Organohalogen Compounds, Volume 61, Pages 115-118 (2003)

SYNTHESIS AND CHARACTERIZATION OF METHOXY- AND HYDROXY- POLYBROMODIPHENYL ETHERS

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Introduction

A number of methoxy- and hydroxyderivatives of PBDE has been reported in the literature[1]. All but one of them were not synthetic chemicals, but isolates from different marine sponges[2]. Also methoxy- and hydroxy-PBDEs were detected in fish in concentrations similar to those of PBDEs[3]. The aim of our work was to develop synthetic methods for these compounds and prepare a series of congeners in substantial amounts and of good purity.

Results and Discussion

As primary synthetic targets we selected 12 congeners (6 methoxy- and 6 hydroxy-PBDEs), derived from PBDE 47, 99 and 100. Compounds 1-10 would have a MeO- or HO- substituent orto to another aryl, compounds 11 and 12 – in para position (Fig. 1).

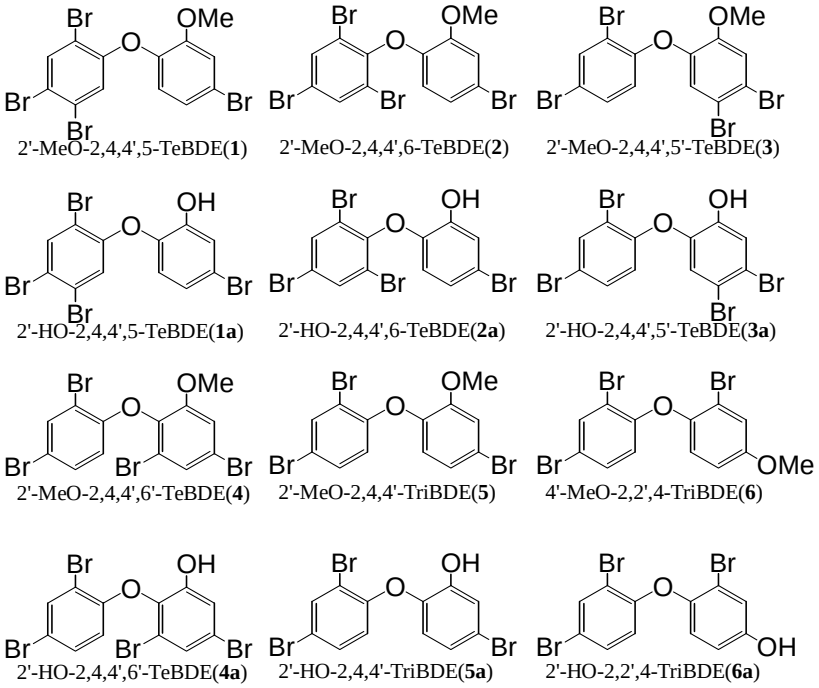
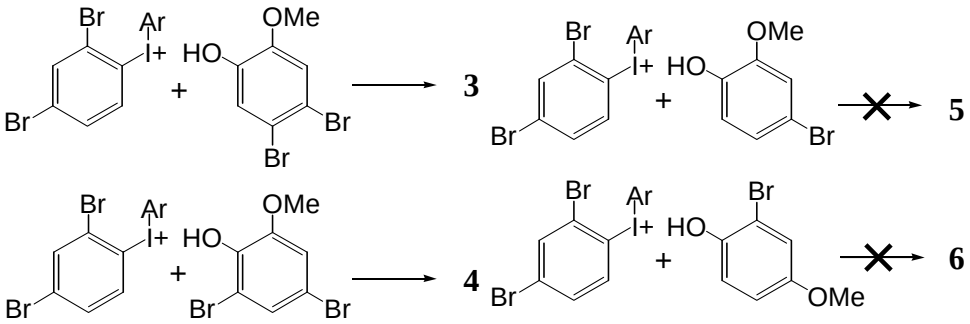
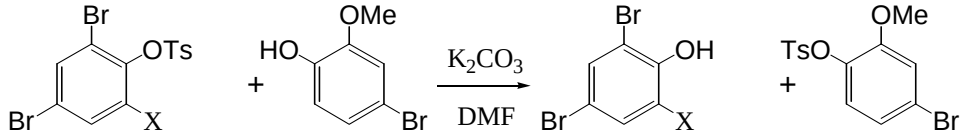


Figure 1. Structures of 6 Methoxy-PBDEs and 6 Hydroxy-PBDEs.

