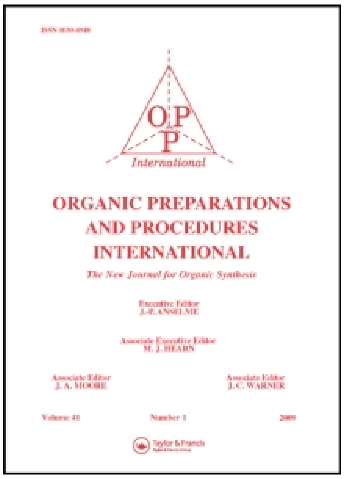

Organic Preparations and Procedures International
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t902189982

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To cite this Article Waller, Stephen C. and Mash, Eugene A.(1997) 'IMPROVED SYNTHESES OF 2,2',3,3',6,6'-HEXACHLOROBIPHENYL', Organic Preparations and Procedures International, 29: 6, 679 — 685
To link to this Article: DOI: 10.1080/00304949709355248
URL: http://dx.doi.org/10.1080/00304949709355248

ORGANIC PREPARATIONS AND PROCEDURES INT., 29 (6), 679-685 (1997)

IMPROVED SYNTHESES OF 2,2',3,3',6,6'-HEXACHLOROBIPHENYL

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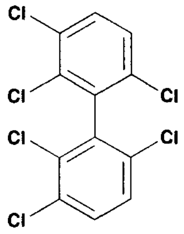
Polychlorinated biphenyls (PCBs) are toxic[1] and carcinogenic[2] compounds that contaminate nearly every ecosystem of our planet.[3] While the use of PCBs has been curtailed,[4] global contamination is expected to be a long-term problem[5] because of the slow rate of oxidative metabolism of some congeners[6] and the slow degradation of PCBs by natural processes.[7,8] For these reasons, studies of the metabolism and toxicity of individual PCB congeners are important. In connection with one such study, we required substantial quantities of 2,2',3,3',6,6'-hexachlorobiphenyl (**1**), as well as a number of putative metabolites of this PCB.[9] Previous syntheses of **1** have employed the Ullmann coupling of 1,2,4-trichloro-3-iodobenzene (**2**) obtained from 2,3,6-trichloroaniline (**3**) *via* the Sandmeyer reaction.[10] Since the reported syntheses of **3** are lengthy and/or inefficient,[10,11] we decided to investigate alternate routes to **1**.



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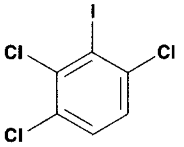

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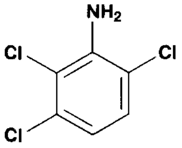
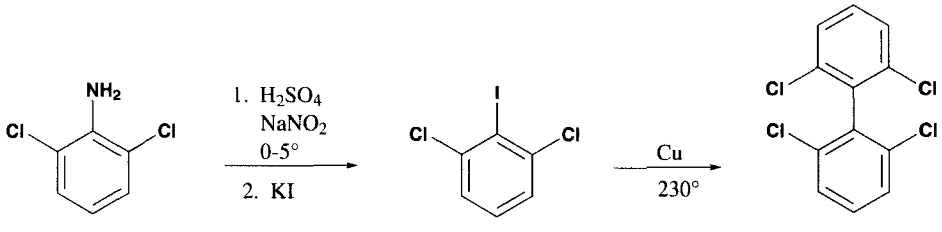


3

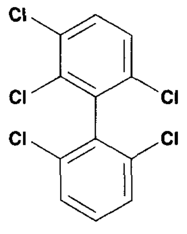
Chlorinations of PCBs which bear strongly activating and directing substituents, such as methoxy or amino groups, are facile and regioselective.[12,13] Less is known about regioselectivity for chlorinations of unactivated PCBs. Technical mixtures of PCBs have been prepared by the polychlorination of biphenyl,[12] but very few chlorinated biphenyls have been synthesized by regioselective chlorination.[12,14,15] Nitrations of many unactivated PCBs exhibit high levels of regioselectivity.[12,16] This suggests that electrophilic chlorinations of unactivated PCBs might also exhibit useful levels of regioselectivity.

2,2',6,6'-Tetrachlorobiphenyl (**6**) was selected for study and was prepared[9] by the Sandmeyer reaction of 2,6-dichloroaniline (**4**) to afford 1,3-dichloro-2-iodobenzene (**5**) in 69% yield, followed by the Ullmann coupling of **5**, using copper at 230° in a sealed tube to give **6** in 59% yield.



