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An Alternative Synthesis of Chlorinated Biphenyl Methylsulfonyl Metabolites

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ABSTRACT

Published methods of synthesizing chlorinated biphenyl methylsulfones require the separation of a complex mixture of impurities and isomers using both normal and reverse phase HPLC. Even with semi-preparative scale equipment, the process is tedious and time-consuming. In this report, the palladium-catalyzed addition of an aryl iodide to an aryl trimethylstannane has been exploited to produce these compounds in high purity (≥99%) using conventional techniques of purification. The reaction has been demonstrated for a group of methylsulfonyl CBs representing 0 to 3 ortho-chlorine interactions between the biphenyl rings and with the methylsulfonyl group at either the 3- or 4-position.

INTRODUCTION

Methylsulfonyl-substituted metabolites of chlorinated biphenyls (CB) were first recognized as persistent, environmental contaminants almost twenty years ago by Jensen and Jansson [1] and by Mio et al. [2]. Subsequent work by Bergman and co-workers demonstrated a concentration of these metabolites in lung and liver tissues of several mammals [3-4]. Most recently, Kato and co-workers [5-6] have shown that a number of 3-substituted methylsulfonyl metabolites of chlorinated biphenyls are potent inducers of hepatic enzymes leading them to speculate that "these metabolites contribute prominently to the induction of microsomal drug-metabolizing enzymes by the parent CB congeners". Depending on the chlorine substitution pattern, some metabolites were nearly 700 times more active than the CB from which they were thought to originate. Although a number of these CB metabolites are commercially available (C.I.L., Andover, MA, USA), researchers wishing to do animal studies with them would likely find their cost prohibitive. For this reason, we considered synthesizing them ourselves.

Haraguchi et al. [7-8] and earlier Bergman and co-workers [9-10] have used three routes to synthesize CB methylsulfonyl metabolites: a) diazo coupling of a substituted aniline with a chlorinated benzene, b) nucleophilic substitution of a CB with methanethiolate, and c) diazo coupling of a chlorinated aniline with a chlorothioanisole. Considering the complexity of the reaction mixtures from each of these routes, it is to their credit that these researchers produced such a large variety of pure metabolites. The tedious and time-consuming nature of the isolation combined with the low recovery of pure product, however, soon led us to seek an approach in which the biphenyl ring could be constructed in a more controlled manner.

Mizutani et al. [11] controlled the congener specificity by using the Ullman reaction between an appropriately substituted iodochlorophenylmethylsulfone and a specifically substituted chloroiodobenzene. Although the products in this reaction mixture are probably more easily separated than those of the reactions above, precious starting materials are lost in the non-selectivity of the Ullman reaction. For this reason, we chose to examine the palladium-catalyzed cross-coupling methodologies for the construction of the biphenyl rings. It has been well established that zero-valent palladium species insert into aromatic halogen bonds (I>Br>Cl) under mild conditions to generate aryl palladium intermediates that will react with aryl metal species [12], aryl boronic acids [13] or aryl stannanes [14] to produce a biphenyl system and regenerate the palladium. To the best of our knowledge, however, this approach has not been used to construct CBs or their metabolites. In order to avoid potential complications in the metallation of polyhalogenated aromatics, we chose to use aryl stannanes which are conveniently prepared

from the corresponding aryl iodides [15].

This report describes the application of this coupling methodology to the synthesis of the seven CB methylsulfones shown in Figure 1.

