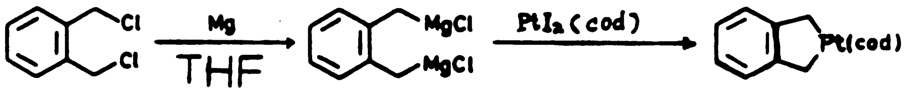


Figure 3. Metallocyclic Complexes from o-$C_6H_4(CH_2MgCI)_2$

In 1984, they prepared the di-Grignard reagent 1,1'-bis(methylene magnesium chloride)biphenyl from 1,1'-bis(chloromethyl)biphenyl by the direct method.[7] More recently, they published an improved method for benzylic type di-Grignards by using as the Mg source the 1:1 adduct of magnesium with anthracene.[8] Yields are 92-96%.

In this thesis, the preparation of the following three types of di-Grignard reagents is described:

A. Di-Grignard Reagents Generated from Di-haloarenes.

B. Di-Grignard Reagents from 1,2,4,5-Tetrahalobenzenes.

C. 1,4-di-Grignard Reagents from Hexahalobenzenes.

Three conventional methods (direct preparation, exchange and entrainment) have been reviewed. Two new methods have been studied: 1. a combination of the direct, exchange and entrainment methods; 2. a combination of the exchange and entrainment methods. They both show better results than conventional methods. These methods, and their applications, are described in Section I of this thesis.

I. PREPARATION OF DI-GRIGNARD REAGENTS

A. Di-Grignard Reagents Generated from Di-Haloarenes

In the following preparation of di-Grignard reagents by the direct method, magnesium can be used in stoichiometric amounts or in excess. Products were analyzed by G.C. and compared with authentic samples.

Experimental Procedure

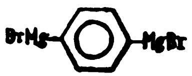
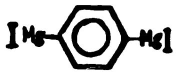
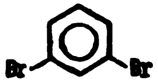
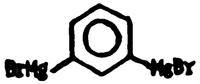
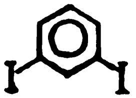
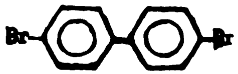
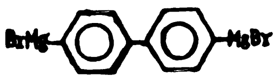
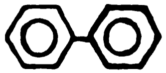
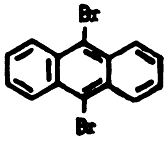
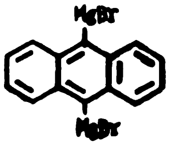
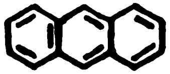
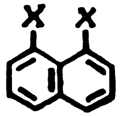
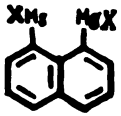
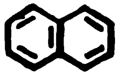
To a dried, Ar protected three-necked round-bottomed 250-mL flask was added Mg powder (0.39g, 16 mmole or a little excess), THF 10 mL and $BrCH_2CH_2Br$ (0.2 mL, 2.32 mmole). The mixture was magnetically stirred at r.t. for 15 minutes. A solution of 6 mmole of the di-haloarene in 50-70 mL THF was added dropwise over 30 min, and the solution was then heated at reflux for 6-8 hrs. During this period, vigorous stirring was important. Then a grey-white precipitate of the di-Grignard reagent can be noted. The solution was cooled to 0°C and 10 mL of dilute hydrochloric acid (5%), or 20 mmole I_2 or Br_2 was added, and the mixture was stirred for a few minutes.

Isolation

After distilling most of the THF, the residue was extracted with 50 mL $CHCl_3$. The solution was washed successively with dilute hydrochloric acid and water, and dried (Na_2SO_4).

Result

Table 1. Di-Grignard Reagents from Di-Haloarenes

Starting Material	Structure of Di-Grignard	Quench Agent	Product	G.C. Analysis (%)	Isolated Yield (%)
		I_2		100	83
		Br_2		100	94
		I_2		95	80
		$HCl-H_2O$		100	94
		$HCl-H_2O$		100	96
 X=Cl,Br,I		$HCl-H_2O$		100	99

B. Di-Grignard Reagents from 1,2,4,5-Tetrahalogenobenzenes

Preparations of the following di-Grignard reagents were carried out using a large excess of magnesium, and ethylmagnesium bromide. The yields of products were determined by G.C. analysis, and products were identified by comparison with authentic samples.

Experimental Procedure

To a dried, Ar-protected three-necked round-bottomed 250-mL flask was added magnesium powder (1g, 40 mmole), THF (40 mL), and CH_3CH_2Br (1.2 mL, 15 mmole). The mixture was rigorously stirred at r.t. for 30 minutes. A solution of 6 mmole 1,2,4,5-tetrahalogenobenzene in 80 mL THF was added dropwise over 0.5-1 hr at 0°C, and the mixture was stirred for 1-2 hrs at 0°C. The reaction was quenched by adding 20 mL of dilute hydrochloric acid at 0°C.

Isolation

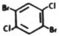
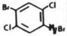
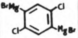
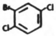
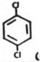
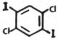
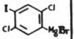
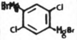
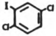
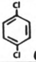
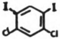
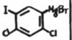
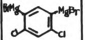
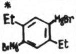
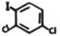
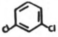
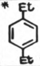
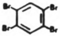
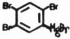
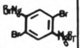
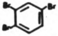
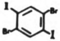
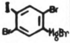
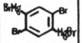
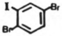
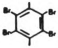
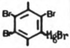
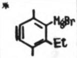
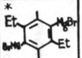
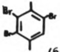
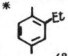
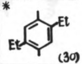
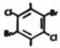
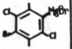
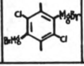
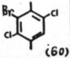
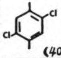
See description in the former section.

Observation

Those 1,2,4,5-tetrahalogenobenzenes that contain iodine usually give greyish white precipitate during the reaction.

Result

Table 2. Di-Grignard Reagents from 1,2,4,5-Tetrahalogenobenzenes

Starting Material	Intermediate of Product		Intermediate of By-Product		Product (%)		By-Product (%)	
	Mono-Grignard	Di-Grignard	A	B	From Mono-Grignard	From di-Grignard	A	B
					 (35)	 (62)		
					 (trace)	 (94)		
					 (2)	 (92)		 (trace)
					 (62)	 (35)		
					 (27)	 (70)		
					 (60)		 (8)	 (30)
					 (60)	 (40)		

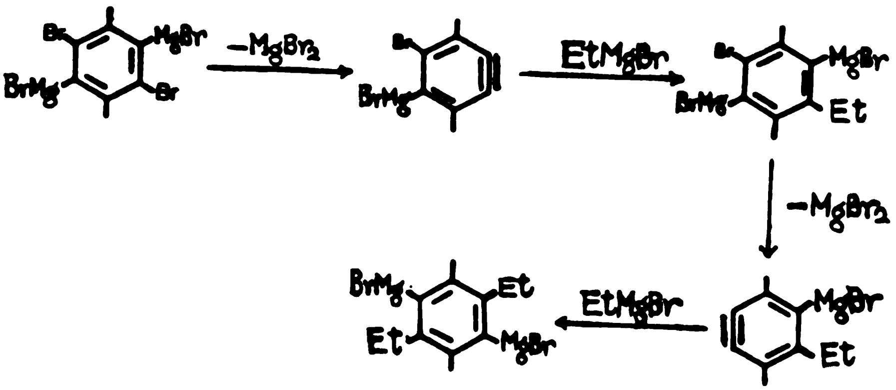


Figure 4. Trapping of Arynes with Alkyl Grignard

Similar processes occurred with 1,3-dichloro-4,6-bis (magnesium bromide)benzene.

C. Di-Grignard Reagents Generated from Hexahalogenobenzenes

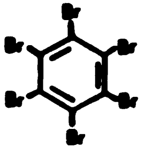
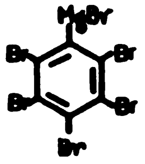
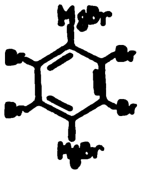
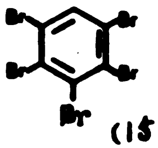
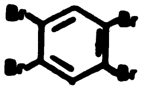
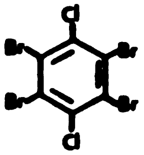
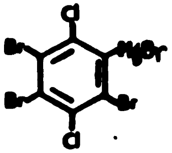
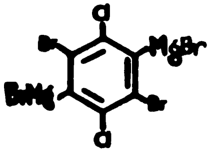
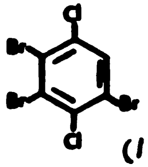
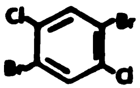
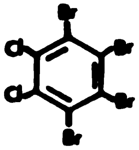
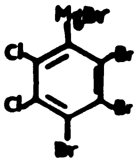
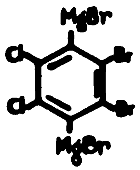
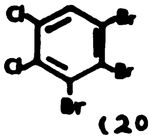
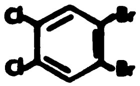
The method of preparing the following di-Grignard reagents was exactly the same as that described above. The yields of products were determined by G.C. analysis, and products were identified by comparison of retention time with those of authentic samples.

