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Practical and Efficient Synthesis of 4,4′-Dihydroxy-3,3′-dinitrodiphenyl Ether and 1,3-*bis*(4-Hydroxy-3-nitrophenoxy)benzene in Aqueous Alkaline Medium

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4,4′-Dihydroxy-3,3′-dinitrodiphenyl ether (**4**) and 1,3-*bis*(4-hydroxy-3-nitrophenoxy) benzene (**9**) are valuable precursors of 3,3′-diamino-4,4′-dihydroxydiphenyl ether[1] (**5**) and 1,3-*bis*(3-amino-4-hydroxyphenoxy)benzene[2] (**10**) respectively. The latter two compounds are interesting because of their amphoteric properties in acid-base behavior[3] and as precursors of symmetrical *bis*phenolic Mannich derivatives of biological interest.[4] Furthermore, they are also important starting materials for thermally stable plastics such as polyamides, polyarylates, polyimides and polybenzoxazoles, which are especially useful as positive-working photosensitive polymer precursor compositions to form electric interlayer insulators and protective films for semiconductors.[5–11]

The critical problem is the synthesis of **4** and **9** as precursors of **5** and **10**. So far, their synthesis has involved the nitration of 4,4′-dihydroxydiphenyl ether[4,7] and 1,3-*bis*(4-hydroxyphenoxy)benzene.[2] However, the preparation of these compounds[12–33] suffers from very serious problems such as low yields due to low conversion, formation of many undesired by-products, the use of high reaction temperatures and of environmentally harmful reagents.

In contrast, 4,4′-diaminodiphenyl ether (**1**) and 1,3-*bis*(4-aminophenoxy)benzene (**6**) are commercially available and can be selectively nitrated, providing 4,4′-diamino-3,3′-dinitrodiphenyl ether (**3**) and 1,3-*bis*(4-amino-3-nitrophenoxy)benzene (**8**) quantitatively.[34,35] Although compound **4** could be obtained by decomposition of the

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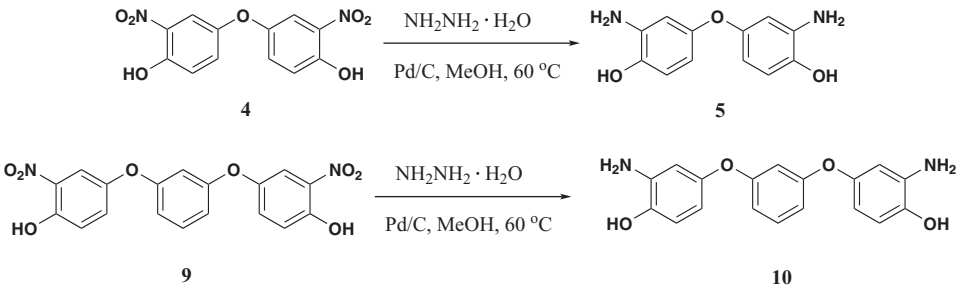
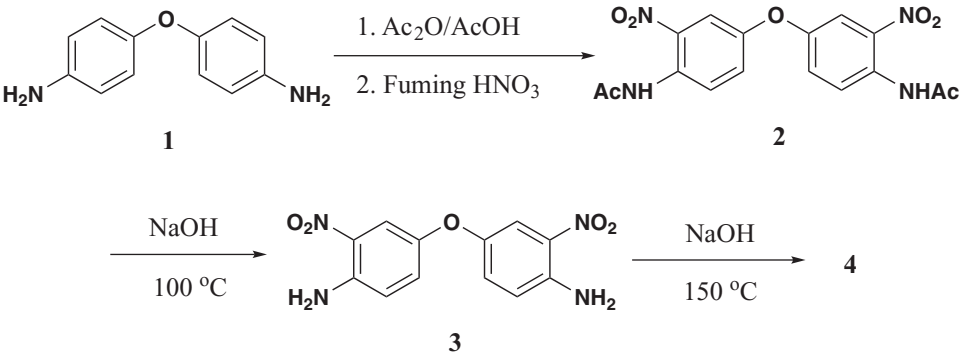


Scheme 1

diazonium salt derived from **3** *via* the Sandmeyer reaction, the yield was very low due to many undesired by-products which required complicated purification.

