A Novel One-Pot Synthesis of Different Derivatives of Tetraarylterephthalaldehyde via a Multiple Aryne Sequence

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Received 2 October 2009; revised 26 October 2009

Abstract: The synthesis of a novel series of tetraarylterephthalaldehyde derivatives in an one-pot reaction is described. In this methodology 1,2,4,5-tetrachloro-3,6-diiodobenzene is treated with various aryl Grignard reagents (excess) in tetrahydrofuran to give tetraarylbenzene-1,4-diylbis(magnesium bromides). After reaction of this product with ethyl formate and aqueous quench, tetraarylterephthalaldehydes are isolated in 33–80% yields. A mechanism involving organometallic aryne intermediates is proposed.

Key words: tetraarylterephthalaldehyde, 1,2,4,5-tetrachloro-3,6-diiodobenzene, aryl Grignard reagents, tetraarylbenzene-1,4-diylbis(magnesium bromide), ethyl formate

Tetraarylterephthalaldehydes are polyaromatic hydrocarbons that may be of interest in the fields of liquid crystals, chiral cyclophanes, benzimidazolophanes, and pharmaceuticals.[1,2]

In 1949 Schonberg and Alyismail[3] reported the first synthesis of 1,2,4,5-tetraphenylbenzene from the reaction of chalcone with oxalyl chloride. Breslow and co-workers[4] later showed that the reduction of the diphenylcyclopropenyl cation with zinc produced bis(diphenylcyclopropenyl), which when heated to 135 °C gave 1,2,4,5-tetraphenylbenzene and 1,2,3,4-tetraphenylbenzene in a ratio of 10:1.

A further method for the preparation of these compounds was reported in 1969 by Bestmann and Denzel;[5] it used the decarboxylation of 2,3-diphenylcycloprop-2-enecarboxylic acid to give 1,2,4,5-tetraphenylbenzene in 92% yield. Various methods have been used by Dodson and Fan,[6] Hoyt and co-workers,[7] Weiss and co-workers,[8] and Di Vona and Rosnati[9] in low yields. Tetraarylbenzene derivatives can be synthesized by organometallic reactions. In 1969, Berry and Wakefield treated[10] hexabromobenzene with magnesium in tetrahydrofuran using 1,2-dibromoethane as the promoter to give pentabromophenylmagnesium bromide in 32% yield. Later, it was shown that this conversion could be greatly improved using exchange with phenyl- or ethylmagnesium bromide.[11] Hart and co-workers obtained[12] good yields of 1,2,4,5-tetraphenylbenzene from the reaction of 1,2,4,5-tetrabromo-3,6-dichlorobenzene with excess phenylmagnesium bromide and using tetrahydrofuran as the solvent; other 1,2,4,5-tetraarylbenzene derivatives were synthesized by this route. Saednya and Hart reported[1] two efficient routes for the synthesis of *m*-terphenyls from 1,3-dichlorobenzene. In the first route, 2,6-dichlorophenyllithium reacted with aryl Grignard reagents to give *m*-terphenyls in 57–93% yield. In the second route, the reaction of 1,3-dichlorobenzene with excess aryllithium in diethyl ether at room temperature gave the corresponding *m*-terphenyls in 59–94% yields.

In this work we investigated the reaction of aryl Grignard reagents with 1,2,4,5-tetrachloro-3,6-diiodobenzene (**1**). We reasoned that **1** would undergo halogen–metal exchange preferentially at iodine to give Grignard **2**. When **2** was treated with ethyl formate and then aqueous quench, tetraarylterephthalaldehydes **3**–**10** were obtained in good yields (Table 1).

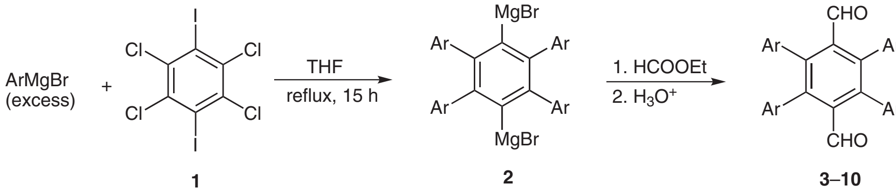
This new synthesis has the following unique features: (1) these compounds are synthesized for first time; (2) six aryl–aryl bonds are formed in a one-pot reaction; (3) the reaction proceeds via a four-aryne sequence; (4) different aryl Grignard reagents are used to generate and trap arynes; (5) substituents are easily incorporated on the central ring; (6) the yield of the reaction is good; and (7) simple and available starting materials are used.