4 **5** **6**

PCB **6** was subjected to electrophilic chlorination using from one to five molar equivalents of sulfuryl chloride and aluminum chloride in dichloromethane at room temperature for one hour, and the percentages of starting material and PCB products were determined by a GC/MS technique (see Experimental Section). Results are presented graphically in Figure 1. Reaction of **6** with one equivalent of sulfuryl chloride and aluminum chloride afforded a mixture consisting of 33% starting material, 55% 2,2',3,6,6'-pentachlorobiphenyl (**7**), and 12% dichlorinated product **1**. Increasing the amounts of sulfuryl chloride and aluminum chloride shifted the composition of the PCB mixture, but in each case one PCB was predominant. Remarkably, reaction of **6** with 2.5 equivalents of sulfuryl chloride and aluminum chloride afforded a mixture of 1% of **7**, 95% of the desired hexachlorobiphenyl **1**, and 4% of 2,2',3,3',5,6,6'-heptachlorobiphenyl (**8**). In each chlorination approximately 1-2% of the other possible monochlorinated regioisomer, 2,2',4,6,6'-pentachlorobiphenyl (**10**) was detected. However, no other regioisomers of the hexa-, hepta-, and octachlorobiphenyls were detected. Apparently **10** is much less reactive toward further chlorination than are **7**, **1**, and **8**.



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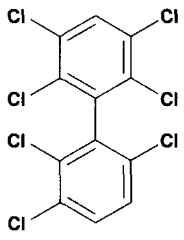

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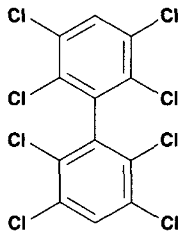

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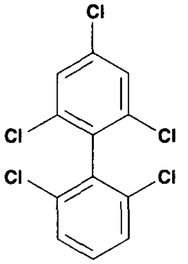
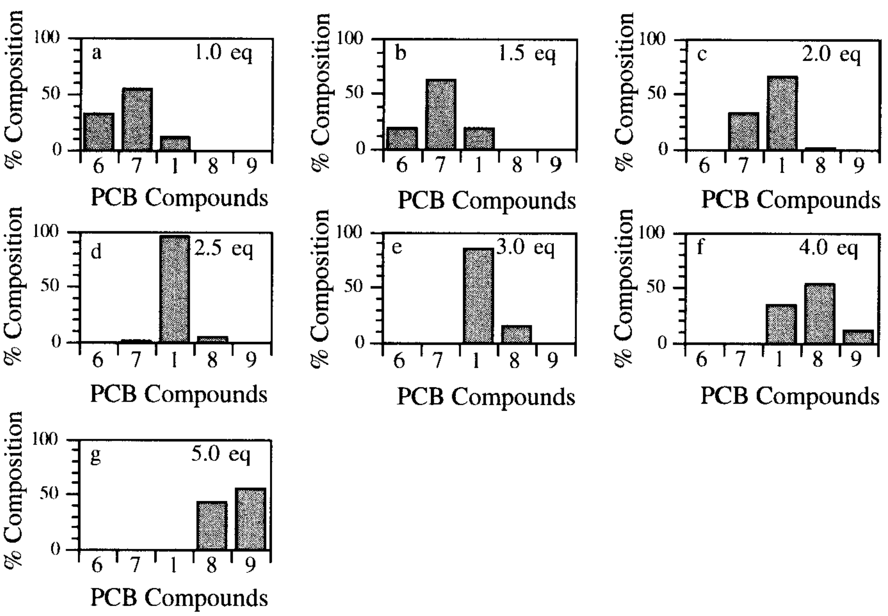


10

Products could be isolated from these chlorination reactions and purified by column chromatography. For example, **1** and **8** were isolated in 74% and 2% yields, respectively, from the reaction of **6** with 2.5 equivalents of sulfuryl chloride and aluminum chloride. Analytical and spectroscopic data for synthetic **1** matched data from an authentic sample.[17,18] The ^{1}H NMR spectral data obtained for synthetic **9** matched the data published for 2,2',3,3',5,5',6,6'-octachlorobiphenyl,[18] and the 125 MHz ^{13}C NMR for synthetic **9** consisted of four lines, as would be expected. Structures **7** and **8** were assigned based on the fact that these compounds were precursors to **1** and **9**, respectively.

Fig. 1.



Relative percent composition of PCB mixtures from reactions of 2,2',6,6'-tetrachlorobiphenyl (**6**) with sulfuryl chloride and aluminum chloride. (*a*) 1.0 equivalent, (*b*) 1.5 equivalents, (*c*) 2.0 equivalents, (*d*) 2.5 equivalents, (*e*) 3.0 equivalents, (*f*) 4.0 equivalents, and (*g*) 5.0 equivalents of sulfuryl chloride and aluminum chloride.

