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Synthesis of 1, 3-diaryl Substituted Iodobenzene Derivatives

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ABSTRACT

The synthesis and characterization a new derivatives of 2'-iodo-meta terphenyl from the reaction of excess aryl-Grignard and 2, 6- dichloroiodobenzene with quenching of m-terphenyl-2'-magnesium bromide by iodine is reported. Via the reactions three carbon-carbon bonds are constructed and m-terphenyls are obtained in good yields.

Keywords: Meta terphenyl; aryl-Grignard; 2, 6 – dichloroiodobenzene; iodine.

INTRODUCTION

The design of organic molecules possessing functional groups that can interact with guest molecules in complementary ways is a challenge in organic chemistry. Because of their shape, *m*-terphenyls are useful intermediates for constructing chiral cyclophanes and related compounds with macrocyclic cavities and they could find application in chiral resolution and asymmetric induction. Therefore when *m*-terphenyl units are employed, the binol cyclophanes could function as excellent receptors for chiral molecules. The properties of dendrimers such as solubility, chemical reactivity and glass transition temperature are strongly influenced by the nature of the peripheral groups. It has been proven that *meta* terphenyls are ideal building blocks in cyclophane chemistry [1a]. In addition, *meta*-terphenyls are ideal precursors in the design of cyclophanes and are useful as tectons in crystal engineering [1b].

The electron-rich *m*-terphenyl will allow intramolecular charge transfer (CT) to take place from the periphery through the dendrimer backbone to the center of the molecule if the core is electron-deficient [2], recently, numerous natural products having a terphenyl architecture such as thelephorin [3], terphenyllin [4], terferol [5], and terprenin [6], have been reported to possess interesting biological properties. Several synthetic terphenyl derivatives have been designed as selective inhibitors for Dihydroortate dehydrogenase [7] and cyclooxygenase [8] enzymes.

Terphenyls containing acidic groups have recently been found to be potent insulin sensitizers [9]. Recently, Nozaki *et al.* [10] have identified a terphenyl based novel auxin signalling inhibitor, terfestatin A, from *Streptomyces* sp. F40. Owing to their interesting optical [11] and electronic [12] properties, terphenyls find several industrial applications as liquid crystals,

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conducting polymers, heat storage and heat transfer agents, as textile dye carriers and as a laser dye.

Meta terphenyls are also used in the preparation of bulky *meta*-terphenyl substituted dialkylphosphin, Langmuir monolayers from substituted 5'-Phenyl-*m*-terphenyl carboxylic acids, benzotriazolophanes- new class of novel cyclophanes, oxacyclophanes, cyclicketones, benzimidazolophanes and tiacyclophanes.

Bulky *meta*-terphenyl ligands have been shown to be effective for the stabilization of numerous compounds with low coordination numbers, previously unknown multiple bonds or heavier main group element compounds with unpaired electrons. Usually the terphenyl ligand is attached directly to the reactive center through the ipso carbon of the central aryl ring and steric protection is provided by the flanking aryls attached at positions *ortho* to this carbon. Recently, this theme has been extended to include terphenyl derivatives that employ hetero atoms such as the pnictogens or chalcogens (or derivatives thereof) attached to the ipso carbon [13].

Terphenyls are one of the important substants for surface behavior (surface pressure and surface potential measurements) of aromatic compounds modified with long alkyl chains [14]. In bowl-shaped molecules, the radially extended *m* –terphenyl units form a large cavity around the central functionality. Also, the stabilization of highly reactive species by utilizing bowl-shaped molecules has been investigated on *m* –terphenyl units [15].

Hart developed a method for the synthesis of m-terphenyls that may be substituted in all *ortho*-positions of the outer aryl rings [16-18]. The key intermediate of Hart's method is the 2'-Grignard reagent, which can be can be treated with various electrophiles.

EXPERIMENTAL SECTION

General Experimental

The ^{1}H and ^{13}CNMR spectra were recorded on a Bruker-Avance 400 NMR spectrometer at 400 and 100 MHz respectively and coupling constants (J) are expressed in Hertz using CDCl3 as solvents and TMS as an internal standard. Elemental analyses were recorded on CHN-Rapid-Hearus at the Research Institute of Petroleum Industry (RIPI). Melting points were recorded on Electro thermal 9100 melting point apparatus in open capillaries and are uncorrected. All reactions were carried out under an argon atmosphere with standard Schlenk or vacuum line techniques. THF was purified by distillation from sodium diphenylketyl under argon atmosphere before use.