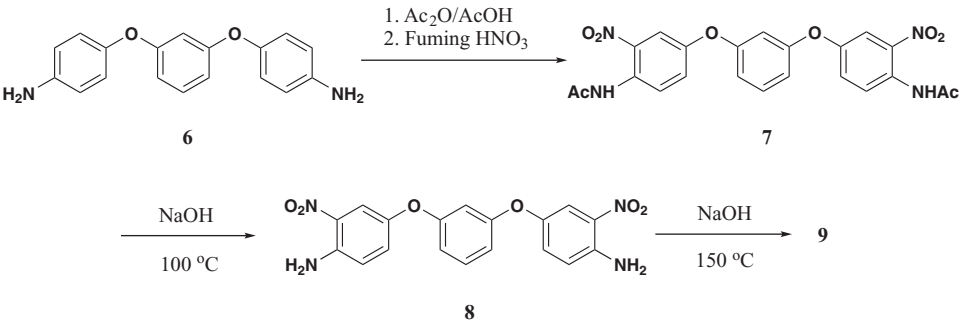
So far, there has been no study on reactions to convert dianilines directly into corresponding diphenols. Although the amino group is generally considered a much poorer leaving group than halide ions in aromatic nucleophilic substitution reactions, there are examples of replacement of aromatic amino groups activated by one or more nitro groups in aqueous alkaline solutions or aqueous organic solvents, providing corresponding phenols,[36–42] naphthols[43] and quinolinols.[44] However, most applications of the reaction are limited to very activated substrates such as derivatives of 2,4,6-trinitroaniline, 2,4-dinitroaniline.

Thus, the investigations of the reactions of **3** and **8** with hydroxide ion have been neglected for a long time. It was thought, however, that amino groups of **3** and **8**, which have only one nitro group *ortho* to the amino group, might become good leaving groups, if the amino groups are protonated and turned into $ArNH_3^+$ in water. From these considerations, the direct conversion of the amino groups might prove to be a practical synthetic methods of **4** and **9**. This consideration prompted us to investigate the direct conversion of **3**, **8** and of their acetylated derivatives (**2** and **7**) into **4** and **9** in aqueous alkaline media.



Scheme 2

Commercially available **1** and **6** were used without further purification. 4,4′-*bis*(*N*-Acetylamino)-3,3′-dinitrodiphenyl ether (**2**) was obtained form **1** in excellent yield. The deacetylation of **2** provided **3** quantitatively. 1,3-*bis*(4-*N*-Acetylamino-3-nitrophenoxy)benzene (**7**) was obtained in the same manner.



Scheme 3

The substitution of **3** in aqueous alkaline media was examined and the results are summarized in *Table 1*. The reaction was very slow at 100°C (*Entries 1* and *2*), but was very rapid at 150°C (*Entry 3*) and provided **4** in an excellent yield after neutralization. Higher concentration of sodium hydroxide (*Entry 4*) or addition of tetrabutylammonium chloride (*Entry 5*) accelerated the reaction only slightly. Use of tetrabutylammonium hydroxide in place of sodium hydroxide at 100°C (*Entry 6*) showed somewhat more acceleration albeit the yield of **4** was only 23% due to the high solubility of **9** in 1.5 M aqueous tetrabutylammonium hydroxide solution. However, cumbersome purification processes were required to remove a large amount of tar generated through the decomposition of quaternary ammonium ions with hydroxide ions (Hoffmann elimination). Under these conditions, the main product was 4-amino-4′-hydroxy-3,3′-dinitrodiphenyl ether (**11**) formed in 50% yield.

The reaction of **2** and **7** in aqueous sodium hydroxide was examined at 150°C in an autoclave and the results are shown in *Table 2*. Even when the acetylated derivative **2** was used, the deacetylation and the hydroxylation proceeded simultaneously to give **4**

Table 1
Hydrolysis of **3** into **4** in 1.5 M Aqueous Sodium Hydroxide

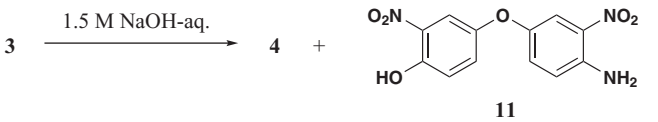
Entry	Temp. (°C)	Time (h)	Recovery of **3** (%)	Yield of **4** (%)	Yield of **11** (%)
1	100	1	100	0	0
2	100	10	93	2	0
3	150[a]	1	0	97	0
4[b]	100	1	91	2	5
5[c]	100	1	90	2	6
6[d]	100	1	21	23	50

[a]Carried out in an autoclave. [b]6.0 M Sodium hydroxide was used. [c]Tetrabutylammonium chloride (10 mol %) was added. [d]1.5 M Aqueous tetrabutylammonium hydroxide was used instead of sodium hydroxide.

Table 2
Hydrolysis in 1.5 M Aqueous NaOH at 150 °C[a]

Entry	Substrate	Product	Time (h)	Yield (%)
1	**2**	**4**	1	98
2[b]	**7**	**9**	5	100

[a]Carried out in an autoclave. [b]3.0 M aqueous sodium hydroxide was used.



in excellent yields. Similarly, the hydroxylation of diacetylated derivative **7** provided **9** quantitatively, though higher concentration of sodium hydroxide and longer reaction time were required.