No general synthetic pathway to these compounds was known. However, two classes of structurally similar compounds – parent PBDEs and methoxy- or hydroxy-PCDEs have been recently synthesized and properly characterized[4,5]. Therefore at first we tried to apply synthetic methods, which led to PBDEs and MeO- or HO-PCDEs for the preparation of the title compounds. The general way to chlorinated methoxydiphenyl ethers is reaction between corresponding chlorosubstituted iodonium salt and chlorosubstituted methoxyphenols. Hydroxydiphenyl ethers can then be synthesized by hydrolysis. The same method was found to be useful for the synthesis of PBDE congeners. We explored this method for the synthesis of compounds **3-6**, via reaction of 2,2',4,4'-tetrabromodiphenyliodonium chloride with 4,5-dibromo-, 4,6-dibromo and 4-bromoguaiacols and with 2-bromo-4-methoxyphenol. Compounds **1** or **2** cannot be prepared by this method because it is impossible to synthesize the required starting hexabromodiphenyliodonium salts. Indeed we obtained ethers **3** and **4** in satisfactory yields (ca. 50%), but were unable to isolate or even detect **5** or **6**. This was in contrast with our expectations: nucleophylic substitution is usually accelerated when more basic and less sterically crowded phenolate is used. In our case, however, use of more active nucleophiles led to reduction of the iodonium salt with formation of iododibromobenzene and dibromobenzene, rather than to nucleophylic substitution. This reduction occurs only to minor extent in case of dibromoguaiacols.



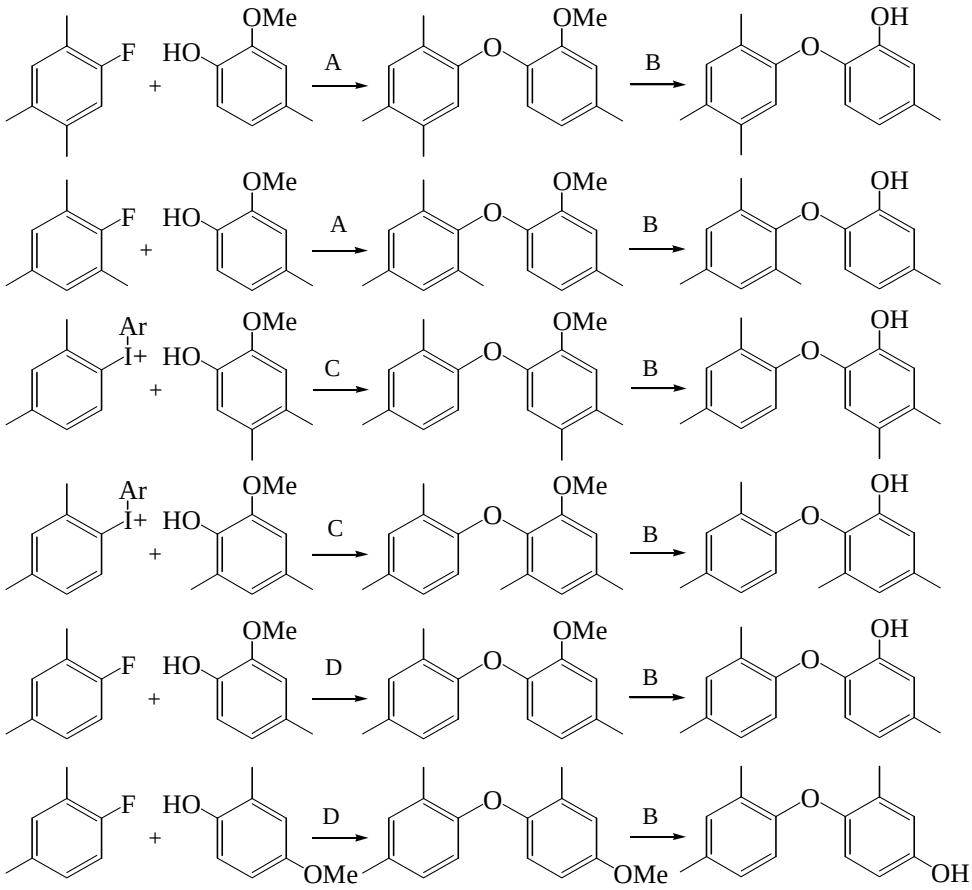
Therefore we had to find substrates, containing different leaving group, which would not undergo reduction. We examined two classes of substrates – aryltosylates and arylfluorides; compounds that contain some of the best leaving groups. Our attempts to use aryltosylates failed. Both 2,4-dibromophenyltosylate and 2,4,6-tribromophenyltosylate with 4-bromoguaiacol gave 4-bromo-2-methoxyphenyltosylate as the only product.