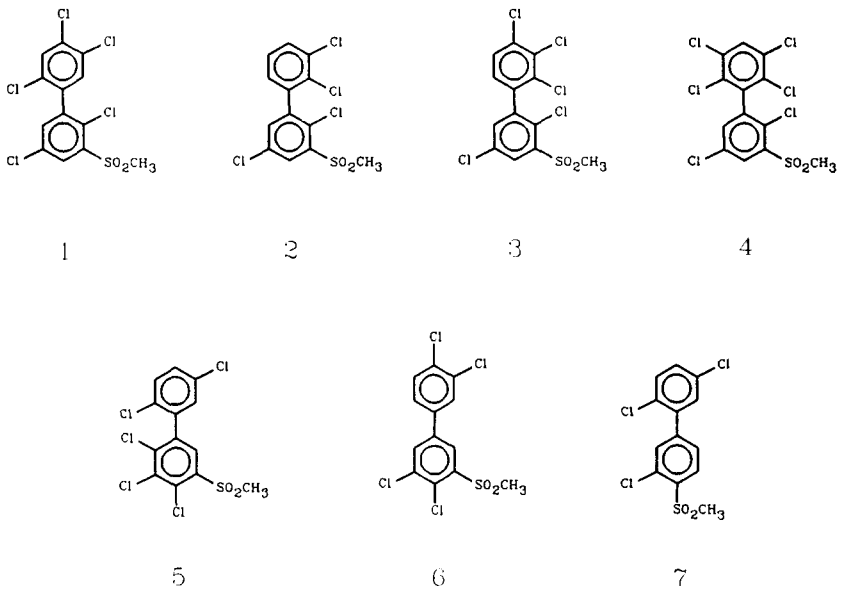


Figure 1. Representative Chlorinated Biphenyl Methylsulfones

EXPERIMENTAL

Materials and Instrumentation

Melting points were done on a Fisher-Johns hot stage and are uncorrected. Thin layer chromatography was done on Whatman MK6F silica gel plates, 1" x 3" (Chromatographic Specialties, Brockville, ON, Canada). Flash chromatography was done with Davisil silica gel, grade 643, 200-425 mesh, ~4% moisture (Aldrich, Milwaukee, WI, USA). Semi-preparative HPLC was done with a Partisil ODS-1 column (25 cm x 9.4 mm, 10 um particle) using 20% methanol-water as mobile phase. NMR spectra were run on a Bruker 200 MHz instrument referenced to TMS. GC-ECD was done with a Varian Vista 6000 with a DB5 capillary column, 30 m x 0.25 mm i.d., 0.25 um df, H_2 = 1.6 mL/min, 70-100°C @ 60°C/min then to 315°C @ 10°C/min. GC-MSD was done on a HP5890 Series II GC interfaced with a HP5970 MSD (autotuned, 70 eV, 1600 V multiplier voltage, 50-500 amu scan range, 1.2 scans/sec) with a DB5ms capillary column, 30 m x 0.25 mm i.d., 0.25 um df, He = 1.5 mL/min, 70-100°C @ 50°C/min then to 280°C

@ 10°C/min (hold 5 min).

Synthesis

To conserve manuscript space, representative examples of experimental details are given for only one example for each type of reaction, however, similar reactions of other compounds were done in the same way.

2,5-Dichlorophenylmethylsulfone 2,5-Dichlorobenzenethiol (Aldrich, 5.2 g) was dissolved in ethanol (20 mL) and water (1.5 mL) under a blanket of nitrogen at ~15°C with stirring. Sodium hydroxide beads (1.3 g) were added followed by dropwise addition of methyl iodide (BDH, 1.85 g). A white precipitate soon formed. After complete addition of the methyl iodide, the reaction mixture was allowed to stand one hour before dilution with an equal volume of water. Filtration yielded a white solid (5.44 g), mp. 67-68°C. TLC with hexane showed a single spot at R_f 0.45. A portion of this solid (2.3 g) was dissolved in dichloromethane (25 mL) and a slight excess of monoperoxy magnesium phthalate hydrate (Aldrich, 9.3 g) added. Trifluoroacetic acid (~0.5 mL) was added to the slurry (partial clearing) and the mixture left overnight. The thick suspension was diluted with dichloromethane and filtered. The filtrate was washed with water (20 mL x 2), dried over anhydrous sodium sulphate and evaporated to dryness to yield a white solid, 2.56 g. Recrystallization from methanol-saturated hexane yielded colourless flakes, mp. 86-87°C. GC-MSD showed a single peak at 9.85 min (M^+ m/z 224, 70%, 2-chlorine isotope pattern). The GC-ECD chromatogram had a single peak at 8.2 minutes.