General procedure for the preparation of iodo meta terphenyls 5a-j:

A round bottom two neck flask that was equipped with pressure-equalizing, dropping funnel and reflux condenser was charged with magnesium (20 mmol). Then distilled aryl bromide in THF (20 mmol) was added to the magnetically stirred flask. The reaction was triggered by swirling and the heat of a human hand. The remaining aryl bromide was added dropwise to the solution. At the end of this step 2, 6 dichloroiodobenzene (5 mmol) in THF (20 ml) was added dropwise with reflux. Refluxing conditions were continued approximately 20 hour. The mixture was cooled in an ice-water bath and iodine (10 mmol) in THF (20 ml) was added dropwise until the iodine color was remained. Then bisulfate sodium solution (10%) was added and the color of solution was changed to yellow. The mixture was extracted with ether three times. The organic layer was washed with water and brine then dried over anhydrous sodium sulfate. The residue obtained after solvent removal was recrystallized and/or chromatographed to

give the products in the isolated yields shown in the table.

4,4''-di methoxy-2' iodo-1,1':3',1''-terphenyl ***(5a):*** m.p. 141-142 ˚C ; ^{1}HNMR(CDCI3) 7.34 (t, 1H, J=7.5 Hz), 7.28 (dt, 4H, J= 8.7, 2, 2.9 Hz), 7.21 (d, 2H, J=7.5 Hz), 6.94 (dt, 4H,J=2, 2.9), 3.84 (s, 6H); ^{13}C NMR (CDCI3) 157.9, 146.65, 137.24, 129.52, 127.55, 126.48, 112.14, 104.03, 54.2;Anal. Calcd for C20H17IO2: C, 57.70; H, 4.12. Found: C, 57.63; H, 3.87.

2,2''-di methoxy-2' iodo-1,1':3',1''-terphenyl ***(5b):*** m.p. 127-128 ˚C ; ^{1}HNMR(CDCI3) 7.42-7.36 (m, 3H), 7.23-7.14 (m, 4H), [7.03 (td, 2H, J=7.5, 1 Hz), 7.025 (td, 2H,J=7.5, 1)], 6.96 (d, 2H, J=8.28), [3.8 (s, 6H)] ; ^{13}C NMR (CDCI3) (155.41, 155.28), 143.7, (133.71,133.29), (129.91,129.65), (128.18, 128.15), (127.75, 127.68), (126.55, 126.42), (119.28, 119.22), (110.07, 109.93), (106.20, 105.86), (54.61, 54.56) ; Anal. Calcd for C20H17IO2: C, 57.7; H, 4.1. Found: C, 57.7; H, 4.3.

4,4''-di chloro-2' iodo-1,1':3',1''-terphenyl ***(5c):*** m.p. 199 ˚C ; ^{1}HNMR(CDCI3) 7.4-7.3 (m, 5H), 7.28 (dt, 4H, J= 8.4, 2.3, 1.9 Hz), 7.21 (d, 2H, J=7.5 Hz); ^{13}C NMR (CDCI3) 145.97, 142.69, 132.68, 129.73, 127.82, 127.17, 126.80, 102.29;Anal. Calcd for C18H17ICl2: C, 50.8; H, 2.6. Found: C, 50.8; H, 3.

3,3''-di methyl-2' iodo-1,1':3',1''-terphenyl ***(5d):*** m.p. 72-73 ˚C ; ^{1}HNMR(CDCI3) 7.35-7.27 (m, 3H), 7.21-7.13 (m, 8H), 7.38 (s, 6H); ^{13}C NMR (CDCI3) 147.10, 144.54, 136.40, 129.06, 127.54, 127.16,126.69, 126.43, 125.46, 102.66, 20.46; Anal. Calcd for C20H17I: C, 62.5; H, 4.4. Found: C, 62.6; H, 4.3.

3,3''-di methoxy-2' iodo-1,1':3',1''-terphenyl ***(5e):*** m.p. 77-78 ˚C ; ^{1}HNMR(CDCI3) 7.19-7.13 (m,3H), 7.07(d, 2H,J=7.5 HZ), 6.79-6.75 (m,6H), 3.63 (S, 6H); ^{13}C NMR ($CDCl_3$) 157.8, 146.7, 145.6, 127.8, 127.4, 126.4, 120.6, 113.9, 112.0, 102.1, 54.0 ; Anal. Calcd for C20H17IO2: C, 57.7; H, 4.1. Found: C, 57.4; H, 4.2.

4,4''-di fluoro-2' iodo-1,1':3',1''-terphenyl ***(5f):*** m.p. 162-163 ˚C ; ^{1}HNMR(CDCI3) 7.37(t,1H J=7.5 Hz), 7.30(dd, 4H, J= 5.4, 8.7Hz) , 7.22(d, 2H, J=7.5 Hz), 7.1(tt, 4H, J=8.7,2, 2.9); ^{13}C NMR ($CDCl_3$) 161.25 (d, J_{C-4-F}=245.4), 146.14, 140.44(d, J_{c-1-F} =3.3), 130.04(d, J_{C-2-F}=8.2), 127.83, 126.68, 113.8 (d, J_{C-3-F}=2.03), 103.160 ; Anal. Calcd for C20H11F2I : C, 55.2; H, 2.8. Found: C, 55.4; H, 3.2.