Use of aryl fluorides was more successful. 2,4,5-Tribromofluorobenzene and 2,4,6-tribromofluorobenzene reacted with 4-bromoguaiacol easily and gave excellent yields of **1** and **2**, respectively. Reaction of 2,4-dibromofluorobenzene with 4-bromoguaiacol and 2-bromo-4-methoxyphenol was slower, but also gave good yields of **5** and **6**. We also checked this way for the preparation of **3** and **4**. In this case reaction was very slow, and therefore cannot be recommended

as a practical method. This influence of structure of reactants on the reaction rate is in perfect agreement with general rule: electron-withdrawing substituents (in this case – Br) in substrate favor the reaction, while those in a nucleophile decelerate it.

We used HBr in boiling AcOH as a reagent for conversion of methoxy-PBDEs into hydroxy-PBDEs. This reaction can be recommended as general synthetic method for the title compounds. Synthesis of all compounds is given on Scheme 1. Structure of all synthesized compounds was confirmed by ^{1}H NMR (Table 1). MP and NMR data for **4a** is in agreement with previously reported in literature[6].



Scheme 1. Synthesis of 6 Methoxy-PBDEs and 6 Hydroxy-PBDEs. Br atoms are omitted. For the explanation of A, B, C, D see: Materials and Methods.

WARNING: Polybromodibenzodioxins can be formed in all reactions described in this work. In fact, we observed their formation in many cases (yields up to 5-10%), and were able to separate several PBDDs as crystalline solids.

Table 1. Melting points, RRTs and ^{1}H NMR spectral data of 6 MeO-PBDEs and 6 HO-PBDEs.

No.	MP	RRT	^{1}H NMR Chemical shift δ, (ppm from TMS)*								Coupling constant J (Hz)			
			H3	H5	H6	H3'	H5'	H6'	O-CH_3	OH	H3/ H5	H5/ H6	H3'/ H5'	H5'/ H6'
1	151	1.021	7.83	-	6.86	7.14	7.10	7.88	3.81	-	-	-	2	8.5
1a	153	1.052	7.88	-	7.16	7.24	7.01	6.69	-	5.59	-	-	2.3	8.6
2	88	0.983	7.74	7.74	-	7.12	6.91	6.25	3.96	-	-	-	2.2	8.6
2a	166	0.993	7.77	7.77	-	7.20	6.87	6.26	-	5.78	-	-	2.2	8.6
3	91	1.050	7.76	7.34	6.67	7.22	-	7.09	3.83	-	2.3	8.7	-	-
3a	111	1.056	7.81	7.46	6.93	7.34	-	6.89	-	5.66	2.2	8.7	-	-
4	122	1.008	7.74	7.23	6.31	7.08	7.40	-	3.77	-	2.3	8.8	2.1	-
4a	177	1.000	7.78	7.29	6.44	7.21	7.34	-	-	5.54	2.2	8.8	2.1	-
5	54	0.872	7.74	7.29	6.59	7.12	7.06	6.80	3.81	-	2.4	8.7	2.2	8.5
5a	Oil	0.875	7.79	7.40	6.61	7.22	6.96	6.86	-	5.64	2.2	8.7	2.2	8.6
6	62	0.903	7.75	7.28	6.51	7.18	6.85	6.96	3.81	-	2.3	8.8	2.9	9.0
6a	93	0.974	7.75	7.29	6.52	7.15	6.79	6.91	-	4.85	2.3	8.7	2.9	8.8

*- There is some uncertainty in assignment of H-3'/H-6' in **3** and **3a**, and of H3'/H-5' in **4** and **4a**

Methods and Materials.

Brominated methoxyphenoles, fluorobenzenes, phenyltosylates and tetrabromodiphenyliodonium chloride were prepared by common methods.

GC conditions were selected as follows: GC-Varian 3700, injector Gerstel split/splitless at 250^{o}C, splitless injection, column – DB-5 (ca. 50m, 0.25 mm i.d., film thickness 0.1μm), detector, electron capture detector at 300^{o}C, carrier gas, nitrogen at flow rate 1.33ml/min, make-up gas, nitrogen at 40ml/min. The temperature program was selected as follows: 160 ^{o}C(2 min), then 20 ^{o}C/min to 280 ^{o}C, 10 min isothermal. RRTs determined against **4a** with RT = 12 min 11s.

NMR spectra were recorded on a Bruker DMX-300.

Methods on Scheme 1: A. Boiling with K_2CO_3 in DMF for 30min; dilution with water. B. Boiling with AcOH/HBr(48%), 2:1 for 2-10 hours; dilution with water. C. Boiling with 5% aqueous NaOH for 1-4 hours. D. Boiling with K_2CO_3 in DMF for 2-10 hours; dilution with water. In all syntheses target compounds were isolated by separation of organic part on silicagel column with hexane, followed by crystallizations.

Acknowledgements

Invaluable cooperation of NMR laboratory of St.Petersburg University is gratefully acknowledged. We would like to thank Dr. Michael Ikonomou(Institute of Ocean Sciences, Sidney, BC, Canada) for the inspiration and financial support of this work.

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