As putative metabolites of PCB **1** are often unsymmetrically substituted, chlorination of 1,3-dichloro-2-iodobenzene (**5**) was of interest. In the event, treatment of **5** with 1 equivalent of sulfuryl chloride and 0.3 equivalents of aluminum chloride in dichloromethane at room temperature for 30 minutes gave 1,2,4-trichloro-3-iodobenzene (**2**) in 70% yield after recrystallization. Ullmann coupling of **2** by a modification of the procedure reported[10] proceeded in 56% yield, providing a second concise synthetic route to PCB **1**.

EXPERIMENTAL SECTION

Mps were determined in a Mel-Temp using a mercury thermometer and are ***uncorrected****; the mps reported in Ref. 21 for compounds* ***1****,* ***6-8*** ***are corrected****.* Proton and ^{13}C-NMR spectra were recorded in $CDCl_3$ solution at 200 and 50 MHz, respectively, except where otherwise noted. Proton NMR spectra were referenced to residual $CHCl_3$ (7.24 ppm). Carbon NMR spectra were referenced to the center line of the $CDCl_3$ signal (77.0 ppm). GC/MS data were obtained at the Southwest Environmental Health Sciences Center Analytical Core Laboratory, Tucson, AZ, on a Fison MD-800 GC/MS, using a DB-5 column (30 m, 250 μm film thickness, 0.25 mm i.d., J & W Scientific, 60° initial, 2 min., 12°/min., 300° final, 8 min.). Elemental analyses were performed by Desert Analytics, Tucson, AZ. All reactions were run exposed to the atmosphere, except where noted. Reaction mixtures were stirred magnetically. Dichloromethane was distilled from calcium hydride under nitrogen. All reagents were 97% pure or better. Organic starting materials were purchased from Aldrich Chemical

Company. A sample of authentic 2,2',3,3',6,6'-hexachlorobiphenyl was purchased from Chemservice. Copper powder (40-100 mesh, 2N5) was purchased from Alfa and was purified by the method of Fuson.[19] Analytical thin-layer chromatography was performed on glass-backed Merck 0.25 mm silica gel 60 F-254 plates. Flash chromatography was performed using Merck silica gel 60 (230-400 mesh).

1,3-Dichloro-2-iodobenzene (5).- To a rapidly stirred mixture of 2,6-dichloroaniline (**4**) (1.64 g, 9.9 mmol) and distilled water (10 mL) was slowly added sulfuric acid (18 M, 3.12 mL, 56.2 mmol). The solution was cooled in an ice bath to ≤5°, and a solution of sodium nitrite (1.39 g, 20.1 mmol) in water (20 mL) was added dropwise over 15 min to maintain the reaction temperature at ≤5°. After 10 min a solution of potassium iodide (3.33 g, 20.0 mmol) in water (20 mL) was slowly added. The mixture was stirred at 0° for 15 min and at rt for 1 h. The reaction mixture was poured into hexanes (100 mL), stirred for 10 min, and filtered through Celite. The organic layer was separated, washed with 5% $NaHSO_3$ (50 mL), dried over a mixture of $MgSO_4$ and decolorizing charcoal, filtered through Celite, and concentrated on a rotary evaporator to give a yellow solid. Flash chromatography on silica gel 60 (75 g) eluted with hexanes gave 1.86 g (6.8 mmol, 69%) of **5** as a white solid, mp. 63-64°, R_f 0.50 (hexanes). The product was further purified by recrystallization from absolute ethanol, mp. 66-67°, lit.[20] mp. 67.2-67.6°. IR (nujol): 1557, 1461, 1423, 1393, 1186, 782, 772 cm^{-1}; ^1H NMR AB_2 system: δ 7.19 (1, m, J = 8.13 Hz), 7.31 (2, m, J = 8.13 Hz); ^{13}C NMR: δ 103.7, 127.2, 129.6, 140.6; mass spectrum (70 ev) *m/z* (rel. intensity): 276 (9), 274 (58), 272 (100) 149 (6), 147 (48), 145 (70).