The essence of our method is to use a Grignard reagent to generate an aryne through metal–halogen exchange and then to trap it by nucleophilic addition. The Grignard reagent is therefore used in excess. Addition of 1,2,4,5-tetrachloro-3,6-diiodobenzene (**1**) in tetrahydrofuran to phenylmagnesium bromide in the same solvent under reflux conditions, followed by stirring for 15 hours gave, after treatment with ethyl formate and then hydrolysis, tetraphenylterephthalaldehyde (**3**) in 46% yield.

Hence, it is clear that the principle reaction product from **1** and excess phenylmagnesium bromide is tetraphenylbenzene-1,4-diylbis(magnesium bromide) (**2**, Ar = Ph). The reaction of this product with ethyl formate and hydrolysis with water under mild acidic condition, gave the desired product **3** in 46% yield. Other aryl Grignard reagents gave analogous products **4**–**10**, as summarized in Table 1. All of the products in Table 1 are new compounds. Their structures are confirmed by ^{1}H and ^{13}C NMR and IR spectra, and elemental analysis. In general, the yields of tetraarylterephthalaldehydes are good, the only poor example being **10** which was obtained in 33% yield (entry 8).

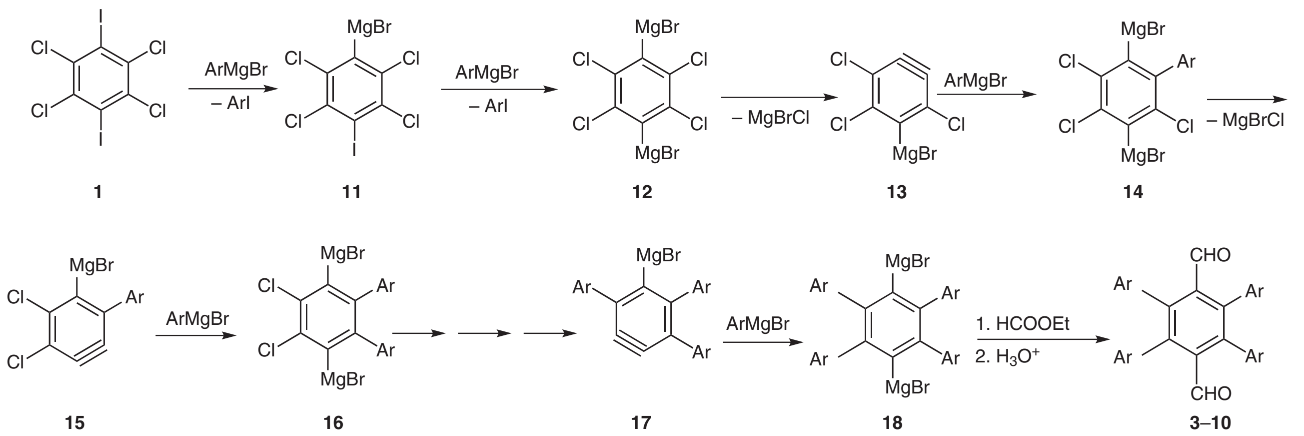
SYNTHESIS 2010, No. 3, pp 0395–0397
Advanced online publication: 07.12.2009
DOI: 10.1055/s-0029-1218593; Art ID: Z20509SS

Table 1 Synthesis of Tetraarylterephthalaldehydes



Entry	Ar	Product	Yield (%)	Mp (°C)
1	Ph	**3**	46	340–341
2	4-MeC_6H_4	**4**	61	317–319
3	4-$MeOC_6H_4$	**5**	50	270–273
4	4-FC_6H_4	**6**	62	312–313
5	4-ClC_6H_4	**7**[a]	80	>360
6	3-$MeOC_6H_4$	**8**	40	205
7	3-MeC_6H_4	**9**	68	246–247
8	4-PhC_6H_4	**10**	33	366–367

[a] The condition of this reaction was stirring at room temperature for 48 h.



Scheme 1

The mechanism involves as key intermediates the 1,4-di-Grignard reagent **12** and various organometallic arynes as outlined for 1,2,4,5-tetrachloro-3,6-diiodobenzene in Scheme 1. Rapid formation of **11** from **1** and arylmagnesium bromide is well established. Grignard exchange and elimination is then repeated to give aryne **17**, which is trapped to give the di-Grignard **18**. The mechanism shows that the major Grignard exchange occurs at iodine not at chlorine, and di-Grignard formation is essential to the tetraarylation reaction. Addition of arylmagnesium bromide to the intermediate organometallic arynes (i.e., **13**, **17**, etc.) occurs regiospecifically always to give 1,4-di-Grignards and not 1,3-di-Grignards.

