

IMPROVED SYNTHESIS OF POLYBROMINATED DIPHENYL ETHERS VIA IODONIUM SALT COUPLING

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Abstract

Improvements in PBDEs synthesis have been developed regarding coupling of (poly)bromophenolates with symmetrical (poly)bromodiphenyliodonium salts. The synthesis of symmetrical hexabrominated diphenyliodonium salts is described for the first time, i.e. the 2,2',4,4',5,5'- and 2,2',4,4',6,6'-hexabromodiphenyliodonium salts. This has resulted in the preparation of new PBDE congeners via symmetrical diphenyliodonium salt coupling, up to the octabromination level, and higher yields have been obtained compared to the traditional coupling method, especially for congeners containing six or more bromine atoms.

Introduction

Polybrominated diphenyl ethers (PBDEs) are a class of brominated flame retardants (BFRs) with special environmental interest, because of their presence in wildlife and humans. Industrial mixtures of PBDEs i.e. the "PentaBDE", "OctaBDE" and "DecaBDE" have been used in high volumes as additives in a variety of articles and products, e.g. in plastic materials, textiles, coatings, and electrical components found in many common goods including, computers, televisions, and electrical appliances¹. PBDEs are today ubiquitous environmental contaminants found in for example human blood plasma and milk²⁻⁴.

Pure authentic PBDE congeners are needed in environmental research to allow qualitative and quantitative exposure assessments, toxicological studies and studies on their chemical/physical properties e.g. photolysis. Reported synthetic methods for authentic PBDE congeners containing 1-7 bromine atoms include basically; bromination of diphenyl ether or a PBDE⁵⁻⁷; bromophenols coupled with symmetrical^{5,8} or unsymmetrical⁸ bromodiphenyliodonium salts; aromatic nucleophilic substitution reactions (S_NAr) by coupling bromophenols with bromofluoronitrobenzenes followed by reduction of the nitro group, diazotization and Sandmeyer reaction⁸; Suzuki coupling by reacting bromophenol with bromoarylboronic acids⁸; Ullmann diphenyl ether synthesis by coupling bromophenol with bromobenzene⁷.

The aim of the present work was to develop a robust diphenyliodonium salt coupling method that is suitable independently of the number of bromine atoms present at the target PBDE, and to prepare relevant symmetrical diphenyliodonium salts at the hexabrominated level, giving opportunities to synthesize a wider range of PBDE congeners than previously reported, i.e. diphenyl ethers with up to eight bromines.

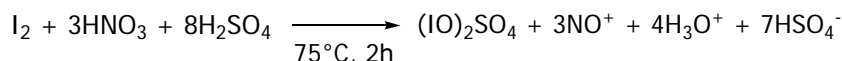
Experimental section

General Remarks

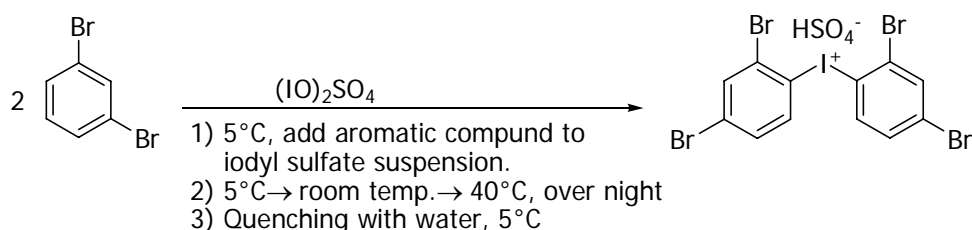
Melting points were determined with a Büchi 353 apparatus. Products were also characterized by GC-MS in EI mode and NMR (data not shown). All organic extracts were dried with anhydrous sodium sulfate before the solvent was evaporated in a rotary evaporator under reduced pressure at temperatures not exceeding 35°C. Silica gel column chromatography was carried out using MATREX Silica, 60 Å, 35–70 µm, Millipore (Bedford, USA). All solvents, acids and other chemicals used were of pro analysis quality. 2,3,4,6-Tetrabromophenol was prepared from 3-bromophenol (not shown) and all other starting materials were commercially available.

Synthesis

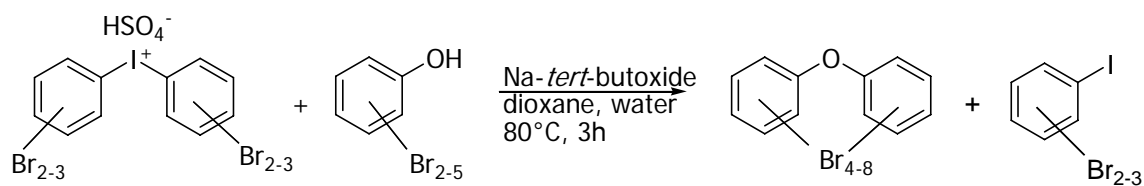
Bromodiphenyliodonium salts: Iodol sulfate was prepared by oxidizing iodine in sulfuric acid and nitric acid (Figure 1). The method was slightly modified as previously described^{9,5}. A solution of concentrated sulfuric acid (13.0 mL) and fuming sulfuric acid (65 %, 6.5 mL) was added dropwise to iodine (5.43 g; 21.4 mmol) under stirring. A solution of concentrated sulfuric acid (1.7 mL), fuming sulfuric acid (65%; 0.8 mL) and fuming nitric acid (100%; 3.0 mL) was slowly and dropwise added to the reaction, which was heated at 75°C for 2 h.

