Russian Journal of Organic Chemistry, Vol. 38, No. 3, 2002, pp. 374–377. Translated from Zhurnal Organicheskoi Khimii, Vol. 38, No. 3, 2002, pp. 396–399.

Polybromoaromatic Compounds: X.* Reactions of Polybromobenzenes with Primary and Secondary Amines

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Received May 10, 2001

Abstract—Polybromobenzenes C_6Br_5X (X = Br, F, CN, NO_2) react with primary amines (methylamine and cyclohexylamine) to give nucleophilic substitution products; reactions of the same substrates with secondary amines (dimethylamine, diethylamine, piperidine, and morpholine) are accompanied by hydrodebromination processes.

We previously showed that reactions of polybromofluorobenzenes with sodium alkoxides in pyridine [2, 3] or methanol [4] result exclusively in replacement of the fluorine atom by alkoxy group, in keeping with the known halogen mobility order in aromatic nucleophilic substitution (S_NAr). However, the major pathway in the reactions of pentabromofluorobenzene with morpholine or piperidine is replacement of bromine by the amine residue, and the process is accompanied by hydrodebromination to an appreciable extent [2]. The reasons for such behavior of C_6Br_5F in the reactions with morpholine and piperidine are not clear.

In continuation of our previous studies, in the present work we examined reactions of substituted polybromobenzenes C_6Br_5X (X = Br, F, NO_2, CN) with some primary (methylamine and cyclohexylamine) and secondary amines (dimethylamine, diethylamine, piperidine, and morpholine). The reactions of C_6Br_6 and C_6Br_5F with methylamine, dimethylamine, and diethylamine were carried out in pyridine under pressure, and those with cyclohexylamine, morpholine, and piperidine, in a large excess of amine under reflux. The results are given in Tables 1 and 2.

The reaction of hexabromobenzene with excess methylamine was fairly slow. After 72 h (20°C), only initial hexabromobenzene was isolated from the reaction mixture. When the mixture was heated for 5 h at 100°C, the conversion of C_6Br_6 was 61%, the major product was *N*-methylpentabromoaniline, and a small amount of disubstituted products was obtained (Table 1). The complete conversion of hexabromobenzene was observed when the mixture was heated for 8 h at 100°C; in this case the yield of hydrodebromination products increased to 6%, the yield of disubstituted products was 19%, and two unidentified compounds were formed (~8%). The reaction of hexabromobenzene with dimethylamine under the same conditions was even slower. After 15 h, the conversion of C_6Br_6 was as low as 50%, and the major product was *N*,*N*-dimethylpentabromoaniline; also, products of reductive debromination were detected. Diethylamine turned out to be less reactive toward C_6Br_6 than dimethylamine. Under the above conditions (15 h, 100°C), the conversion of hexabromobenzene did not exceed 40%, and the major products were those formed by hydrodebromination (Table 1). Also, up to 25% of a mixture of compounds soluble in sulfuric acid was found (9 components, according to the GLC data). Obviously, these compounds contain an amine residue and their concentrations in the mixture are comparable.

A slow reaction occurred on heating of hexabromobenzene with a large excess of cyclohexylamine at the boiling point. After 5.5 h, the reaction mixture still contained traces of initial hexabromobenzene. The products were *N*-cyclohexylpentabromoaniline (major), pentabromobenzene (~2%), and unidentified compound whose concentration increased as the reaction was prolonged (this compound appeared in the mixture even at a C_6Br_6 conversion of ~70%).

As follows from the data in Table 1, the reaction of C_6Br_6 with amines includes mainly two competing

* For communication IX, see [1].

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Table 1. Reactions of hexabromobenzene with amines (Nu)

Nucleophile Nu	Time, h (temperature, °C)	Conversion of C_6Br_6, %	Product composition, %				
			$C_6Br_4H_2$	C_6Br_5H	C_6Br_5Nu	C_6Br_4HNu	disubstituted and unidentified products
CH_3NH_2	5 (100)	61	Traces	Traces	92		9
cyclo-$C_6H_{11}NH_2$	5.5 (135)	96	Traces	2	94		5
$(CH_3)_2NH$	15 (100)	40	4	30	54		12
$(C_2H_5)_2NH$	15 (100)	30	23	53			25 (9 substances)
Piperidine	10 (106)	82	8	26	32	33	Traces
Morpholine	10 (128)	74	1	26	53	20	Traces

Table 2. Reactions of pentabromofluorobenzene with amines (Nu)

Nucleophile Nu	Time, h (temperature, °C)	Conversion of C_6Br_6, %	Product composition, %				
			C_6Br_4HF	C_6Br_5Nu	C_6Br_4FNu	C_6Br_3HFNu	disubstituted and unidentified products
CH_3NH_2	72 (20)	100	–	97	–	–	30
cyclo-$C_6H_{11}NH_2$	1 (135)	96	3	90	–	–	67
$(CH_3)_2NH$	6 (100)	71	7	34	32		28
$(C_2H_5)_2NH$	10 (100)	20	55				45
Piperidine	10 (106)	78	22	4	64	10	~0.5
Morpholine	10 (128)	76	18	Traces	71	11	Traces

processes: nucleophilic substitution of bromine by the amine residue and hydrodebromination. Their relative contributions are strongly determined by steric factor. Primary amines (methylamine and cyclohexylamine) give rise mainly to nucleophilic substitution products. As the size of nucleophile increases, the contribution of hydrodebromination rises: in the reactions with dimethylamine, piperidine, and morpholine the contributions of nucleophilic substitution and hydrodebromination processes are comparable, while the latter process predominates in the reaction with diethylamine.