Anal. Calcd for $C_6H_3Cl_2I$: C, 26.41; H, 1.11. Found: C, 26.44; H, 1.02

1,2,4-Trichloro-3-iodobenzene (2).- A mixture of **5** (4.85 g, 17.8 mmol), CH_2Cl_2 (50 mL), sulfuryl chloride (1.50 mL, 2.52 g, 18.1 mmol), and aluminum chloride (0.79 g, 5.9 mmol) was allowed to stir under argon for 30 min at rt. The reaction mixture was then poured into water (100 mL) and extracted with CH_2Cl_2 (3 x 50 mL). The organic extracts were combined, dried (Na_2SO_4), filtered, and concentrated on a rotary evaporator to a thick brown oil. The residue was crystallized from absolute methanol to give 3.85 g (12.5 mmol, 70%) of **2** as white needles, mp. 37-37.5°, lit.[10b] mp. 35-36°, R_f 0.47 (hexanes). IR (nujol): 1462, 1417, 1377, 1341, 1172, 816, 807, 733 cm^{-1}; ^1H NMR: δ 7.27 (1, d, J = 8.6 Hz), 7.38 (1, d, J = 8.6 Hz); ^{13}C NMR: δ 105.0, 127.5, 130.3, 130.5, 138.7, 138.9; mass spectrum (70 ev) *m/z* (rel. intensity): 312 (4), 310 (30), 308 (93), 306 (100), 185 (3), 183 (23), 181 (74), 179 (76).

Anal. Calcd for $C_6H_3Cl_2I$: C, 23.45; H, 0.66. Found: C, 23.09; H, 0.55

2,2',6,6'-Tetrachlorobiphenyl (6).- A mixture of **5** (1.01 g, 3.7 mmol) and purified copper (1.01 g, 15.9 mmol) under argon was allowed to react in a sealed glass tube submerged completely in a sand bath at 230° for 12 days. After cooling to room temperature, the tube was crushed, stirred with CH_2Cl_2 (25 mL) for 15 min, and then filtered. To the solution was added silica gel 60 (2 g), volatiles were removed on a rotary evaporator, the residue was loaded onto a silica gel 60 column (75 g), and the column eluted with hexanes to give 0.31 g (1.1 mmol, 59%) of **6** as a white solid, mp. 190-192°, lit.[21] mp. 197-198°, R_f 0.29 (hexanes), GC retention time 17.38 min, relative response factor vs. biphenyl 0.74. IR (nujol): 3083 (w), 3061 (w), 1557, 1431, 1199, 781, 722 cm^{-1}; ^1H NMR AB_2 system: δ 7.31 (2, m, J = 8.13 Hz), 7.43 (4, m, J = 8.13 Hz);[18] ^{13}C NMR: δ 127.9, 130.2, 135.0, 135.1; mass spectrum

(70 ev) *m/z* (rel. intensity): 298 (1), 296 (9), 294 (45), 292 (99), 290 (80), 261 (1), 259 (6), 257 (17), 255 (18), 224 (9), 222 (60), 220 (100).

Anal. Calcd for $C_{12}H_6Cl_4$: C, 49.36; H, 2.07. Found: C, 49.45; H, 2.02

Procedure for the Chlorination of 2,2',6,6'-Tetrachlorobiphenyl (6).- To solutions of **6** (0.1 M, 2.0 mL, 0.20 mmol) in CH_2Cl_2 under argon were added the required amounts of sulfuryl chloride *via* micropipette and aluminum chloride as a solid to prepare reaction mixtures containing 1.0, 1.5, 2.0, 2.5, 3.0, 4.0, and 5.0 molar equivalents of each reagent. Each reaction was allowed to stir at room temperature under argon for 1 h. Silica gel 60 (0.50 g) was then added, stirring was continued for 10 min, and volatiles were removed on a rotary evaporator. For each sample, the resulting silica gel/PCB mixture was placed into a clean 2.4 cm wide column and the PCB mixture eluted from the silica gel with CH_2Cl_2 (58.2 mL). Samples for GC analysis were prepared by mixing 50 μL of each eluent and 10 μL of biphenyl (6.49 x 10^{-3} M in CH_2Cl_2) with dilution with CH_2Cl_2 to 1.0 mL total volume. GC yields of the PCBs were calculated versus biphenyl as an internal standard using predetermined relative response factors from the total ion chromatograph resulting from the injection of 1 μL samples on a Fison MD-800 GC/MS. Data are reported herein as a percentage of total PCBs.

The individual PCBs were subsequently isolated *via* column chromatography on flash silica gel 60 (75 g) using hexanes as elutent. All PCBs were separable with the exception of 2,2',3,6,6'-pentachlorobiphenyl (**7**, major isomer, 98%) and 2,2',4,6,6'-pentachlorobiphenyl (**10**, minor isomer, 2%). Physical and spectroscopic data are tabulated below.