Experimental Procedure

To a dried, Ar-protected three-necked round-bottomed 500 mL flask was added Mg powder (1g, 40 mmole), THF (40 mL) and CH_3CH_2Br (0.8 mL, 10 mmole). The mixture was rigorously stirred at r.t. for 30 minutes. A solution of 4 mmole hexahalogenobenzene in 100 mL THF was added dropwise over 1-1.5 hrs at 0°C, and followed by additional stirring for 2 hrs at 0°C. The reaction was quenched with 20 mL of dilute hydrochloric acid at 0°C.

Result

Table 3. Di-Grignard Reagents from Hexahalogenobenzenes

Halide	Intermediate		Product (Yield %)	
	Mono-Grignard	Di-Grignard	From Mono-Grignard	From Di-Grignard
			 (15)	 (75)
			 (16)	 (78)
			 (20)	 (75)

II. DISCUSSION OF PREPARATION METHOD OF DI-GRIGNARD REAGENTS

A. Direct Reaction of Hexahalogenobenzene with Magnesium

In the following experiments, the hexahalogenobenzene reacts with a large excess of magnesium powder and 1,2-dibromoethane as an entrainer, under different temperature (T), and different time periods (t) sequence control. The yields of mono- or di-Grignard reagents were determined by ethylene oxide quenching.

In all runs, there was no or only a trace of 3,6-dichloro-2,4,5-tribromo-1-(2-hydroxyethyl)benzene.

Experimental Procedure

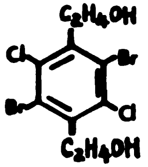
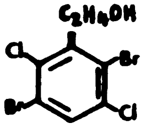
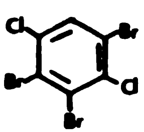
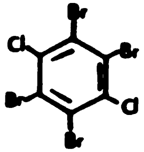
To a dried, Ar-protected three-necked 100-mL round-bottomed flask was added Mg powder (0.2g, 8 mmole), THF (40 mL), $BrCH_2CH_2Br$ (0.2 mL, 2.32 mmole), and the mixture was stirred magnetically at r.t. for 15 mins. A solution of 1 mmole (0.462g) 1,2,4,5-tetrabromo-3,6-dichlorobenzene in 35 mL THF was added dropwise over 30 mins at T_1, and the mixture was stirred for t_1 at T_1. Ethylene oxide (0.5 mL, 10 mmole) in 5 mL THF or ether was added at T_2, and the mixture was stirred for t_2 at T_2, and then for t_3 at T_3. Finally, the solution was cooled to 0°C, and 10 mL of dilute hydrochloric acid (5%) was added.

Observation

The color of the Grignard reagents solution was dark brown. When ethylene oxide was added, the color changes to light brown. If the solution was heated over 65°C for several hrs, a reddish brown color

Result

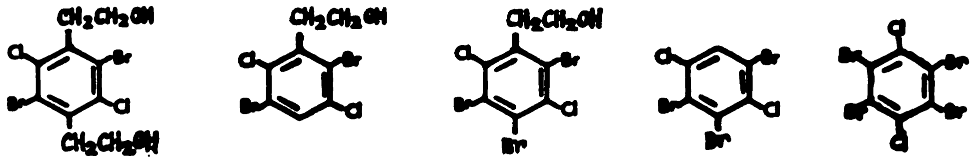
Table 4. Products of Di-Grignards Reacting with Ethylene Oxide

Run	T_1 (°C)	t_1 (hr)	T_2 (°C)	t_2 (hr)	T_3 (°C)	t_3 (hr)				
1	0	24	0	12					10%	80%
2	15	10	15	8			2%	5%	60%	5%
3	15	5	15	8			2%	5%	50%	15%
4	15	3	15	8			2%	5%	50%	20%
5	25	3	25	5			5%	30%	30%	8%
6	25	5	25	5			5%	40%	15%	5%
7	25	3	0	3	50	5	24%	5%	20%	8%
8	25	5	0	3	50	5	30%	5%	10%	5%

was observed. When the mono-adduct became di-adduct, a greyish yellow precipitation deposited around the edge of container.

Isolation

After distilling most of THF, the residue was extracted with 50 mL $CHCl_3$. The extract was washed successively with dilute hydrochloric acid and water, and dried over Na_2SO_4. For product isolation by chromatography, a silica gel column was used, with a mixed solvent eluent of CH_2Cl_2:$CHCl_3$ (1:1). The R_f values (on 0.2 m m MN silica gel N-H R/UV_{254} plates) are:



0.17 (A) 0.28 (B) 0.33 (C) 0.72 0.72

Figure 5. R_f Values of the Products of Di-Grignards Reacting with Ethylene Oxide

Identification

The following three adducts were all previously unknown compounds.

(A) 3,6-dichloro-2,5-dibromo-1,4-bis(2-hydroxyethyl)benzene: yellowish needles, m.p. 102-104°C; MS:m/e (relative intensity) 392(M^+, 12), 344(100), 331(53), 311(15), 295(13), 283(18), 265(52), 252(30), 229(13), 216(22), 170(23), 149(20), 136(34); H^1 NMR ($CDCl_3$):δ3.48(t, ^3J's 9 Hz, 4H), 3.59-3.79(m, 4H), 1.28(t, ^3J's 4 Hz, 2H). Anal. Calcd for $C_{10}H_{10}O_2Br_2Cl_2$:C, 30.57; H, 2.57. Found: C, 30.63; H, 2.59.

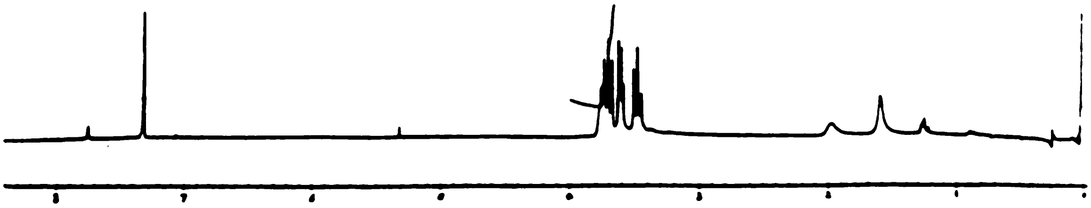


Figure 6. H^1 NMR of 3,6-Dichloro-2,5-dibromo-1,4-bis (2-hydroxyethyl)benzene

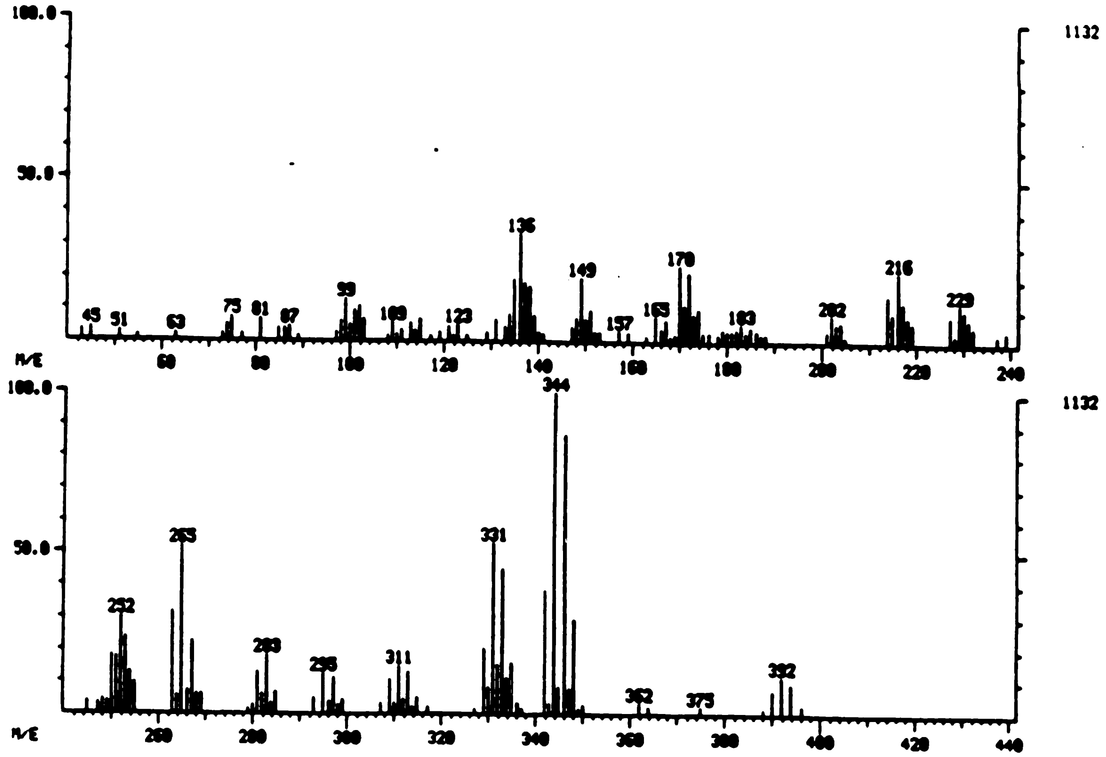


Figure 7. MS Spectrum of 3,6-Dichloro-2,5-dibromo-1,4-bis(2-hydroxyethyl)benzene

The protons of α- and β-CH_2 absorb at δ3.48 and δ3.59-3.79 respectively, and protons of α-CH_2 is split into a triplet (^3J's 9 Hz). Protons of β-CH_2 is split by those of α-CH_2 and hydroxyl into a multiplet. The addition of D_2O produces δ3.69(t, ^3J's 9 Hz, 4H), δ3.48(t, ^3J's 9 Hz, 4H). The β-CH_2 (δ3.69) is more deshielded than the α-CH_2 (δ3.48). The OH proton is at δ1.28, and is split by protons of β-CH_2 into a triplet peak (^3J's 4 Hz). Mass spectrum; 392:molecular ion; 344 (base peak):M-(CH_2OH and OH); 331:M-(CH_2OH and CHOH); 295:M-(2CH_2OH and Cl); 283:M-(CH_2OH, CH_2CH_2OH and Cl); 265:M-(CH_2OH, OH and Br); 252:M-(2CH_2OH and Br).