4,4''-di methyl-2' iodo-1,1':3',1''-terphenyl ***(5j):*** m.p. 138-139 ˚C; ^{1}HNMR (CDCI3) 7.36(t, 1H, J=7.5 Hz), 7.27-7.21(m, 10H), 2.5(S, 6H); ^{13}C NMR ($CDCl_3$) 147.02, 141.8, 136.2, 128.3, 127.57, 127.55, 126.5, 20.3; Anal. Calcd for C20H11F2I : C, 62.5; H, 4.4. Found: C, 62.6; H, 4.5.

RESULT AND DISCUSSION

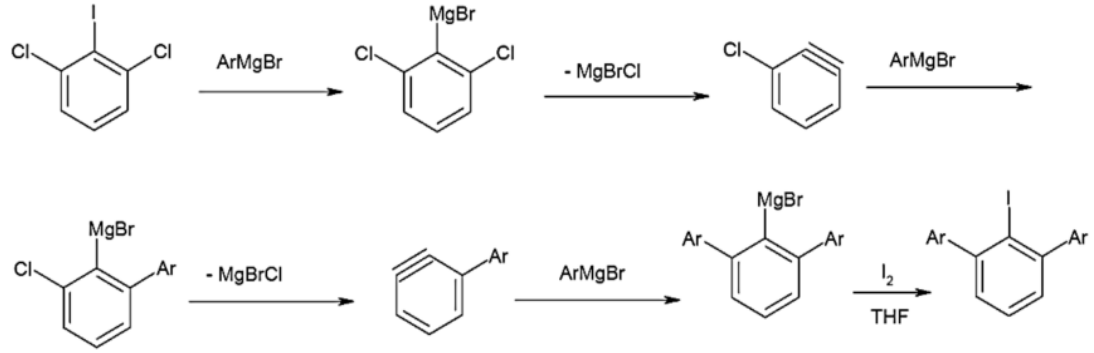
2, 6- dichloroiodobenzene **(3)** is not commercially available and must be synthesized in quantity from 2, 6-dichloroaniline via diazotization and treatment with sodium iodide.

Our initial attempts to test the feasibility of this reaction employed readily accessible 2, 6 -dichloroiodobenzene and phenyl magnesium bromide in THF which afforded 2, 3-diphenyl magnesium bromide reagent. Then the addition of iodine gave the desired product **5a** in 77% yield (Table). We next investigated the scope of the reaction using aryl magnesium bromides with diverse substituents at *ortho*-, *meta*- and *para*-positions. As a result, 2'-iodo *meta* terphenyl derivatives were obtained in good yields (Table). The structures of the isolated products were confirmed by mp, ^{1}HNMR, ^{13}CNMR and elemental analysis.

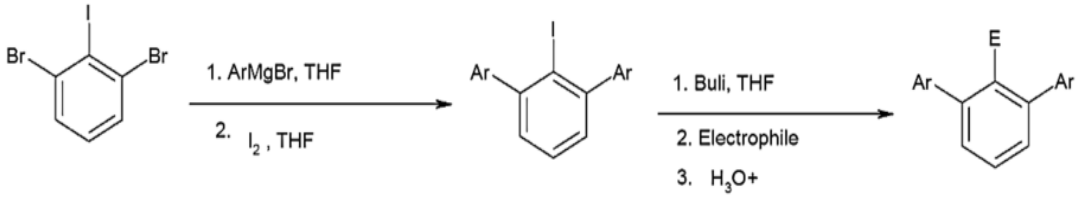
2, 6- dibromobenzene in place of **(3)** gave lower yield of products. *M* –terphenyl-

Grignard, in principle, can be treated with various electrophiles. But this may lead to difficultly separable mixtures because some excess or unreacted aryl-Grignard reagent is present and will also react with the added electrophile. For example reaction with BuLi in this step, give side products. For inhibiting of such products, quenching with iodine works well. Then reaction of 2'-iodo-*m* –terphenyl with BuLi give 2, 6-diarylphenyllithium that is one of the most important substance in various reactions in the organic chemistry and it is the best advantage of our synthesized products.