**Figure 1** Synthesis of iodyl sulfate

The reaction mixture was diluted with conc. sulfuric acid (20 mL) and cooled to 5°C before slow addition of bromobenzen (106 mmol). Thereafter the temperature was allowed to rise to room temperature and the mixture was stirred at 40°C for 12 h regarding 2,4-dibromobenzene, 24 h for 2,4,5-tribromobenzene and 72 h for 1,3,5-tribromobenzene. The reaction was carefully quenched with water (100 mL) on an ice-bath. The nitrogen oxides were driven off, using nitrogen. The salt was washed with water (ca. 3 × 100 mL) to obtain neutral pH, before drying in a desiccator. The crude product was washed with toluene 100 mL and dried. Finally, the product was dissolved in acetonitrile and residues of halobenzenes were removed by washing with hexane. 2,2',4,4'-Tetrabromodiphenyliodonium sulfate (I) (25.4 g; 37 mmol; 87 %), 2,2',4,4',5,5'-hexabromodiphenyliodonium sulfate (II) (19.8 g; 23 mmol; 55 %) and 2,2',4,4',6,6'- hexabromodiphenyliodonium sulfate (III) (20.4 g; 24 mmol; 57%) were obtained after evaporation of the solvent.

**Scheme 1** Synthesis of 2,2',4,4'-tetrabromodiphenyliodonium sulfate.

General coupling procedure for the preparation of PBDEs (Scheme 2): The bromophenol (2.5 mmol) and sodium *tert*-butoxide (2.75 mmol) were dissolved in water (45 mL) and dioxin (90 mL) at room temperature. The bromodiphenyliodonium sulfate (3.0 mmol) was slowly added and the solution was heated to 80°C for 3h.

**Scheme 2** The general coupling of a bromophenolate and a bromodiphenyliodonium salt.

The solution was diluted with water (25 mL) and extracted with dichloromethane (3 × 50 mL). The organic phase was washed with sodium hydroxide (1 M; 100 mL) and water (1 × 100 mL), and dried. The crude product was purified from bromiodobenzene, on an open silica gel column with hexane as the mobile phase. The PBDE product was eluted through a charcoal-celite column in order to eliminate any potential polybrominated dibenzo-*p*-dioxins and/or dibenzofurans being formed in the synthesis. One gram charcoal:celite (1:4) were used for each 100 mg of the PBDE product. Finally the products were recrystallized and analyzed. The purity of the compounds was determined using GC-MS, HPLC-UV and by melting point measurements.

Result and Discussion

The improved symmetrical bromodiphenyliodonium salt coupling with water and dioxane in 1:2 ratios gave single congeners in a purity of 98 to over 99%, and in yields ranging between 21 and 84% (Table 1).

Table 1 The PBDE abbreviation number, bromine positions, starting building block, yield and melting points of the synthesized PBDE congeners are presented in the table.

PBDE, no	Structure	Iodonium salt	Bromophenol	Yield (%)	Mp (°C)
47	2,2',4,4'	I	2,4	60	82.6-83.0
99	2,2',4,4',5	II	2,4	40	85.2-87.0
100	2,2',4,4',6	I	2,4,6	84	97.6-98.0
139	2,2',3,4,4',6	I	2,3,4,6	64	126.7-127.5
154	2,2',4,4',5,6'	II	2,4,6	67	137.8-138.2
155	2,2',4,4',6,6'	III	2,4,6	21	150.5-153.8
183	2,2',3,4,4',5',6	II	2,3,4,6	59	169.5-170.5
184	2,2',3,4,4',6,6'	III	2,3,4,6	24	143-144.8
203	2,2',3,4,4',5,5',6	II	2,3,4,5,6	50	234.0-234.6
204	2,2',3,4,4',5,6,6'	III	2,3,4,5,6	29	185.2-186.4

Traditionally, PBDE synthesis via symmetrical bromodiphenyliodonium salt couplings has been carried out in water with equivalent amounts of the (bromo)phenol, the bromodiphenyliodonium salt and with sodium hydroxide as the base. This method works rather well for the synthesis of PBDE congeners containing up to 4-5 bromine atoms. However, synthesis of PBDE congeners containing more than 4-5 bromine atoms results in poor yields mainly due to solubility problems. For this reason the improved method includes, larger solvent volumes and the use of 1,4-dioxane as co-solvent to water. The best results were obtained in water/dioxane when a ratio of 1:2 was applied. Further, to minimize side-reactions, the temperature has been lowered and the use of *tert*-butyloxy instead of hydroxide as the base, eliminate possible formation of unwanted phenols from the bromodiphenyliodonium salt, which in turn might give a symmetrical PBDE by-product. Finally, a slight excess of the base and the bromodiphenyliodonium salt (1.2 equiv.) was used in order to receive higher yields.

The symmetrical iodonium salts, 2,2',4,4',5,5'-hexabromoiodonium salt (55% yield) and 2,2',4,4',6,6'-hexabromoiodonium salt (57% yield) have been prepared for the first time. The synthesis of these salts has previously failed due to solubility problems. However, compared to the traditional bromodiphenyliodonium salt synthesis, more sulfuric acid was added prior to the addition of the actual bromobenzene and longer reaction times were used as well. An unsymmetric bromodiphenyliodonium salt has previously been used for the preparation of a 2,4,5-tribromo substitution pattern of the PBDE product. However, the 2,2',4,4',5,5'-hexabromoiodonium salt also gives the 2,4,5-tribromo- pattern, but compared to the unsymmetric bromodiphenyliodonium salt, fewer steps in the synthesis are required to obtain the diphenyliodonium salt product.

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