(B) 3,6-dichloro-2,5-dibromo-1-(2-hydroxyethyl)benzene: yellowish needles, m.p. 143-145°C; MS:m/e (relative intensity) 348(M^+, 17), 318(62), 283(26), 269(63), 239(97), 203(48), 157(86), 121(91), 85(100); H^1 NMR ($CDCl_3$):δ3.48(t, ^3J's 9 Hz, 2H), 3.90(t, ^3J's 9 Hz, 2H), 1.28(t, ^3J's 4 Hz, 1H), 7.69(s, 1H). Anal. Calcd for $C_8H_6OBr_2Cl_2$:C, 27.54; H, 1.73. Found: C, 27.99; H, 1.90.

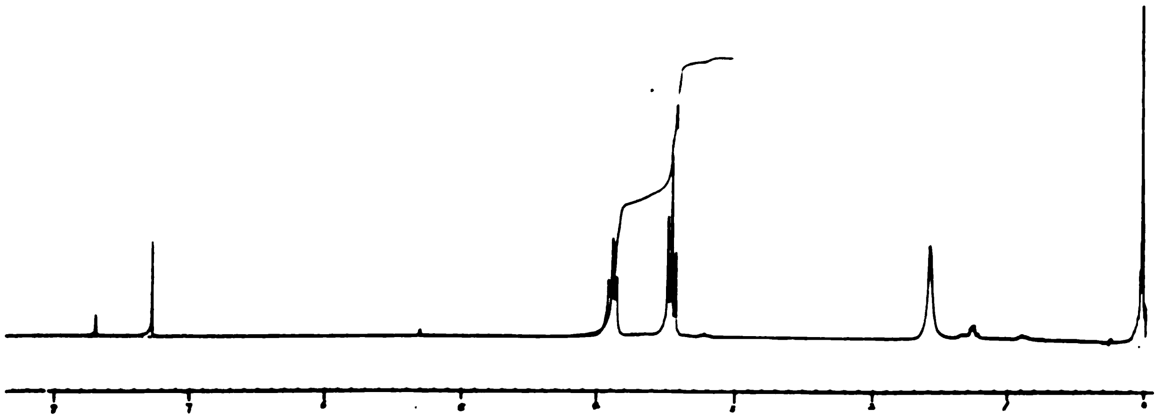


Figure 8. H^1 NMR of 3,6-Dichloro-2,5-dibromo-1-(2-hydroxyethyl)benzene

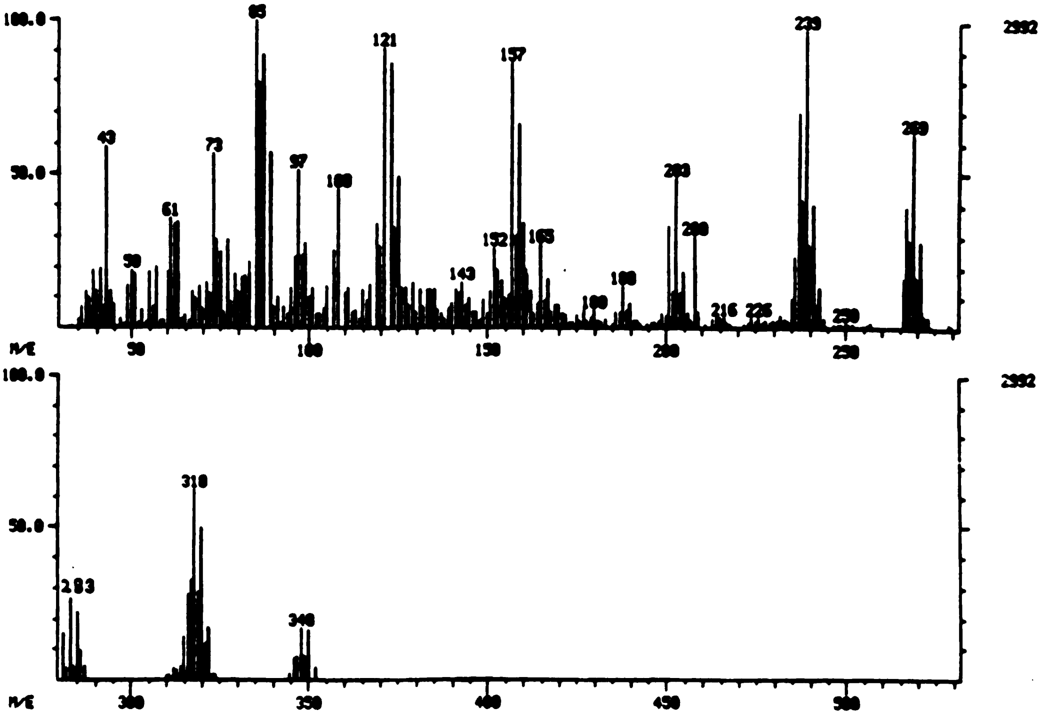


Figure 9. MS Spectrum of 3,6-Dichloro-2,5-dibromo-1-(2-hydroxyethyl)benzene

The protons of α- and β-CH_2 are at δ3.48 and 3.90 respectively, and each group of protons is split by the other into a triplet (^3J's 9 Hz). The β-CH_2 (δ3.90) is more deshielded than the α-CH_2 (δ3.48). The OH proton at δ1.28 is a triplet, split by protons of β-CH_2 (^3J's 4 Hz). The aromatic proton at δ7.69 appears as a singlet. Mass spectrum; 348:molecular ion; 318:M-CHOH; 283:M-(CHOH and Cl); 269:M-($CHCH_2OH$ and Cl); 239:M-(CHOH and Br); 203:M-(CH_2OH, Cl and Br).

(C) 3,6-dichloro-2,4,5-tribromo-1-(2-hydroxyethyl)benzene: yellowish needles, m.p. 150-152°C; MS:m/e (relative intensity) 428(M^+, 30), 398(94), 347(100), 317(90), 269(27), 237(98), 203(27), 121(32), 85(37), 40(68); H^1 NMR (CDCl$_3$):δ3.48(t, ^{3}J's 9 Hz, 2H), 3.90(t, ^{3}J's 9 Hz, 2H), 1.28(s, 1H). Anal. Calcd for C$_8$H$_5$OBr$_3$Cl$_2$:C, 22.46; H, 1.18.