The Pd-charcoal-catalyzed hydrogenation of **4** and **9** with aqueous hydrazine hydrate in methanol provided **5** and **10** in excellent yields, respectively.

In conclusion, we have developed an efficient synthesis of 3,3′-diamino-4,4′-dihydroxydiphenyl ether (**5**) and of 1,3-*bis*(3-amino-4-hydroxyphenoxy)benzene (**10**) by the facile and direct conversion of 4,4′-diamino-3,3′-dinitrodiphenyl ether (**3**) and 1,3-*bis*(4-amino-3-nitrophenoxy)benzene (**8**) into 4,4′-dihydroxy-2,2′-dinitrodiphenyl ether (**4**) and 1,3-*bis*(4-hydroxy-3-nitrophenoxy)benzene (**9**), respectively. The present method is environmentally friendly, because the reactions proceed in water without organic solvents and consume just one equivalent amount of H_2O to provide the target compounds, releasing ammonia as the sole by-product. Further studies directed toward expansion of the scope of application and elucidation of the mechanism are in progress in our laboratory.

Experimental Section

Melting points were determined on a Yamato MP-21 melting point apparatus. ^1H and ^{13}C NMR spectra were recorded at 400 MHz and 100 MHz, respectively (Bruker Co. Ltd., Avance 400) and mass spectra were recorded on an ESI-TOF/MS Per Septive Biosystems Mariner. A stainless-steel autoclave manufactured by Nac-autoclave Co. Ltd. (SIF-2 type, SUS316) was used for the reactions.

4,4′-Dihydroxy-3,3′-dinitrodiphenyl Ether (4)

In a 300 mL stainless-steel autoclave were placed 4,4′-diamino-3,3′-dinitrodiphenyl ether (9.3 g, 32.0 mmol) and 1.5 M sodium hydroxide aqueous solution (224 g, 336 mmol) and the mixture was heated and kept at 150°C for 1 h. TLC (silica gel 60, EtOAc/hexane 1:1) showed that the spot of the starting compound (Rf: 0.50) had disappeared and only the spot of 4,4′-dihydroxy-3,3′-dinitrodiphenyl ether (Rf: 0.85) appeared. The smell of ammonia indicated the satisfactory progress of the reaction. Upon cooling the solution and addition of 28.5 g (276 mmol) of 95% sulfuric acid, the red solution turned to an orange-colored slurry.

Then the slurry was cooled to 5°C and the precipitated orange-colored solid was collected. The solid was extracted into EtOAc (100 mL) and washed with water. The combined organic layer was dried over Na_2SO_4, and the solvent was removed under reduced pressure to give 9.0 g (97%) of 4,4′-dihydroxy-3,3′-dinitrodiphenyl ether (**4**) as an orange-colored solid, mp. 156–157°C (*lit:*[20] 156–157°C). The solid was sufficiently pure as confirmed by its NMR, though recrystallization from methanol gave orange colored needles (91%, mp. 157–158°C). ^{1}H-NMR (400 MHz, DMSO): δ 7.17 (d, 2H, Ph), 7.35 (dd, 2H, Ph), 7.55 (d, 2H, Ph). ^{13}C-NMR (100 MHz, DMSO): δ 114.42, 120.55, 126.27, 136.50, 148.10, 148.46. *m/z* 291 (M-H).

1,3-bis(4-Hydroxy-3-nitrophenoxy)benzene (9)

1,3-*bis*(4-*N*-Acetylamino-3-nitrophenoxy)benzene (14.9 g, 32.0 mmol) was transformed into **9** as described above [3.0 M NaOH aqueous solution was used instead of 1.5 M NaOH aqueous solution. The reaction time was 5 h at 150°C] to yield 12.3 g (100%) of 1,3-*bis*(4-hydroxy-3-nitrophenoxy)benzene as an orange-colored solid, mp. 128–130°C (*lit*.[2] 128.5–130°C). ^{1}H-NMR (400 MHz, DMSO): δ 6.67 (s, 1H, Ph), 6.73 (d, 2H, Ph), 7.17 (d, 2H, Ph), 7.36 (d, 2H, Ph), 7.39 (t, 1H, Ph), 7.58 (s, 2H, Ph), 10.88 (br s, 2H, OH). ^{13}C-NMR (100 MHz, DMSO): δ 107.51, 112.37, 115.54, 120.60, 127.23, 131.28, 136.59, 147.00, 148.89, 158.48. *m/z* 383 (M-H).

The melting point, ^{1}H-NMR and ^{13}C-NMR are agreement with data given in the literature.[2]

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