Pentabromofluorobenzene reacts with methylamine and cyclohexylamine at a much higher rate than does hexabromobenzene, and the major products are those formed by replacement of the fluorine atom by the amine residue (Table 2). The reactions of C_6Br_5F with secondary amines (piperidine, morpholine, dimethylamine, and diethylamine) are accompanied by hydrodebromination whose contribution ranges from 18 to 61% (it is lesser than in the reactions with hexabromobenzene, where the contribution of hydrodebromination ranges from 34 to 75% under analogous conditions). The main process is nucleophilic substitution of bromine rather than fluorine atom, and the rates of the reactions of C_6Br_5F and C_6Br_6 with the above amines (except for dimethylamine) are comparable. Unfortunately, we failed to determine the site of bromine replacement in C_6Br_5F in reactions with secondary amines. Probably, the orientation of halogen replacement in reactions of C_6Br_5F with primary and secondary amines strongly depends on steric factors. Primary amines replace the labile fluorine atom in C_6Br_5F. In reactions with secondary amines which are bulkier nucleophiles less labile bromine atoms in the *ortho* position with respect to fluorine are replaced, for they are considerably less shielded than the fluorine atom having two neighboring bromine atoms. Analogous change of orientation with increase in the size of nucleophile was observed in reactions of pentachlorobenzene with ammonia [5], methylamine [6], and diethylamine [7], where the contribution of *ortho*-substitution (with respect to hydrogen) sharply increased in the respective order.

Polybromoaromatic compounds C_6Br_5X reacted with cyclohexylamine in pyridine (115°C) at a very

low rate. The conversion of C_6Br_6 was only 20% in 10 h, whereas the reaction of hexabromobenzene with sodium methoxide under similar conditions is complete in less than 5 min (the corresponding rate constants differ by more than 5 orders of magnitude [8]). Strong electron-acceptor groups, such as NO_2 and CN, notably increase the rate of nucleophilic substitution in polybromaromatic ring: $k_{ap}(C_6Br_5X) \times 10^5$, l mol^{-1} × s^{-1}: 0.8 ± 0.3 (X = Br), 27.6 ± 7.8 (X = NO_2), 430 ± 12 (X = CN). It should be noted that the reaction of pentabromonitrobenzene with cyclohexylamine gives products of replacement of the nitro group and bromine atom at a ratio of 1 : 2.5 (according to the GLC data). The site of bromine replacement was not determined.

The reactions of $C_6Br_5NO_2$ and C_6Br_5CN with piperidine and morpholine were carried out in a way similar to that reported in [2] for C_6Br_5F and C_6Br_6. Pentabromonitrobenzene reacts with piperidine at a sufficiently high rate. Even after 1 h, the initial pentabromonitrobenzene disappears from the reaction mixture. The major products had very similar retention times, so that we failed to separate them. In the ^{1}H NMR spectrum of the product mixture we observed a six-proton multiplet signal in the region δ 1.37–1.87 ppm and three multiplets at δ 2.45–2.66, 2.66–2.93, and 2.93–3.37 ppm with an overall intensity corresponding to 4 protons. The ^{1}H NMR spectrum of *N*-(pentabromophenyl)piperidine (as a possible product of replacement of the nitro group) contains two multiplets in the regions δ 1.45–1.88 ppm (6H, 2β- and γ-CH_2) and 2.90–3.28 ppm (4H, 2α-CH_2) [2]. The product mixture showed in the IR spectrum strong absorption bands at 1560 and 1330 cm^{-1}, which are typical of symmetric and antisymmetric stretching vibrations of a nitro group in polybromoaromatic ring [9, 10]. Thus, the spectral data suggest that the reaction involves replacement of both bromine atom and nitro group, but we did not succeed in estimating the contribution of each of these processes.

Likewise, the reaction of pentabromonitrobenzene with morpholine led to formation of a complex mixture of products, but at a lower rate. We failed to isolate any individual product by column chromatography on silica gel or aluminum oxide (using hexane and petroleum ether–benzene as eluent) or by gradient reprecipitation with water from concentrated H_2SO_4.