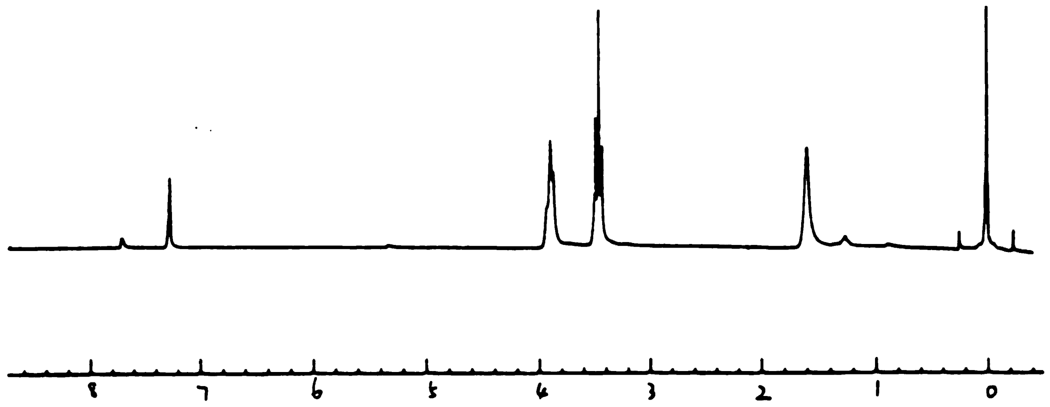


Figure 10. H^1 NMR of 3,6-Dichloro-2,4,5-tribromo-1-(2-hydroxyethyl)benzene

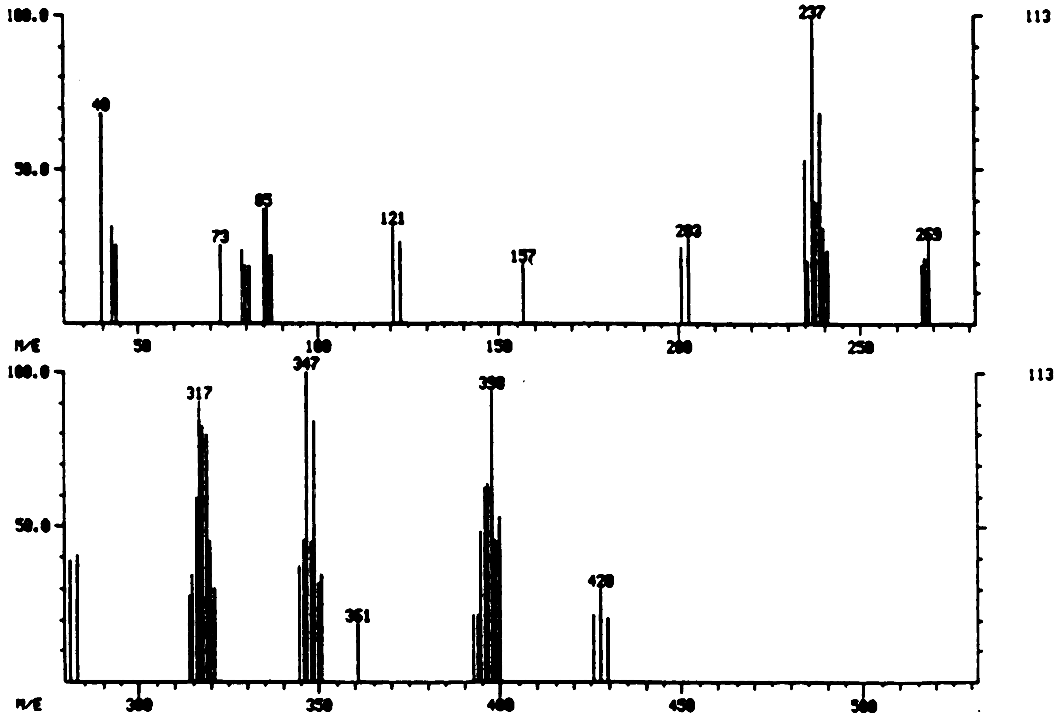


Figure 11. MS Spectrum of 3,6-Dichloro-2,4,5-tribromo-1-(2-hydroxyethyl)benzene

The protons of α- and β-CH_2 are at δ3.48 and 3.90 respectively, and each group of protons is split by the other into a triplet (^3J's 9 Hz). The β-CH_2 (δ3.90) is more deshielded than the α-CH_2 (δ3.48). The OH proton at δ1.28 is a broadened singlet. Mass spectrum interpretation; 428:molecular ion; 398:M-CHOH; 347:M-(CH_2CH_2OH and Cl); 317:M-(CH_2OH and Br); 269:M-(CH_2CH_2OH, Br and Cl); 237:M-(CH_2OH and 2Br).

B. Ease of Formation, Stability and Reactivity of Di-Grignard Reagents

Ease of Formation

From the results shown in the above sections, we get a relative rate of polyhalogeno benzene reacting with Mg:-I > -Br > -Cl; the order is identical to the situation of mono-halogeno benzene: C_6H_5I > C_6H_5Br > C_6H_5Cl > C_6H_5F,[9] and of alkyl halides: RI > RBr > RCl.[9] Even in the exchange method of preparing di-Grignard reagents, we have the same order. For example, no significant yield of p-bis(magnesium bromide)benzene was obtained from 4-chlorobromobenzene; instead, only 4-chlorophenylmagnesium bromide was formed (exchange at Br, but not at Cl).

Stability

Di-Grignard reagents generated from di-haloarenes usually show good stability in the temperature range 0-80°C, and can exist for more than 24 hrs, no significant change to the yields of quenching experiments (see Section III, A.).

Di-Grignard reagents prepared from polyhalogenobenzene are usually stable at 0°C for 4-6 hrs; later they begin to decompose slowly, producing arynes. Data table in the former section shows that total yields of products, intermediates and recovered starting material decrease when reaction time increases, while the yields of by-products polyethyl substituted benzene or polyhalogenobenzene increase. Electron-withdrawn groups stablize di-Grignard reagents, but electron-donating groups destablize di-Grignard reagents. For example, 2,5-bis (magnesium bromide)-3,6-dibromo-p-xylene decomposes at 0°C, whereas 3,6-bis(magnesium bromide)-p-dibromobenzene is stable at 0°C. The methyl substituents destabliize the former reagent. The stronger the electron-withdrawing group is, the more stable is the di-Grignard reagent. Thus 2,5-bis (magnesium bromide)-3,6-dichloro-p-xylene at 0°C is more stable than the corresponding 3,6-dibromo compound. This rule is also applyable to mono-Grignard reagents made from polyhalogenobenzenes. The more electron-withdrawing groups a mono- or di-Grignard reagent contains, the more stable is the reagent. For example, 2-(magnesium bromide)halogenobenzene (X=I, Cl, Br, F) decomposes at room temperature, but 2-(magnesium bromide)-1,4,5-tribromobenzene (with two more halogens on the aromatic ring) is stable, and 2-(magnesium bromide)-3,6-dichloro-1,4,5-tribromobenzene is stable even at 50°C.

Temperature Effect and Reactivity

2,3,5,6-Tetrabromo-1,4-dichlorobenzene will not react with Mg at 0°C. At 15°C, a good yield of the corresponding mono-Grignard can be obtained, but no di-Grignard is formed. At room temperature, the halide reacts with Mg very rapidly, and over 70% of the mono-Grignard can be obtained within 2 hrs. The di-Grignard also forms rapidly, but decomposes rapidly to an aryne.

The di-Grignard reagent from 2,3,5,6-tetrabromo-1,4-dichlorobenzene reacts very fast with one equivalent of ethylene oxide in the temperature range 0-30°C, but the resulting product will not react with a second equivalent of ethylene oxide in the same temperature range, even overnight. At a temperature over 50°C, however reaction occurs. In contrast, the mono-Grignard derived from 2,3,5,6-tetrabromo-1,4-dichlorobenzene will not react with ethylene oxide in the temperature range 0-50°C, or even at higher temperatures; only trace amounts of the corresponding product results. This result means that the remaining Grignard moiety in the molecule 4-(magnesium bromide)-2,5-dichloro-3,6-dibromo-1-(magnesium ethoxide)benzene is more reactive than mono-Grignard 4-(magnesium bromide)-2,5-dichloro-1,3,6-tribromobenzene. So actually, the main products after isolation are diol and 2,5-dichloro-1,3,4-tribromobenzene, small amount of 3,6-dichloro-2,5-dibromo-1-(2-hydroxyethyl)benzene.

Generally speaking, di-Grignard reagents are more reactive toward electrophiles than mono Grignards, even at low temperature. On the other hand, to increase reactivity of mono-Grignard, generated from di-Grignard reacting with one equivalent of reactant, we may elevate the temperature, or mix in some sort of low basic solvent, that has low coordination ability, together with adding reactant. For example, adding ethylene oxide, mixed with ether or cyclohexane (1/3 volume of di-Grignard solution), in di-Grignard solution (THF), we can change mono-alkoxide to di-alkoxide at lower temperature 35-40°C, within shorter time.

C. Exchange Method

Here the conventional method for preparing a di-Grignard from a polyhalogenobenzene is followed, using CH_3CH_2MgBr as the exchanger. The yield of di-Grignard is examined by ethylene oxide quenching.

Procedure

To a dried, Ar-protected three-necked 100-ml round-bottomed flask was added 1 mmole (0.462g) 2,3,5,6-tetrabromo-1,4-dichlorobenzene and THF (35 mL). The mixture was stirred magnetically, and a solution of 2 mmole CH_3CH_2MgBr in 10 mL ether or THF was added by dropwise over 30 mins at 0°C. After stirring for 3 hrs at 0°C, 10 mmole ethylene oxide in 5 mL ether was added and the mixture was stirred at 0°C for 2 hrs, at r.t. for 1 hr, and then at 50°C for 5 hrs. The reaction was quenched by adding 5 mL diluted hydrochloric acid at 0°C.

The products were isolated by the procedure described in section II, A. The by-product $CH_3CH_2CH_2CH_2OH$, formed from ethylmagnesium bromide and ethylene oxide, can be removed in the diluted aqueous hydrochloric acid layer.

Observation and Results

The color of the reaction solution was light yellow from the beginning to the end, much different from the color in direct preparation method (dark brown).

The reaction products were 3,6-dichloro-2,5-dibromo-1,4-bis(2-hydroxyethyl)benzene (5%), 3,6-dichloro-2,5-dibromo-1-(2-hydroxyethyl)benzene (2%), 2,5-dichloro-1,3,4-tribromo-benzene (76%), and recovered starting material (12%).

D. Entrainment Method

The conventional method was used to prepare the di-Grignard reagent of hexahalogenobenzene. The yield was examined by ethylene oxide quenching. Ethylene dibromide and ethyl bromide was used as the entrainers.

Procedure

To a dried, Ar-protected three-necked 100-mL round-bottomed flask was added Mg powder (0.2g, 8 mmole), THF (4 mL), $BrCH_2CH_2Br$ (0.2 mL, 2.32 mmole). The mixture was magnetically stirred at r.t. for 15 minutes. A solution of 1 mmole (0.462g) 1,2,4,5-tetrabromo-3,6-dichlorobenzene and 4 mmole CH_3CH_2Br, both in 35 mL THF was added dropwise over 30 mins at 15°C. Rapid stirring was continued for 5 hrs at 15°C, after which 0.5 mL ethylene oxide (10 mmole) was added. After stirring at 15°C for 1 more hr, the mixture was heated at 50°C for 5 hrs. The reaction was quenched by adding diluted hydrochloric acid at 0°C. Isolation is same as the procedure described in II, A.