2,5-Dichloro-3-nitrophenylmethylsulfone 2,5-Dichlorophenylmethylsulfone (1.9 g) was dissolved in conc. sulfuric acid (5 mL) with potassium nitrate (1.7 g) and heated at ~60°C for 3 hours. The orange solution became turbid within 20 minutes. The reaction mixture was cooled to room temperature, poured into ice water and extracted with ethyl acetate (20 mL x 2). The combined organic layers were washed with saturated bicarbonate, dried over anhydrous sodium sulfate, filtered and evaporated to dryness to yield a colourless solid (2.1 g). The product was first recrystallized from ethyl acetate-hexane (3:7, 150 mL) to remove the more polar, ortho-nitro by-product (0.45 g). The residue from the evaporated mother liquor was then recrystallized from isopropanol to yield colourless, fine needles (1.0 g), mp. 106.5-108°C (lit.[11], mp. 111°C). GC-ECD showed a single, major peak (10.8 min) with only traces of the other two isomers (<2%). GC-MSD showed a single, major peak (12.4 min, M^+ m/z 269, 50%, 2-chlorine isotope pattern). ^{1}H-NMR ($CDCl_3$): 8.38 ppm, d, 1H, J=2.45Hz; 8.00 ppm, d, 1H, J=2.45 Hz; 3.34 ppm, s, 3H.

2,5-Dichloro-3-iodophenylmethylsulfone 2,5-Dichloro-3-nitrophenylmethyl-

sulfone from above (1 g) was dissolved in THF and ethanol (7 mL, 6:1) and stirred with 10% Pd-C (Aldrich, 50 mg) and a solution of sodium hypophosphite hydrate (Aldrich, 1.45 g) in water (2 mL). The reaction was moderated by immersing the reaction vessel in a cold water bath. Within 45 minutes, all starting material was consumed (TLC) and the reaction mixture was filtered through a cotton plug into water (20 mL). The resulting light-khaki precipitate (0.78 g) was filtered off. This crude product was stirred in conc. hydrochloric acid-water (8 mL, 1:1) in an ice bath while a solution of sodium nitrite (0.45 g) in water (2 mL) was added dropwise over ~15 minutes. After complete addition, the mixture was stirred for an additional 30 minutes before a solution of sodium iodide (1.3 g) in water (3 mL) was added all at once. Rapid effervescence was observed and a dark brown precipitate was formed. The reaction mixture was poured into 10% aqueous sodium sulfite (30 mL) and extracted with ethyl acetate (20 mL x 2). The combined ethyl acetate layer was washed with 5% sodium bicarbonate-1% sodium thiosulfate and then with saturated sodium chloride solution, dried over anhydrous sodium sulfate, filtered and evaporated to yield an orange-brown solid (0.98 g). TLC with dichloromethane showed a single, major spot at R_f 0.79. The product was flash chromatographed with dichloromethane on silica to yield a cream-coloured solid (0.79 g) which recrystallized from isopropanol as fine needles (0.68 g), mp. 155-155.5°C (lit.[11], mp. 156-157°C). ^{1}H-NMR ($CDCl_3$): 8.17 ppm, d 1H, J=2.5 Hz; 8.13 ppm, d, 1H, J=2.5 Hz; 3.29, s, 3H. Both GC-ECD (12.2 min) and GC-MSD (13.65 min) showed a single peak. The mass spectrum was consistent with the expected structure: M^+ m/z 350, 50%, 2-chlorine isotope pattern.

2,3,4-Trichlorophenyltrimethylstannane 2,3,4-Trichloroiodobenzene (0.75 g), bis(triphenylphosphine)palladium dichloride (Aldrich, 35 mg), and hexamethyldditin (Aldrich, 2.5 g) were dissolved in dry DMF (2mL) in a 5 mL Reactivial with a stirring bar and heated in an aluminum block at 110°C. The reaction mixture darkened within minutes and gradually deposited a black precipitate. After one hour, a diluted aliquot was examined by GC-ECD and showed practically no starting iodide (7.2 min) but a single, major product peak (8.5 min). The reaction was filtered through a cotton plug into water (25 mL) and extracted with hexane (15 mL x 2). The combined hexane layers were washed with water and then with saturated sodium chloride solution, dried over anhydrous sodium sulfate, filtered and evaporated to yield a colourless oil (0.64 g). TLC with hexane showed a single, major spot at R_f 0.77. The crude product was flash chromatographed with hexane on silica to yield a colourless liquid (0.56 g). GC-MSD showed a single peak (9.9 min) whose principal fragment (100%) was a cluster of ions centered around m/z 329 (M^+-CH_3).