In conclusion, we have found **1** to be a useful tetraaryne equivalent that reacts with excess Grignard reagent to give tetraaryl di-Grignards **18**. With subsequent addition of ethyl formate and then hydrolysis, tetraarylterephthalaldehydes **3–10** can easily be obtained from simple precursors in one step.

^{1}H and ^{13}C NMR spectra were recorded at 400 MHz and 100 MHz, respectively, on a Bruker-Avance spectrometer using $CDCl_3$ as a solvent and TMS as an internal standard. Melting points were determined with an Electrothermal 9100 apparatus and are uncorrected. FT-IR spectra were obtained on a Bruker-Tensor 27 spectrophotometer using KBr pellets. Elemental analysis was recorded on CHN-Rapid-Hearus apparatus. Anhyd Na_2SO_4 was the drying reagent throughout. Chromatography used silica gel 230–400 mesh. TLC was carried out using pre-coated plates of Merck silica gel 60 F_{254}. All reactions were performed under dry argon using reaction vessels previously dried at 120 °C. THF and Et_2O were distilled from benzophenone sodium ketyl prior to use.

1,2,4,5-Tetrachloro-3,6-diiodobenzene (1)

A soln of 1,2,4,5-tetrachlorobenzene (10.79 g, 49.95 mmol) and I_2 (27.9 g, 110 mmol) in oleum (29% SO_3, 40 mL) was vigorously stirred (magnetic) at 60 °C for 3.5 h. The mixture was poured into ice water and neutralized with 10% aq Na_2CO_3 and then 10% aq $NaHCO_3$ and washed with 10% aq sodium bisulfite to remove excess I_2. After extraction with THF and Et_2O, the combined organic layers were dried (Na_2SO_4). Removal of the solvent gave **1** (10.03 g, 43%) as a white solid; mp 208–209 °C.

Tetraphenylterephthalaldehyde (3); Typical Procedure

A soln of **1** (2.4 g, 5 mmol) in anhyd THF (40 mL) was added slowly over 2 h to a soln of PhMgBr [prepared from PhBr (3.2 mL, 30 mmol), and Mg (1 g, 40 mmol) in THF (40 mL)] and the mixture was stirred for an additional 15 h at reflux. The reaction was quenched with ice and it was treated with ethyl formate (10 mL). It was then cooled in an ice-water bath and quenched with dil HCl. The aqueous mixture was extracted with THF–Et_2O. The combined organic layers were dried and the solvent evaporated under reduced pressure. Recrystallization of the residue (Et_2O) gave nearly pure **3** (46% yield); mp 340–341 °C.

FT-IR (KBr): 2843, 2741, 1699, 700 cm^{-1}.

^{1}H NMR: $\delta = 9.73$ (s, 2 H), 7.20–7.14 (m, 12 H), 7.05–7.01 (m, 8 H).

^{13}C NMR: $\delta = 193.8$, 141.9, 137.7, 136.4, 130.5, 127.6, 127.2.

Anal. Calcd for $C_{32}H_{22}O_2$: C, 87.6; H, 5.0. Found: C, 87.5; H, 5.3.

Tetra(4-tolyl)terephthalaldehyde (4)

Mp 317–319 °C.

FT-IR (KBr): 2846, 2735, 1704 cm^{-1}.

^{1}H NMR: $\delta = 9.68$ (s, 2 H), 6.97 (d, $J = 7.8$ Hz, 8 H), 6.89 (d, $J = 8$ Hz, 8 H), 2.26 (s, 12 H).

^{13}C NMR: $\delta = 194.3$, 141.5, 138.3, 136.6, 133.5, 130.4, 128.3, 21.2.

Anal. Calcd for $C_{36}H_{30}O_2$: C, 84.4; H, 6.1. Found: C, 84.4; H, 6.2.

Tetra(4-methoxyphenyl)terephthalaldehyde (5)

Mp 270–273 °C.

FT-IR (KBr): 2842, 2741, 1699, 1514, 1246 cm^{-1}.

^{1}H NMR: $\delta = 9.70$ (s, 2 H), 6.92 (d, $J = 8.7$ Hz, 8 H), 6.71 (d, $J = 8.7$ Hz, 8 H), 3.74 (s, 12 H).

^{13}C NMR: $\delta = 194.4$, 158.5, 141.3, 138.6, 131.8, 128.7, 113.1, 55.0.