Result

There was obtained 3,6-dichloro-2,5-dibromo-1,4-bis(2-hydroxyethyl)benzene (10%), 3,6-dichloro-2,5-dibromo-1-(2-hydroxyethyl)benzene (5%), 2,5-dichloro-1,3,4-tri-bromobenzene (60%), and recovered starting material (5%).

Observation and Discussion

The color of the reaction solution from the time of adding the solution until the end was light yellow, just as in the exchange method. It seems likely that the so-called CH_3CH_2Br entrainment method is actually the same as the exchange method, judging from the results. As an entrainer, $BrCH_2CH_2Br$ functions through the reaction:

$$BrCH_2CH_2Br + Mg \longrightarrow MgBr_2 + CH_2{=}CH_2$$

The entrainer cleans the surface of the Mg, so that the halide can react with Mg successfully. In the direct preparation method described above, the surface of the Mg was cleaned by washing with $BrCH_2CH_2Br$ beforehand. Only the mono-Grignard product was obtained at 15°C; that is, the mono-Grignard does not react further with Mg below r.t.

Di-Grignard can be obtained below room temperature only by exchange. So the likely reaction course is that the CH_3CH_2Br reacts with the Mg first, to give CH_3CH_2MgBr; then CH_3CH_2MgBr exchanges with substrate. Three aspects of the preparation can be mentioned: 1. the higher yield of di-Grignard reagent than in the exchange method (at 0°C) arises from the higher reaction temperature (15°C); 2. for the same reason, a portion of the di-Grignard reagent decomposed; 3. adsorption of CH_3CH_2Br rather than 1,2,4,5-tetrabromo-3,6-di-chlorobenzene on Mg surface is favored. In both methods, exchange and entrainment, CH_3CH_2Br is regenerated after exchange of CH_3CH_2MgBr with hexahalogenobenzene. Perhaps the regenerated CH_3CH_2Br reacts with Mg again, consequently resulting in a second generation of CH_3CH_2MgBr, and the cycle is repeated. The following two procedures are designed based on this possibility.

E. Combination of Direct, Exchange and Entrainment

Idea

In the following procedure, 1,2,4,5-tetrabromo-3,6-dichlorobenzene reacts with excess Mg at 15°C first, resulting in over 60% of the mono-Grignard (see I. A). Then 2 equivalents of CH_3CH_2MgBr are added, and exchange occurs. The regenerated CH_3CH_2Br may react with the excess Mg present; consequently exchange between the second generation of CH_3CH_2MgBr and the starting material or mono-Grignard may occur.

Procedure

To a dried, Ar-protected three-necked 100-mL round-bottomed flask was added Mg powder (0.2g, 8 mmole), THF (4 mL), $BrCH_2CH_2Br$ (0.2 mL, 2.32 mmole). The mixture was magnetically stirred at r.t. for 15 mins, after which a solution of 1 mmole (0.462g) 1,2,4,5-tetrabromo-3,6-dichlorobenzene in 35 mL THF was added dropwise over 30 mins at 15°C. After stirring for 2 hrs at 15°C, a solution of 2 mmole CH_3CH_2MgBr in 10 mL of ether was added dropwise at 0°C. The mixture was stirred for 3 hrs at 0°C. Ethylene oxide (0.5 mL, 10 mmole) in 5 mL ether was added. The mixture was stirred at 0°C for 2 hrs, at r.t. for 1 hr, and at 50°C for 5 hrs. The reaction was then quenched with diluted hydrochloric acid at 0°C. Isolation is same as the procedure described in II. A.

Result

There was obtained 3,6-dichloro-2,5-dibromo-1,4-bis-(2-hydroxyethyl)benzene (35%), 3,6-dichloro-2,5-dibromo-1-(2-hydroxyethyl)benzene (10%) and 2,5-dichloro-1,3,4-tribromobenzene (26%).

Observation and Discussion

The color of the solution was dark brown from the beginning to the end, just as in the direct preparation method. The yield of di-Grignard is good, but still not ideal, and the procedure is not convenient. The regenerated CH_3CH_2Br did not seem to react with Mg again, resulting in a second generation of CH_3CH_2MgBr, as expected. Judging from the color of the solution and the low yield of di-Grignard, perhaps the 1,2,4,5-tetrabromo-3,6-dichlorobenzene adsorbed on the Mg makes the surface of the Mg inert. Consequently the CH_3CH_2Br could not react with Mg again. To overcome this disadvantage, one might drop the substrate into CH_3CH_2MgBr containing excess Mg. In this case, the surface of the Mg would be occupied by CH_3CH_2Br first. After exchange of CH_3CH_2MgBr with substrate, the regenerated CH_3CH_2Br might then react with Mg again.

F. Combination of Exchange and Entrainment

To a dried, Ar-protected three-necked 100 mL round-bottomed flask was added Mg (0.2g, 8 mmole), CH_3CH_2Br (0.15 mL, 2 mmole) and ether 10 mL, and the mixture was stirred at r.t. for 30 mins. A solution of 1 mmole 1,2,4,5-tetrabromo-3,6-dichlorobenzene in 35 mL THF was added dropwise over 30 mins at 0°C, and stirring was continued for 3 hrs. Ethylene oxide (0.5 mL, 10 mmole) in 5 mL ether was added at 0°C. Stirring was continued at 0°C for 2 hrs, at r.t. for 1 hr, and at 50°C for 5 hrs. The reaction was then quenched with diluted hydrochloric acid at 0°C. Isolation was same as the procedure described in II. A.

Result

There was obtained 3,6-dichloro-2,5-dibromo-1,4-bis-(2-hydroxyethyl)benzene (60%), 3,6-dichloro-2,5-dibromo-1-(2-hydroxyethyl)benzene (11%), and 2,5-dichloro-1,3,4-tribromo-benzene (15%).

Observation and Discussion

The color of the reaction solution was light yellow from the beginning to the end. The increased yield of bis-hydroxyethyl product may result from reaction of regenerated CH_3CH_2Br with excess Mg again, resulting in a second generation of CH_3CH_2MgBr which can further exchange. Of course, direct reaction of the polyhalogenobenzene with Mg is still possible. Thus we obtain a higher yield of di-Grignard reagent. This is the best new method and a relatively simple procedure.

III. APPLICATION OF DI-GRIGNARD REAGENTS

Some limited applications of di-Grignard reagents to synthesis have been carried out and are described in the following sections.

A. Addition of Di-Grignard Reagent to Ethylene Oxide

Procedure and Result

See I, C for the preparation of 2,5-dibromo-3,6-dichlorophenylbis (magnesium bromide), and II. A for isolation of the products. After preparing the di-Grignard (4 mmole) by the method of combination of exchange and entrainment, there was added 2 mL ethylene oxide (40 mmole) in 10 mL ether dropwise at 0°C. After stirring at 0°C for 2 hrs, 10 mL of dilute hydrochloric acid was added. The only product was the mono-adduct 3,6-dichloro-2,5-dibromo-1-(2-hydroxyethyl)benzene (75%). In an alternative route, after adding the ethylene oxide the temperature was elevated to 50°C, and maintained there for 2 hrs. The mixture was then quenched with dilute hydrochloric acid at 0°C. The main product was the diol, 3,6-dichloro-2,5-dibromo-1,4-bis(2-hydroxyethyl)benzene (60%).

Discussion

The advantage of the reaction can be seen by comparing the result with the di-Grignard reagent with that obtained using the di-lithium reagent, 2,5-dibromo-3,6-dichlorophenylbis(lithium). This reagent, prepared in toluene, is stable at -60°C, and in ether at -78°C. But ethylene oxide does not react at these low temperatures, even overnight, and no addition occurs. Even when the solution was warmed to r.t. for several hours, neither the mono- or di-adduct was formed. See ΔSUPPLEMENT EXPERIMENTS about preparation of the di-lithium reagent from hexahalogenobenzene.

B. Addition of Di-Grignard Reagents to Benzaldehyde

Experimental Procedure

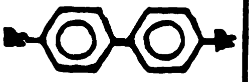
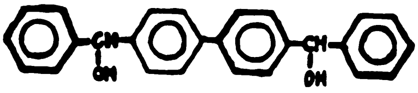
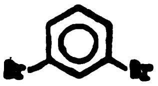
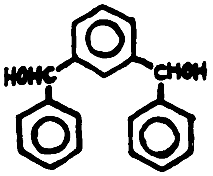
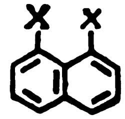
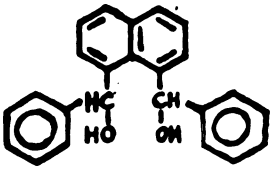
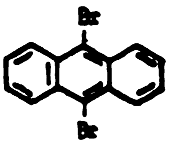
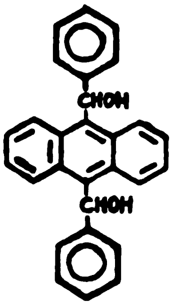
See I. A for the preparation of the di-Grignard reagents. After preparing the di-Grignard reagents (6 mmole), the solution was cooled to r.t., and 1.5 mL benzaldehyde (15 mmole) in 10 mL THF was added dropwise. Stirring was continued at r.t. for 1 hr. In runs 4 and 5, it was necessary to heat the solution at 45°C for 1 hr.