2,2',3,6,6'-Pentachlorobiphenyl (7), mp. 109-110°, lit.[21] mp. 119-120°, R_f 0.33 (hexanes), GC retention times 18.95 min (major isomer) and 19.63 min (minor isomer), relative response factor vs. biphenyl 0.69. IR (nujol): 1426, 1375, 1176, 811, 789, 778 cm^{-1}; ^{1}H NMR: δ 7.33 (1, m, J = 8.1 Hz), 7.37 (1, d, J = 8.8 Hz), 7.42 (2, m, J = 8.1 Hz), 7.48 (1, d, J = 8.8 Hz); ^{13}C NMR (75 MHz): δ 128.0, 128.4, 130.5, 130.8, 131.9, 133.2, 133.5, 134.7, 135.0, 136.8; mass spectrum (70 ev) *m/z* (rel. intensity) 332 (3), 330 (20), 328 (64), 326 (100), 324 (65), 295 (2), 293 (7), 291 (15), 289 (12), 260 (3), 258 (24), 256 (76), 254 (81); (minor isomer) mass spectrum (70 ev) *m/z* (rel. intensity): 332 (2), 330 (16), 328 (48), 326 (81), 324 (49), 295 (7), 293 (32), 291 (67), 289 (55), 260 (3), 258 (29), 256 (92), 254 (100).

2,2',3,3',6,6'-Hexachlorobiphenyl (1), mp. 106-108°, lit.[21] mp. 112-113.5°, R_f 0.38 (hexanes), GC retention time 20.40 min, relative response factor vs. biphenyl 0.84. IR (nujol): 1458, 1377, 1176, 1044, 811 cm^{-1}; ^{1}H NMR: δ 7.38 (2, d, J = 8.7 Hz), 7.49 (2, d, J = 8.7 Hz);[10a,18] ^{13}C NMR: δ 128.5, 131.1, 132.0, 133.0, 133.3, 136.7; mass spectrum (70 ev) *m/z* (rel. intensity): 368 (1), 366 (8), 364 (33), 362 (79), 360 (100), 358 (53), 294 (7), 292 (31), 290 (66), 288 (52).

Anal. Calcd for $C_{12}H_4Cl_6$: C, 39.94; H, 1.12. Found: C, 39.56; H, 1.12

2,2',3,3',5,6,6'-Heptachlorobiphenyl (8), mp. 124-125°, lit.[21] mp. 129-131°, R_f 0.46 (hexanes), GC retention time 21.47 min, relative response factor vs. biphenyl 0.69. IR (nujol): 1445, 1392, 1342, 1176, 1169, 1057, 818, 809 cm^{-1}; ^{1}H NMR: δ 7.39 (1, d, J = 8.8 Hz), 7.51 (1, d, J = 8.8 Hz), 7.70 (1, s); ^{13}C NMR (75 MHz): δ 128.6, 131.3, 131.3, 131.7, 132.2, 132.2, 132.7, 133.0, 136.6, 137.8; mass spectrum (70 ev) *m/z* (rel. intensity): 402 (3), 400 (14), 398 (46), 396 (89), 394 (100), 392 (43), 363 (3), 361 (7), 359 (9), 357 (5), 330 (2), 328 (14), 326 (44), 324 (69), 322 (46).

2,2',3,3',5,5',6,6'-Octachlorobiphenyl (9), mp. 149-150°, lit.[21] mp. 157-159°, R_f 0.51 (hexanes), GC retention time 22.32 min, relative response factor vs. biphenyl 0.70. IR (nujol): 1461, 1377, 1165, 1069, 869, 756, 677 cm^{-1}; ^{1}H NMR: δ 7.71 (2, s);[18] ^{13}C NMR (125.8 MHz): δ 131.04, 131.08, 131.96, 137.33; mass spectrum (70 ev) *m/z* (rel. intensity): 438 (1), 436 (7), 434 (25), 432 (63), 430 (100), 428 (91), 426 (36), 399 (1), 397 (4), 395 (7), 393 (7), 391 (2), 364 (5), 362 (22), 360 (51), 358 (71), 356 (35).

2,2',3,3',6,6'-Hexachlorobiphenyl (1) *via* Ullmann Coupling of 2.- A mixture of **2** (1.11 g, 3.6 mmol) and purified copper (1.15 g, 18.1 mmol) under argon was allowed to react in a sealed glass tube submerged completely in a sand bath at 230° for 2 days. After cooling to rt, the tube was crushed and stirred with hexanes (25 mL) for 15 min. The solution was chromatographed on silica gel 60 (75 g) eluted with hexanes to give 360 mg (1.0 mmol, 56%) of **1**. Physical and spectroscopic data were identical to those obtained from **1** prepared *via* chlorination of **6**.

Acknowledgement.- This material is based upon work supported by NIEHS under award number ES06694.

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(Received April 4, 1997; in revised form July 31, 1997)