Anal. Calcd for $C_{36}H_{30}O_6$: C, 77.4; H, 5.4. Found: C, 77.0; H, 5.4.

Tetra(4-fluorophenyl)terephthalaldehyde (6)

Mp 312–313 °C.

FT-IR (KBr): 2861, 2756, 1747, 1512, 1229 cm^{-1}.

^{1}H NMR: $\delta = 9.70$ (s, 2 H), 7.00–6.95 (m, 8 H), 6.91 (t, $J = 8.7$ Hz, 8 H).

^{13}C NMR: $\delta = 192.1$, 160.9 (d, $J_{C4\text{-}F} = 246.5$ Hz), 140.3, 136.9, 131.01 (d, $J_{C2\text{-}F} = 8.2$ Hz), 130.8 (d, $J_{C1\text{-}F} = 3.5$ Hz), 114.03 (d, $J_{C3\text{-}F} = 21.5$ Hz).

MS (EI, 70 eV): *m/z* (%) = 44 (100), 481 (71), 510 (64), 356 (28).

Anal. Calcd for $C_{32}H_{18}F_4O_2$: C, 75.2; H, 3.55. Found: C, 75.2; H, 3.8.

Tetra(4-chlorophenyl)terephthalaldehyde (7)

Following the typical procedure using 1-bromo-4-chlorobenzene (25 mmol) and Mg (25 mmol) in THF (30 mL) at r.t. for 48 h. When the mixture was extracted with THF–Et_2O or CH_2Cl_2, the product precipitated; mp >360 °C.

FT-IR (KBr): 2835, 2742, 1700, 1090, 806 cm^{-1}.

^{1}H NMR: $\delta = 9.67$ (s, 2 H), 7.20 (d, $J = 8.4$ Hz, 8 H), 6.94 (d, $J = 8.4$ Hz, 8 H).

^{13}C NMR: $\delta = 191.7$, 140.1, 136.8, 133.2, 132.9, 130.6, 127.2.

Anal. Calcd for $C_{32}H_{18}Cl_4O_2$: C, 66.6; H, 3.1. Found: C, 65.2; H, 3.1.

Tetra(3-methoxyphenyl)terephthalaldehyde (8)

Mp 205 °C.

FT-IR (KBr): 2842, 2739, 1701, 1594, 1244, 1041 cm^{-1}.

^{1}H NMR: $\delta = 9.76$ (s, 2 H), 7.18–7.07 (m, 4 H), 6.79–6.52 (m, 12 H), 3.66 (s, 6 H), 3.62 (s, 6 H).

^{13}C NMR: $\delta = 193.7$, 158.8, 141.4, 137.6, 128.6, 123.2, 116.0, 115.8, 113.3, 55.1.

Anal. Calcd for $C_{36}H_{30}O_6$: C, 77.4; H, 5.4. Found: C, 77.3; H, 5.5.

Tetra(3-tolyl)terephthalaldehyde (9)

Mp 246–247 °C.

FT-IR (KBr): 2920, 2736, 1704, 1307, 702 cm^{-1}.

^{1}H NMR: $\delta = 9.67$ (s, 2 H), 6.99–6.87 (m, 8 H), 6.77–6.73 (m, 8 H), 2.13 (s, 12 H).

^{13}C NMR: $\delta = 193.03$, 140.8, 136.6, 135.9, 135.6, 135.3, 130.3, 126.8, 126.6, 126.2, 20.2.

Anal. Calcd for $C_{32}H_{30}O_2$: C, 84.4; H, 6.1. Found: C, 85.3; H, 6.1.

Tetra(biphenyl-4-yl)terephthalaldehyde (10)

Mp 366–367 °C.

FT-IR (KBr): 2923, 2852, 1698, 732 cm^{-1}.

^{1}H NMR: $\delta = 9.86$ (s, 2 H), 7.57–7.52 (m, 8 H), 7.46 (d, $J = 8.3$ Hz, 8 H), 7.41 (t, $J = 7.2$ Hz, 8 H), 7.32(tt, $J = 7.2,1.2$, 2 Hz, 4 H) 7.16 (d, $J = 8.3$ Hz, 8 H).

^{13}C NMR: $\delta = 193.9$, 141.6, 140.2, 139.9, 131.09, 128.7, 127.4, 126.9, 126.3.

Anal. Calcd for $C_{56}H_{38}O_2$: C, 90.5; H, 5.1. Found: C, 88.4; H, 6.8.

Acknowledgment

The authors are indebted to Tabriz university for supporting of this work and Mrs. Aghazadeh for her helpful suggestions during the manuscript preparation.

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