Isolation

After distilling most of the THF, the residue was extracted with 50 mL $CHCl_3$. The solution was washed successively with dilute hydrochloric acid and aqueous sodium bisulfite. The excess benzaldehyde reacted with the $NaHSO_3$ to give a water-soluble product. The organic phase was dried with Na_2SO_4. Further purification was done by silica gel column, using CH_2Cl_2 as the eluent.

Result

Table 5. Diols from Reaction of Di-Grignards with Benzaldehyde

Run	Halide	Product	Yield %	m.p. °C	Ref.
1	 (X = Br,I)		86	170-172	10
2			80	123-125	11
3			82	154-156	12
4	 X=Cl,Br,I		65	197-200	13
5			70	296-298	14

Melting points agreed with those in the cited literature references.

C. Reaction of Di-Grignard Reagents with Acetyl Chloride

Procedure

See I. A for the preparation of the di-Grignard reagents. After preparing the di-Grignard reagents (6 mmole), the solution was cooled to 0°C, and 2.2 mL acetyl chloride (30 mmole) in 10 mL THF was added. The mixture was stirred at 0°C for 1 hr, then warmed to r.t. over 1 hr.

Isolation and Result

After distilling most of the THF, the residue was extracted with 50 mL benzene. The organic solution was washed with H_2O, dried with Na_2SO_4. Further purification was carried out by silica gel column, using CH_2Cl_2 as the eluent.

The yields of 1,4-diacetylbenzene (A) and 4,4'-diacetylbiphenyl (B) were 90% and 85% respectively. Melting points of the two compounds agreed with those cited in the literature references. For (A) m.p. is 108-110°C (Lit.[15] 111-3°C); for (B) m.p. is 192-194°C (Lit.[16] 192-3°C).

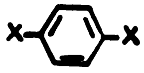
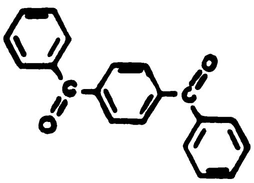
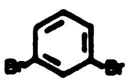
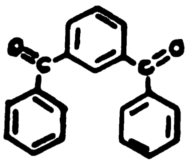
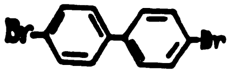
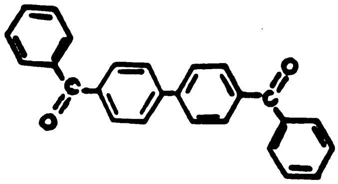
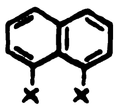
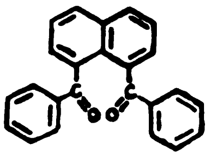
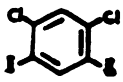
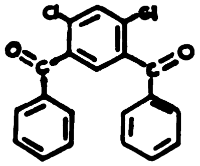
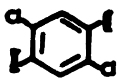
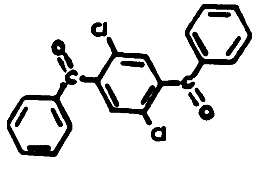
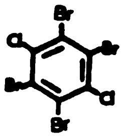
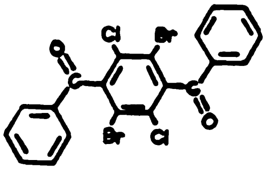
D. Reaction of Di-Grignard Reagents with Benzoyl Chloride

Experimental Procedure

See I. A,B,C about the preparation of the di-Grignard reagents. After preparing the di-Grignard reagent (6 mmole for runs 1-6, 4 mmole for run 7), the solution was cooled to 0°C, and 2.4 mL benzoyl chloride (20 mmole) in 10 mL THF was added. In runs 5-7, 3.5 mL benzoyl chloride (30 mmole) was added. The mixture was stirred at 0°C for 30 mins, then 10 mL H_2O was added. In some cases, to complete the reactions more quickly, the solutions may be warmed to r.t., and stirred for approximately 10 mins after adding the benzoyl chloride. See description in former section about isolation.

Result

Table 6. Diketones from Reaction of Di-Grignards with Benzoyl Chloride

Run	Halide	Product	Yield %	m.p. °C	Ref.
1	 (X = Br, I)		50	157-159	17
2			46	97-99	18
3			50	215-217	19
4	 (X = Br, I)		40	186-188	20
5			35	viscous liquid	unknown
6			40	142-144	unknown
7			40	284	unknown

Melting points agreed with those in the cited literature references, for the products of runs 1-4, melting points (°C) in cited literature references are 159-160, 99.5-100, 218 and 189-190 respectively. The products of runs 5-7 are previously unknown.

Identification of Unknown Compounds

Carbon tetrachloride was used as the solvent for all of the following IR spectra. 2,4-Dichloro-1,5-dibenzoylbenzene: Colorless viscous liquid; MS:m/e (relative intensity) 354(M^+, 4), 277(6), 214(2), 207(3), 172(2), 105(100), 77(65), 51(36); H^1 NMR ($CDCl_3$):δ7.43(s, 1H), 7.81(s, 1H), 7.82(d, ^3J's 10 Hz, 4H), 7.64(t, ^3J's 10 Hz, 2H), 7.50(t, ^3J's 10 Hz, 4H); IR shows carbonyl group at 1675 cm^{-1}. Anal. Calcd for $C_{20}H_{12}O_2CI_2$:C, 67.63; H, 3.41. Found: C, 66.81; H, 3.86.