2,5,2',3',4'-Pentachloro-3-methanesulfonylbiphenyl 3 2,5-Dichloro-3-iodo-

phenylmethylsulfone (0.19 g), 2,3,4-trichlorophenyltrimethystannane (0.2 g), bis(triphenylphosphine)palladium dichloride (19 mg), triphenylarsine (Aldrich, 17 mg) and copper iodide (Aldrich, 20 mg) were stirred in dry DMF (3 mL) in a 5 mL Reactivial in an aluminum block at 110°C for 24 hours. The initially yellow-orange solution gradually darkened and deposited a small amount of black precipitate. After cooling, the reaction mixture was filtered through a cotton plug into water (~50 mL) containing a few drops of conc. ammonium hydroxide and extracted with ethyl acetate-hexane (1:3, 15 mL x 2). The combined solvent layers were washed with water and then with saturated sodium chloride solution, dried over anhydrous sodium sulfate, filtered and evaporated to yield a yellow syrup (0.25 g). The crude product was flash chromatographed with dichloromethane on silica to yield a cream-coloured solid (88 mg) which recrystallized from isopropanol as colourless, fine needles (66 mg), mp. 167-168°C (lit.[8], mp. 165-165.5°C). The GC-ECD chromatogram showed a single peak (18.6 min). The GC-MSD showed a single peak (19.94 min): M^+ m/z 402, 100%, 5-chlorine isotope pattern. ^{1}H-NMR ($CDCl_3$): 8.25 ppm, d, 1H, J=2.6 Hz; 7.52 ppm, d, 1H, J=8.3 Hz; 7.51 ppm, d, 1H, J=2.6 Jz; 7.12 ppm, d, 1H, J=8.3 Hz; 3.33 ppm, s, 3H. ^{13}C-NMR ($CDCl_3$): 141.69, 140.22, 135.93, 135.64, 135.17, 133.63, 132.74, 130.96, 130.07, 128.65, 128.56, 42.73 ppm.

2,3,4-Trichlorophenylmethylsulfone 12 2,3,4-Trichloroaniline was stirred in ice-cold, conc. hydrochloric acid (2.5 mL) while an aqueous solution (2 mL) of sodium nitrite (0.8 g) was added dropwise over 20 minutes. Once addition was complete, stirring at ice-temperature was continued until all the solid had dissolved. This diazonium ion solution was then added dropwise (CAUTION!! 1 drop per 2-3 seconds) to a room-temperature, stirred solution of potassium ethyl xanthate (2.1 g) in water (5 mL) containing nickel chloride (25 mg). As each drop was added, there was a brief burst of effervescence and formation of an oily precipitate. The mixture was left for 30 minutes after complete addition, diluted with water (20 mL) then extracted with ethyl acetate (10 mL x 2). The combined organic layers were washed with water, saturated sodium chloride solution, dried over anhydrous sodium sulfate, filtered and evaporated to yield a brown liquid. This crude product was stirred in refluxing 95% ethanol (20 mL) with NaOH beads (1.5 g) under a blanket of nitrogen for 5 hours. The reaction mixture was cooled to room temperature and methyl iodide (0.5 mL) was added. The reaction was left overnight before pouring into water (50 mL) and extracting with ethyl acetate (15 mL x 2). The combined organic layers were washed with 1N sulfuric acid, water, and saturated salt solution, then dried over anhydrous sodium sulfate, filtered and evaporated under reduced pressure to yield an amber solid (1.05 g). This material was oxidized with monoperoxy magnesium phthalate as described above and after workup gave a light orange solid (1.2 g). The GC-ECD chromatogram showed a single, major peak at 10.1 min and the GC-MSD gave

a mass spectrum with M^+ m/z 258 and a 3-chlorine isotope pattern. Recrystallization of a portion of the crude (0.17 g) from isopropanol gave slender needles (0.11 g), mp. 161-162°C.