We measured the rates of the reactions of some polybromoaromatic compounds with morpholine and piperidine using excess reagent as solvent. The kinetic curves were linear in the coordinates typical of pseudofirst-order reactions, $k(C_6Br_5X) \times 10^3$, s^{-1}: 0.033 ± 0.009 (piperidine, 106°C, X = Br); 0.047 ± 0.008 (X = F); 2.8 ± 1.8 (X = NO_2), 35.6 ± 6 (X = CN); 0.020 ± 0.006 (morpholine, 128°C, X = Br), 0.044 ± 0.011 (X = F); 0.56 ± 0.2 (X = NO_2); 7.4 ± 2.4 (X = CN). It is seen that reactions of polybromoaromatic compounds with piperidine are faster than with morpholine; obviously, the reason is that piperidine is a stronger base than morpholine (by 3 orders of magnitude [11]).

The rates of the reactions of pentabromobenzonitrile with the amines under study exceed those for the reactions of pentabromonitrobenzene with the same amines by more than an order of magnitude: $k(C_6Br_5CN)/k(C_6Br_5NO_2) \approx 12.4$ (piperidine), 13.2 (morpholine), 15.8 (cyclohexylamine), though the cyano group is usually a weaker electron acceptor than NO_2 [11]. These data indicate partial distortion of conjugation between the nitro group and the aromatic ring, caused by steric effect of the *ortho*-bromine atoms. A similar pattern was observed by us while studying reactions of analogous polybromoaromatic compounds with sodium methoxide [12].

EXPERIMENTAL

The IR spectra were recorded on a UR-20 spectrometer in mineral oil. The ^{1}H NMR spectra were measured on Tesla BS-467 (60 MHz) and Bruker AC-200 (200 MHz) instruments using HMDS as internal (with CCl_4 or $CDCl_3$ as solvent) or external reference (DMSO-d_6). The initial compounds, final products, and reaction mixtures were analyzed by GLC on a Chrom-42 chromatograph using glass columns 3000 × 3.5 mm and 1500 × 3.5 mm, packed with 5% of OV-17 on Chromaton N-Super (0.16–0.20 mm) and 5% of SE-30 on Chromaton N-AW-HMDS (0.16–0.20 mm); oven temperature 200–260°C; thermoionic detector; carrier gas nitrogen.

Hexabromobenzene [8], pentabromofluorobenzene [13], pentabromonitrobenzene [9], pentabromobenzonitrile [9], pentabromoaniline [14], and *N*-methylpentabromoaniline [12] were synthesized by known procedures.

***N,N*-Dimethylpentabromoaniline.** A mixture of 2.5 g of pentabromoaniline and 10 ml of freshly distilled dimethyl sulfate was heated for 3 h at 130°C under vigorous stirring, 50 ml of a 5% aqueous solution of NaOH was added, and the mixture was heated for 0.5 h under reflux. The precipitate was filtered off, washed with water, dried, and recrystallized from 2-propanol. Yield 2.2 g (87%), mp 80–81°C. IR spectrum, cm^{-1}: 760 w, 855 m, 1000 s, 1085 w, 1125 w, 1215 w, 1275 w, 1315 m, 1332 m, 1547 m. ^{1}H NMR spectrum (CCl_4), δ, ppm: 2.75 s (NMe_2).

Reactions of hexabromobenzene and pentabromofluorobenzene with methylamine and dimethylamine. A glass ampule was charged with 0.5 mmol of appropriate polybromoaromatic compound and 3 ml of pyridine. The ampule was cooled, and 1 ml of methylamine or dimethylamine was condensed thereto. The ampule was evacuated and sealed and was then heated at a specified temperature. At definite time intervals the ampule was opened, and the mixture was analyzed by GLC and ^{1}H NMR spectroscopy.

Reactions of hexabromobenzene and pentabromofluorobenzene with cyclohexylamine. A mixture of 2 mmol of appropriate polybromoaromatic compound and 4 ml of cyclohexylamine was heated at the boiling point over a specified period. Excess cyclohexylamine was evaporated under reduced pressure, and the residue was washed with dilute hydrochloric acid and water, dried, and analyzed. Recrystallization from petroleum ether (bp 70–100°C) gave colorless crystals of *N*-cyclohexylpentabromoaniline; yield 76% (from C_6Br_6) and 82% (from C_6Br_5F), mp 88–89°C [3]. IR spectrum, ν, cm^{-1}: 740 m, 820 w, 900 w, 940 w, 1090 m, 1170 w, 1260 w, 1310 w, 1330 w, 3360 w. ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 1.09–2.02 m (10H, 2β-CH_2, 2γ-CH_2, 2δ-CH_2), 3.50–3.69 m (1H, CH), 4.11 s (1H, NH).

The kinetic measurements for reactions of polybromoaromatic compounds with cyclohexylamine in pyridine were performed as described in [8] for the methoxydebromination reaction [8].

Reactions of polybromoaromatic compounds with cyclic amines. A 50-ml portion of piperidine or morpholine was heated to the boiling point, and 6 mmol of appropriate polybromoaromatic compound was added. At definite time intervals 4-ml samples of the mixture were withdrawn, poured into 3% hydrochloric acid, and treated with benzene, and the extract was dried and evaporated. The residue was analyzed by GLC and ^{1}H NMR and IR spectroscopy.

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