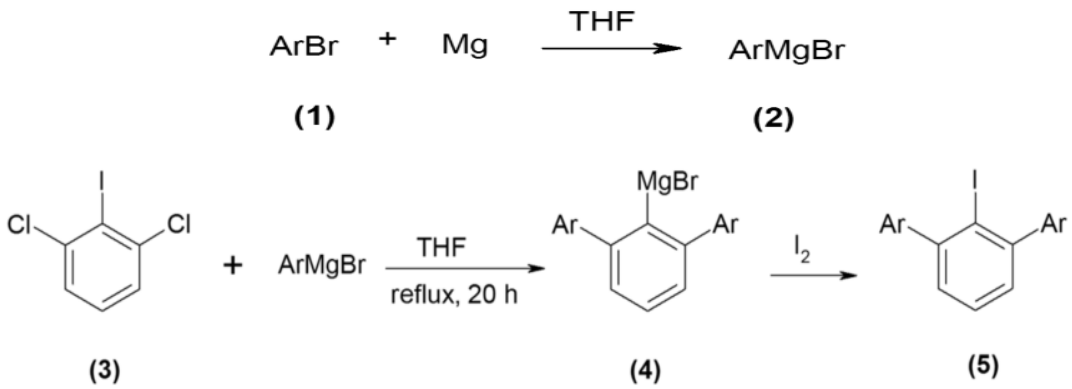
In the current study, we examine a facile one pot synthesis of 2'-iodo *meta* terphenyl starting from 2, 6– dichloroiodobenzene. Cascade reaction of aryl magnesium bromides with 1,2,3-trihalobenzene **(3)** followed by quenching with electrophile gives *m*-terphenyls **(5)** in a one pot reaction. By varying the substituents of the aryl groups of the Grignard reagent, different *m*-terphenyl derivatives can be obtained in good yields.



Scheme 1. Mechanism of synthesis 1, 3-diaryl Substituted Iodobenzene Derivatives.

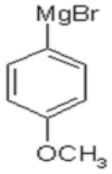
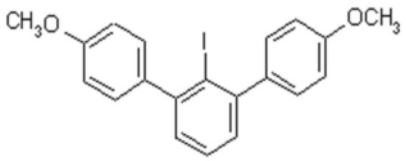
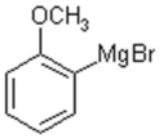
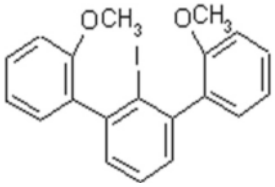
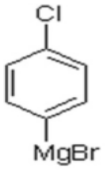
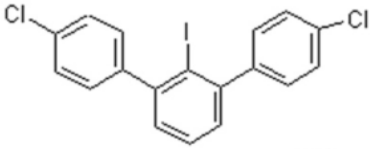
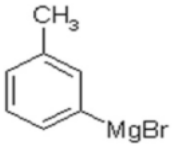
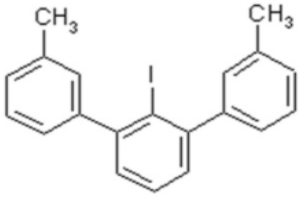
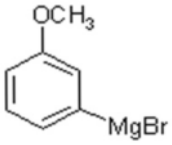
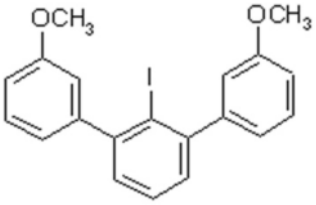
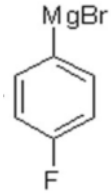
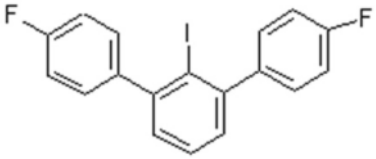
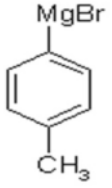
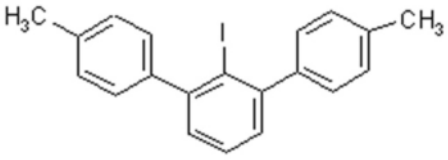


Scheme 2. Synthesis of 2'- substituted -*m* –terphenyl derivatives.



Scheme 3. Synthesis of 1, 3-diaryl Substituted Iodobenzene Derivatives.

Table 1.' iodo-*m* –terphenyls from (3) and Aryl-Grignards

Entry	ArMgBr	Product	Yield (%)
1		 **(5a)**	77
2		 **(5b)**	88
3		 **(5c)**	75
4		 **(5d)**	85
5		 **(5e)**	85
6		 **(5f)**	90
7		 **(5j)**	73

CONCLUSIONS

In conclusion, we have developed an efficient approach to 2'- iodo-*m* –terphenyl derivatives using readily accessible starting materials. To the best of our knowledge it is the first report on the synthesis of 2'- iodo-*m* –terphenyl derivatives with higher yield and versatility.

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