RESULTS AND DISCUSSION

The Cadogan reaction [16] has been the principal reaction used in the past to prepare the CB methylsulfonyl metabolites [7-10]. When we attempted to prepare the toxicologically important 2,2',4,5,5'- and 2,2',3',4',5-pentachloro-3-methylsulfonylbiphenyls from the chloroaniline and methylsulfonylchlorobenzene precursors using this reaction, we found it necessary to use equimolar amounts of the methylsulfonylchlorobenzene rather than the recommended large excess due to subsequent difficulty in removing the surplus. This factor along with the steric hindrance of the *ortho*-chlorine atoms and the deactivation of the ring containing the methylsulfonyl group resulted in yields below 1%. The tarry reaction containing both 3- and 4-methylsulfonyl products required separation on a silica column followed by multiple runs on a semi-preparative reversed phase column. These runs required up to 30 min per injection to permit removal of late-eluting, non-polar impurities. We were able to prepare sufficient material for analytical standards (≥99% pure) using this approach, however, we found it to be an impractical procedure to obtain enough product for toxicological testing.

As a potentially congener-specific approach to the synthesis of CB methylsulfonyl metabolites, we chose to examine the Stille reaction, summarized in Figure 2. Although it has been applied to biaryl synthesis

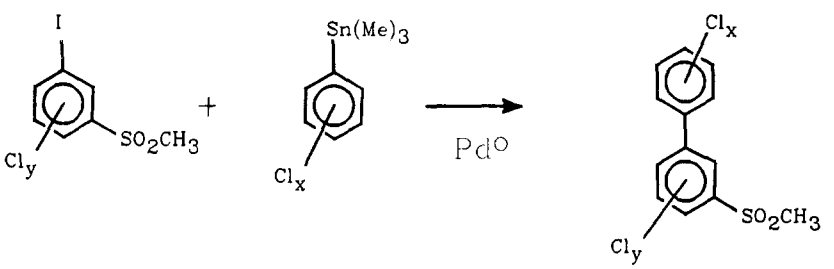
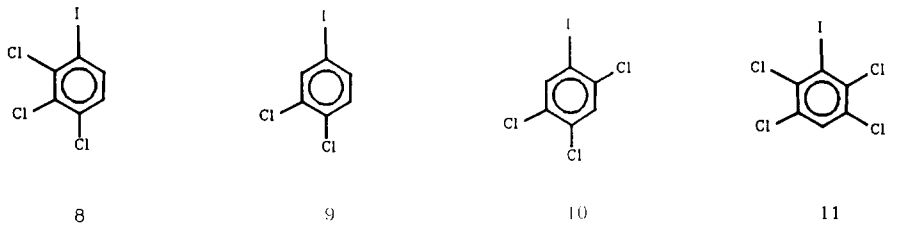


Figure 2. Generalized Stille Reaction for Biphenyl Synthesis

before [14,17-19], it has not been used to prepare CBs or their metabolites. Advantages of the Stille reaction are the commercial availability of catalysts and ligands, the simplicity of the manipulation and the relatively

mild conditions of the reaction. Although the starting materials bearing the appropriately substituted chlorine atoms are not commercially available, many of their precursors are. In particular, there is a wide range of chlorinated anilines for sale. Starting aryliodides which were used to prepare the aryltrimethylstannanes and which could not be purchased were readily synthesized by the Sandmeyer reaction of the corresponding aniline. Figure



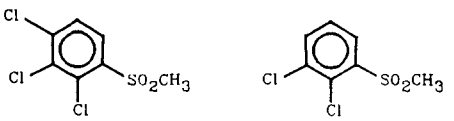
8 9 10 11

Figure 3. Products from the Sandmeyer Reaction

3 shows the four aryliodides prepared in this way and subsequently converted to aryltrimethylstannanes. The iodides and trimethylstannanes were partially purified by filtering through a short silica column in hexane to remove polar impurities. Extensive purification was unnecessary as minor, unreactive, non-polar impurities, such as by-product CBs, were conveniently removed from the polar, CB methyl-sulfones after the Pd-catalyzed coupling reaction.