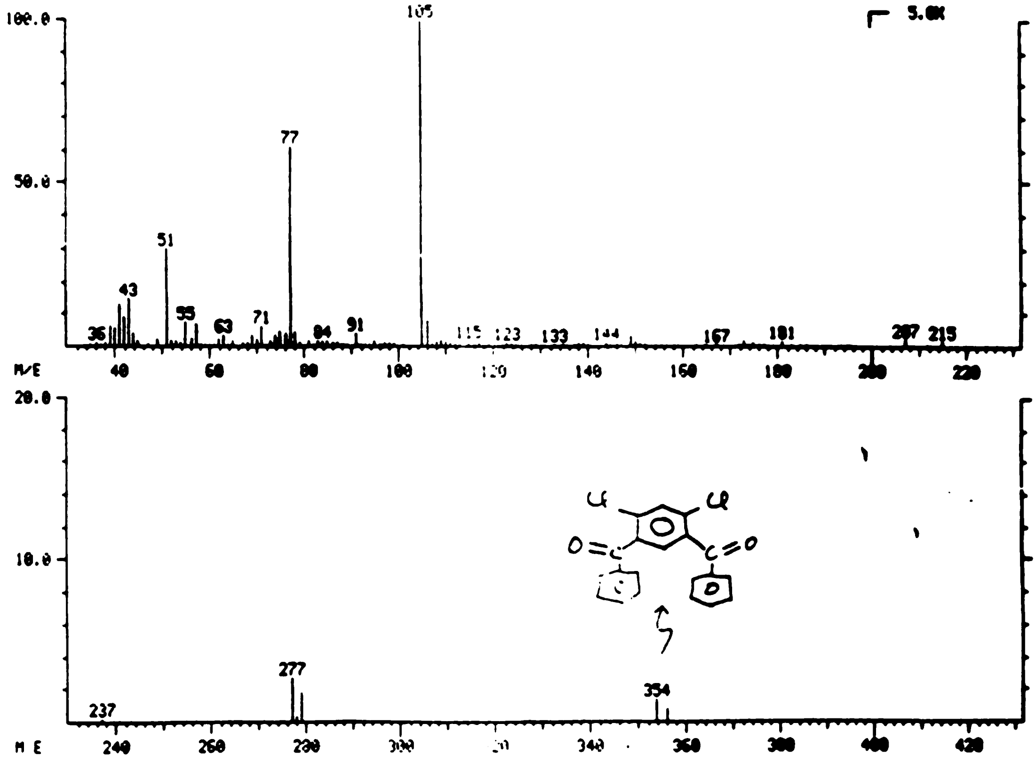


Figure 12. MS Spectrum of 2,4-Dichloro-1,5-dibenzoylbenzene

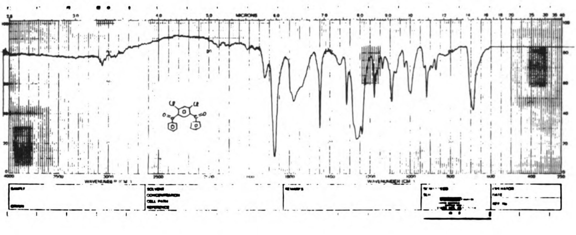


Figure 13. IR Spectrum of 2,4-Dichloro-1,5-dibenzoylbenzene

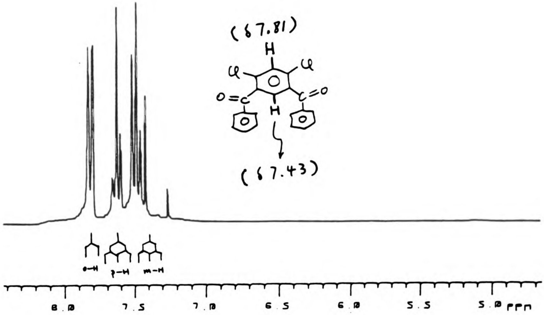


Figure 14. H^1 NMR of 2,4-Dichloro-1,5-dibenzoylbenzene

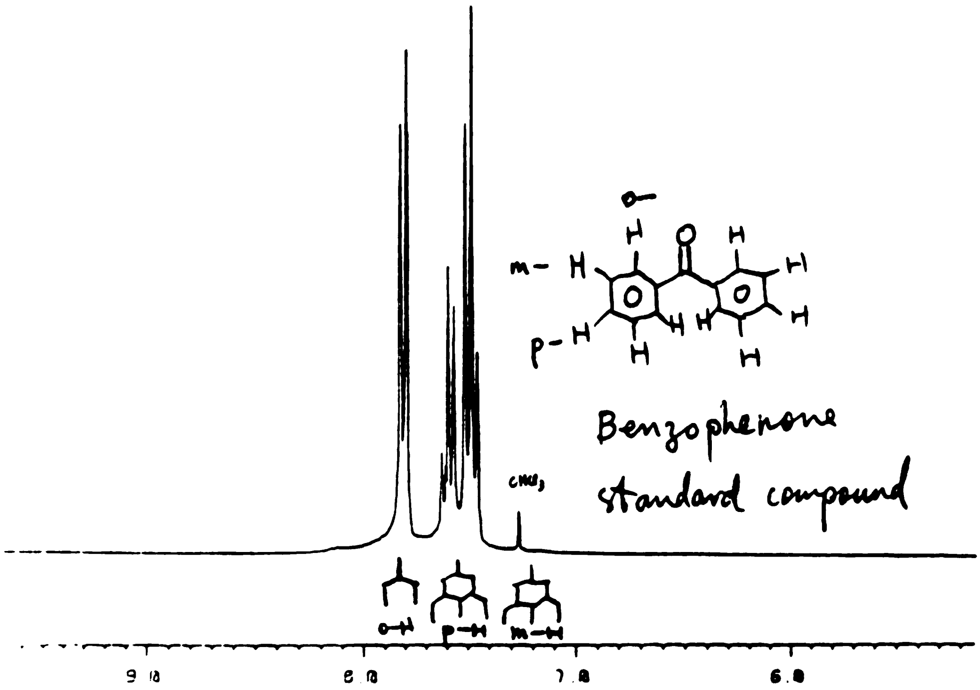


Figure 15. H^1 NMR of Benzophenone

2,5-Dichloro-3,6-dibromo-1,4-dibenzoylbenzene:

Colorless needles, m.p. 284°C; MS:m/e (relative intensity) 510(M$^+$, 2), 432(2), 355(1), 300(1), 246(2), 105(base, 100), 77(61), 51(20); H^1 NMR (CDCl$_3$):δ7.88(d, ^{3}J's 8 Hz, 4H), 7.69(t, ^{3}J's 8 Hz, 2H), 7.55(t, ^{3}J's 8 Hz, 4H); IR shows carbonyl group at 1688 cm^{-1}. Anal. Calcd for $C_{20}H_{10}O_2Br_2Cl_2$:C, 46.83; H, 1.97. Found: C, 46.72; H, 2.01.

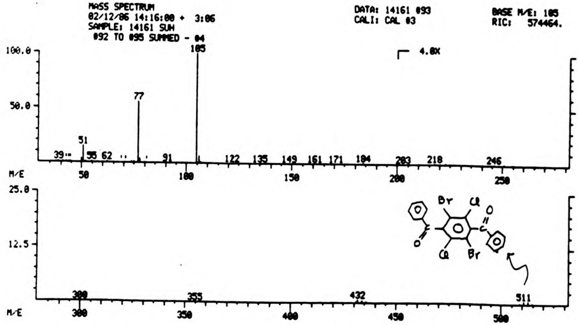


Figure 16. MS Spectrum of 2,5-Dichloro-3,6-dibromo-1,4-dibenzoylbenzene

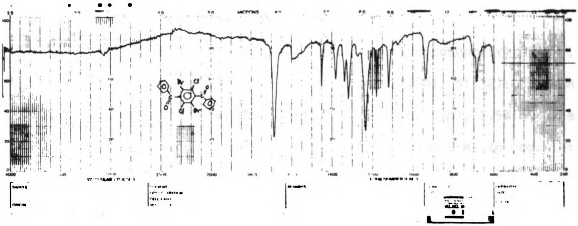


Figure 17. IR Spectrum of 2,5-Dichloro-3,6-dibromo-1,4-dibenzoylbenzene

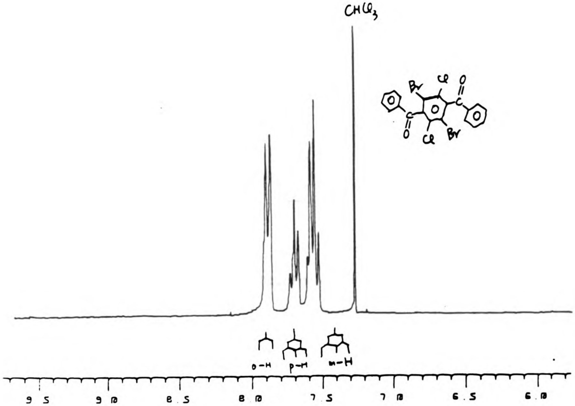


Figure 18. H^1 NMR of 2,5-Dichloro-3,6-dibromo-1,4-dibenzoylbenzene

2,5-Dichloro-1,4-dibenzoylbenzene:

Colorless needles, m.p. 142-144°C; MS:m/e (relative intensity) 354(M^+, 4), 319(1), 277(2), 249(2), 214(2), 105(100), 77(50), 51(32); H^1 NMR ($CDCl_3$):δ7.83(d, ^3J's 10 Hz, 4H), 7.68(t, ^3J's 10 Hz, 2H), 7.54(t, ^3J's 10 Hz 4H), all the peaks are split further by 3-H and 6-H to doublet (J's 2 Hz) through long range coupling. 7.57(s, 2H); IR shows carbonyl group at 1682 cm^{-1}. Anal. Calcd for $C_{20}H_{12}O_2CI_2$:C, 67.63; H, 3.41. Found: C, 67.86; H, 3.23.