Preparation of the chlorinated iodophenylmethylsulfones was more demanding as few chlorinated thiophenols are commercially available. Our initial approach was based on the work of Migita et al. [20]. 2,3-Dichloroiodobenzene was refluxed with sodium methanethiolate in ethanol with tetrakis(triphenylphosphine) palladium catalyst. The reaction began well enough but appeared to stop after 10% conversion. In spite of the unreacted starting material and addition of more catalyst and thiolate, the reaction remained stalled. Variations in palladium catalyst or solvent did not improve this result. Although the reaction was considerably accelerated in DMF (starting material was completely consumed after 2 hours at 55°C), we found little selectivity. GC-MSD analysis revealed that all possible mono-, di- and tri-substituted products had been formed. Fortunately, xanthation of the diazonium salt of the corresponding chlorinated anilines provided an alternative approach to the necessary thiophenols [21]. Although Bergman et al. [10] successfully thiomethylated the diazonium salt of 4-nitroaniline, there have been a number of reports of violent explosions with diazonium sulfides [22]. As a result, the less direct, xanthation, hydrolysis and methylation sequence was used to

prepare the required chlorinated phenylmethylsulfides. In the presence of a trace of nickel salt [21], decomposition of the diazonium salt solution in the xanthate solution was rapid and smooth. Purification of the products after each step was unnecessary and was only done after peracid oxidation of the sulphide. Figure 4 shows the sulfones prepared in this way (sulfone 12, mp. 161-162°C; sulfone 13, mp. 64-64.5°C).



12 13

Figure 4. Sulfones Prepared by Xanthation of Chloroanilines

In order to functionalize the position meta to the methylsulfonyl group, we adopted the nitration reaction used by Mizutani et al. [11] as a number of attempts at direct iodination were unsuccessful. Although a mixture of isomers was produced, the meta-isomer was the major product. For example, in the case of 2,5-dichlorophenylmethylsulfone, the ratio of isomers was 6:1:3 for meta:para:ortho (by ^{1}H-NMR and GC-MSD). Similarly, nitration of sulfones 12 and 13 gave crude products with 90% and 80% of the meta isomer, respectively. Recrystallization of the mixtures was effective in purifying the meta isomer to ≥98%; the nitrated product of sulfone 12 from isopropanol (mp. 133-135°C), and the nitrated product of sulfone 13 from acetonitrile (mp. 216-216.5°C). Congener specificity of the final CB methylsulfones depends on the high purity of these products. 2-Chloro-4-nitrophenylmethylsulfone was prepared by a more direct route. Taking advantage of the ready substitution of a halogen para to an aromatic nitro function, 3,4-dichloronitrobenzene was reacted with sodium methanethiolate in DMF to yield 2-chloro-4-nitrophenylmethylsulfide.

The nitrated sulfones were then conveniently reduced to the corresponding aminosulfones by hypophosphite and a palladium/carbon catalyst [23]. Provided the conditions are mild (small excess of hypophosphite, room temperature, 1 hour), no dehalogenation of the ring chlorine atoms was observed [24]. The aminosulfones were not purified, but immediately converted to the corresponding iodosulfones by the Sandmeyer reaction. These products were purified by flash chromatography.