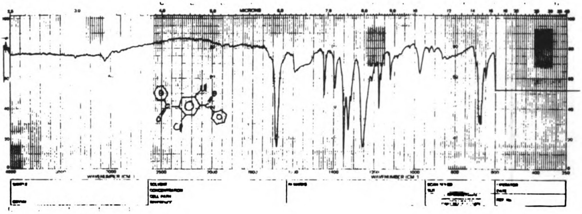


Figure 19. IR Spectrum of 2,5-Dichloro-1,4-dibenzoylbenzene

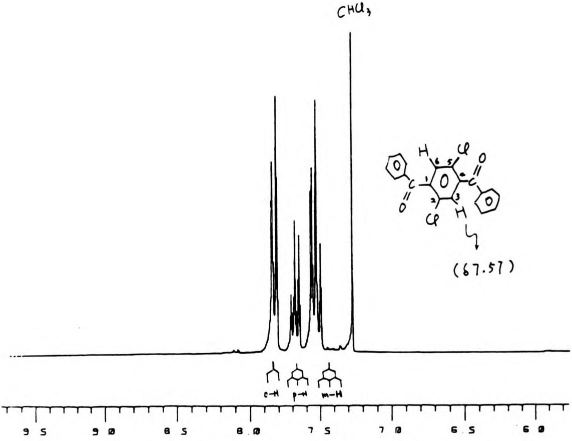


Figure 20. H^1 NMR of 2,5-Dichloro-1,4-dibenzoyl

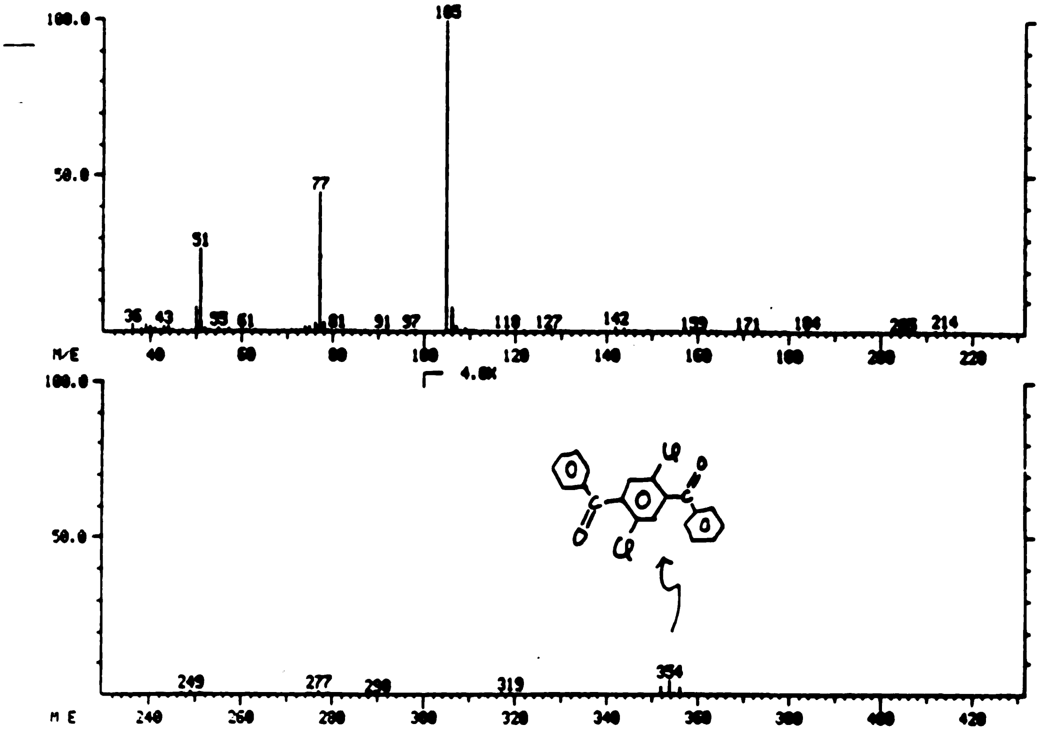


Figure 21. MS Spectrum of 2,5-Dichloro-1,4-dibenzoylbenzene

E. Preparation of Mono-, Di- or Tri-Grignard Reagents from 1,3,5-Tribromobenzene by Temperature Control and Quenching Experiments

In all of the following three experiments, the substrates reacted with Mg directly in THF, and the resulted Grignard reagents were quenched with iodine (H_2O for exp. 1) or benzoyl chloride. For iodine quenching, yields of products were determined by GC-MASS. For benzoyl chloride quenching, products were isolated.

Exp. 1: 1,3,5-Tribromobenzene reacted with Mg in THF at r.t., resulting mono-Grignard, 3,5-dibromo-1-(magnesium bromide)benzene absolutely. H_2O quenching gave 1,3-dibromobenzene (95%) benzoyl chloride quenching gave 3,5-dibromo-benzophenone (60%).

Exp. 2: At 45-50°C, corresponding mono- and di-Grignard reagents resulted. Iodine quenching gave 1,3-dibromo-5-iodobenzene (20%), and 1-bromo-3,5-diiodobenzene (76%); benzoyl chloride quenching gave 5-bromo-1,3-dibenzoylbenzene (45%), and 3,5-dibromo-benzophenone (15%).

Exp. 3: At refluxing, corresponding di- and tri-Grignard reagents resulted. Iodine quenching gave 1-bromo-3,5-diiodobenzene (40%), and 1,3,5-triiodobenzene (52%). Benzoyl chloride quenching gave 5-bromo-1,3-dibenzoylbenzene (30%), and 1,3,5-tribenzoylbenzene (25%).

Experimental Procedure

To a dried, Ar-protected three-necked round-bottomed 250-mL flask was added magnesium powder (0.5g, 20 mmole), $BrCH_2CH_2Br$ (0.2 mL, 2.32 mmole) and THF (10 mL). The mixture was stirred magnetically at r.t. for 10 minutes. A solution of 1,3,5-tribromobenzene (1.6g, 5 mmole) in 80 mL THF was added dropwise over 30 minutes at r.t. The mixture was rigorously stirred for 1 hr at r.t. for preparing mono-Grignard; for 8 hrs at 45-50°C for preparing di-Grignard; was refluxed for 8 hrs with rigorously stirring for preparing tri-Grignard, then cooled to 0°C, and H_2O (20 mL) was added for exp. 1, or 7.62g iodine (30 mmole I_2) in 10 mL THF were added for exp. 2 and 3, or a solution of 3.5 mL (30 mmole) benzoyl chloride in 10 mL THF was added (for all of the three experiments). After an additional 30 minutes at 0°C, the solution was quenched with 20 mL H_2O at 0°C. See description about isolation in section III. C, for benzoyl chloride quenching, and section I. A, for iodine quenching.

Identification

3,5-Dibromobenzophenone:

colorless needles, m.p. 74-75°C, Lit[21] 75°C. 1,3,5-Tribenzoylbenzene: colorless needles, m.p. 115-117°C, Lit[22] 118-119°C. 5-Bromo-1,3-

dibenzoylbenzene: colorless viscous liquid, previously unknown compound. MS:m/e (relative intensity) 364(M$^+$, 5), 287(3), 285(2), 259(1), 152(3), 105(100), 77(49); H^1 NMR (CDCl$_3$):δ8.14-8.07(m, 2H), 7.87-7.74(m, 4H), 7.63-7.57(m, 2H), 7.52-7.35(m, 5H); IR shows carbonyl group absorption at 1725 and 1665 cm^{-1}. Anal. Calcd for $C_{20}H_{13}BrO_2$:C, 65.77; H, 3.59. Found: C, 66.07; H, 3.82.

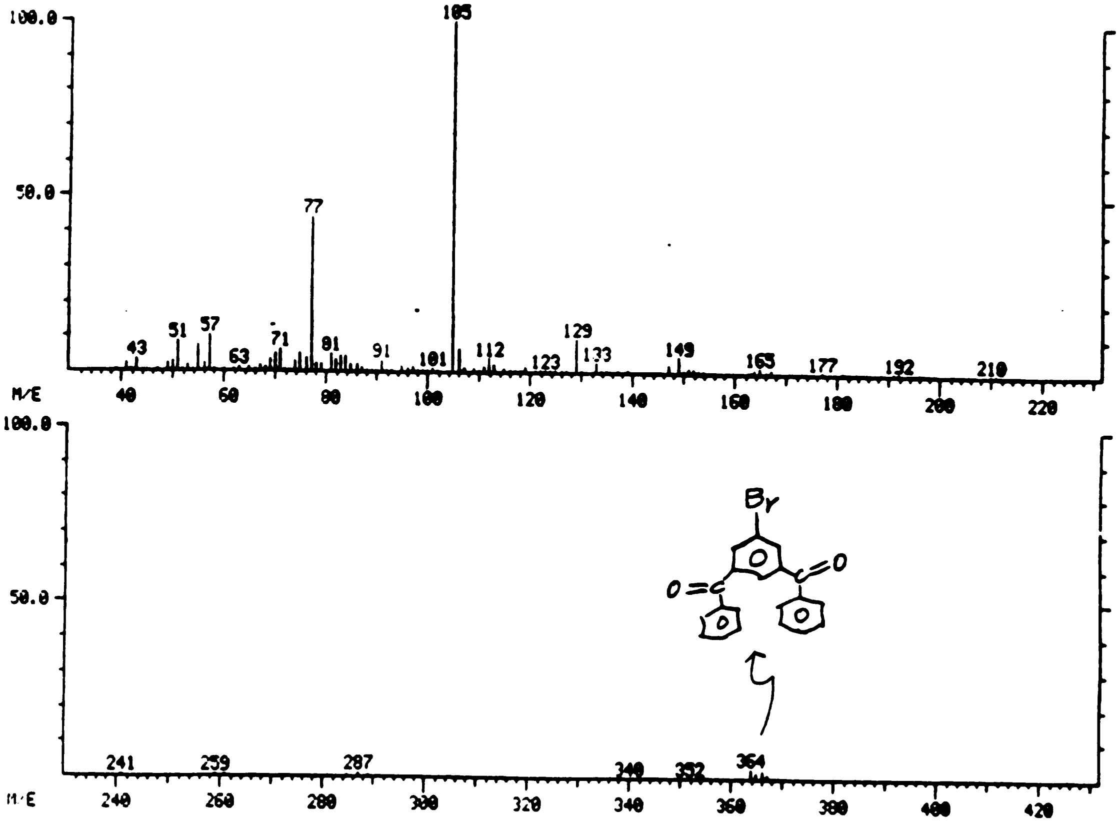


Figure 22. MS Spectrum of 5-Bromo-1,3-dibenzoylbenzene

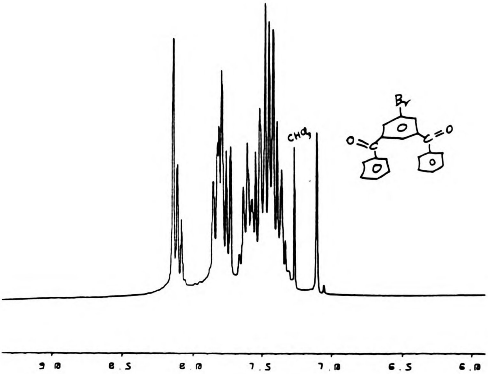


Figure 23. H^1 NMR of 5-Bromo-1,3-dibenzoylbenzene

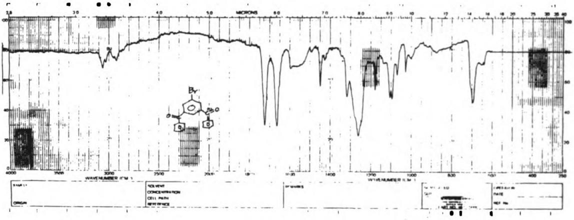


Figure 24. IR Spectrum of 5-Bromo-1,3-dibenzoylbenzene

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