The Pd-catalyzed coupling reaction is a deceptively simple manipulation; the

reagents were weighed into a 5 mL Reactivial with a stirring bar and dry DMF and the mixture heated in an aluminum block at 110°C overnight. By the end of the reaction period, various quantities of black precipitate (Pd) were observed and, in some cases, there was a metallic sheen on the interior of the vial. Although the role of the copper iodide is unclear, Liebeskind and Fengl [25] have shown it to accelerate the coupling reaction, and Saa and Martorell [26] have found it to substantially improve the yields of highly hindered biphenyls. In our initial experiments with 2,3-dichlorophenyltrimethylstannane and 2,5-dichloro-3-iodophenylmethylsulfone, we observed that a side reaction in which a methyl group is transferred from the tin atom rather than a phenyl group was practically eliminated in the presence of copper iodide. As a result, this salt was added to all subsequent reactions. Triphenylarsine was included in the reaction mixture for a similar reason. Farina and Krishnan [27] found that using triphenylarsine as a palladium ligand produced rate increases of two to three orders of magnitude over those observed with triphenylphosphine. Unfortunately, it was beyond the scope of our project to optimize these reactions further. Table 1 lists the yields of CB methylsulfones produced in this way. For ortho-chlorine interactions of 0, 1 or 2, the yields were good but, in the case of CB sulfone 4 where there are 3 ortho-chlorine interactions, the yield dropped dramatically. In two

Table 1. Tabulation of Metabolite Yields and Some Physical Data

Metabolite	Yield, %[1]	mp., °C	mp., °C[2]	r.t.,min (GC-ECD)	r.t.,min (GC-MSD)
2,5,2',4',5'-pentaCB-3-MSF 1	52	212-212.5	204-205.5	18.1	19.6
2,5,2',3'-tetraCB-3-MSF 2	63	95.5-97	75-76	16.9	18.3
2,5,2',3',4'-pentaCB-3-MSF 3	41	167-168	165-165.5	18.6	20.0
2,5,2',3',5',6'-hexaCB-3-MSF4	6	179-180.5	179.5-180.5	18.7	20.0
4,5,6,2',5'-pentaCB-3-MSF 5	72	195-195.5	not listed	18.2	19.6
4,5,3',4'-tetraCB-3-MSF 6	49	188-189	192-193	18.9	20.4
3,2',5'-triCB-4-MSF 7	100	143-144	85-86	16.7	18.1

1. yield of chromatographically-pure product from the Pd-catalyzed coupling reaction.

2. reported melting point [8].

cases, our melting points were significantly higher than those reported by Haraguchi et al. [8]. In the case of metabolite 2, this difference may be due to slight differences in purity as our ^{1}H-NMR spectrum matched that given by Haraguchi. We found that the material isolated from the silica column and prior to recrystallization (a cream-coloured foam), although showing only a few percent of impurity in the GC-MSD, had a low and broad melting point (50-60°C). The melting point increased markedly once the material was recrystallized. In the case of metabolite 7, however, the huge difference in melting points is harder to rationalize. Our ^{1}H-NMR (200 MHz) spectrum was very similar to that of Haraguchi's (90 MHz) [8] (at 200 MHz, the para coupling, J=0.8 Hz, was evident in the 3'-signal) and both were consistent with the assigned structure. The methylsulfonyl group was definitely at the 4-position because the lowest field NMR signal (8.22 ppm) had a coupling constant of 8.2 Hz and was the only signal to show a nuclear Overhauser enhancement when the methyl group was irradiated. This established that the signal at 8.22 ppm was ortho both to another ring proton and to the sulfonyl group. Haraguchi prepared his material by thiomethylating 3,4,2',5'-tetrachlorobiphenyl under Bergman's conditions [9] with the assumption that the major product would be from thiomethylation at the 4-halogen position because of the halogen's para relationship to the other phenyl ring. We found little or no reaction between 3,4,2',5'-tetrachlorobiphenyl and sodium thiomethylate under Bergman's conditions but, in DMF, all the CB was rapidly consumed and gave a mixture of mono- and di-thiomethylated products (GC-MSD) with one major mono-thiomethylated CB. After oxidation, purification by column chromatography and recrystallization from isopropanol, white crystals of 94% purity were isolated. The GC retention times, mass spectrum and ^{1}H-NMR spectrum of this material were identical to those of CB sulfone 7. Its melting point was 139-139.5°C. We conclude that Haraguchi's reported melting point is incorrect.

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