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SYNTHESIS OF A NOVEL TYPE OF AROMATIC DIAMINES CONTAINING BOTH OXYGEN AND NITROGEN DONORS

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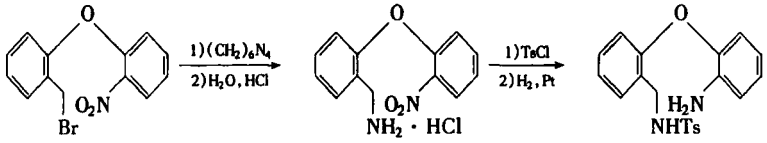
Abstract: A novel type of aromatic diamines (**20 ~ 28**) containing both oxygen and nitrogen donors were synthesized by Raney nickel-catalyzed hydrazine or amalgamated aluminum reduction of the corresponding nitro-compounds (**3, 12 ~ 19**), which were prepared by condensation of N-substituted nitrogen mustards (**4 ~ 11**) with 2-nitrophenol in the presence of potassium carbonate in DMF at 80 ℃ for 6 h.

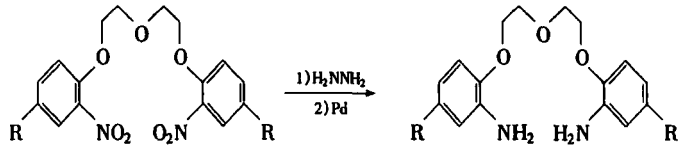
It is important to have simple and inexpensive methods to prepare diamine starting materials for the cyclization portion of the sequence to form azacrown compounds and macrocyclic Schiff bases, which are precursors of macrocyclic polyamines. A reduction process has been used to prepare aromatic diamines from nitro- and azide-containing ethers. The preparation of an aromatic diamine using known methods was reported by Glinka, who treated an aromatic nitro halide with hexamethylenetetraamine followed by hydrolysis to give an aromatic nitro amine. The nitro amine was reduced to the diamine



Scheme 1.

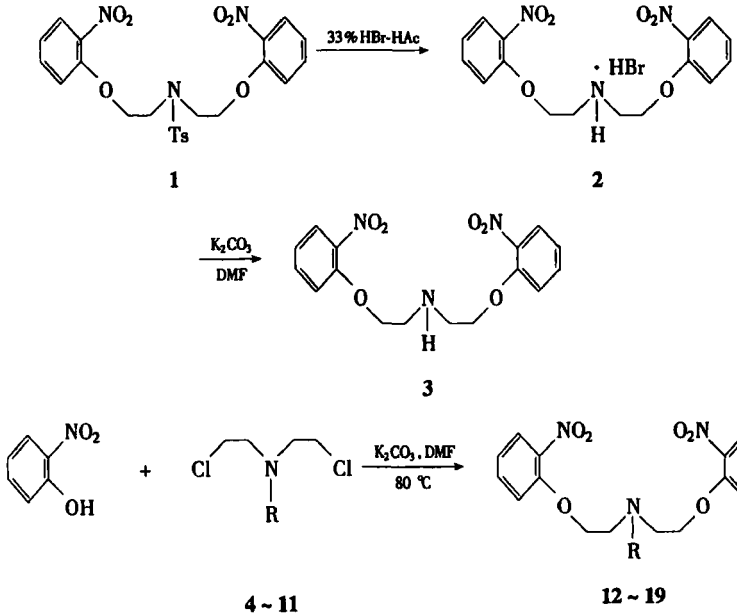
* To whom correspondence should be addressed.

after tosylation to block the original amine group[1](Scheme 1.). A palladium-catalyzed hydrazine or amalgamated aluminum reduction of some bis-nitro aromatic compounds appears to be a good method for the preparation of dianiline-substituted ether compounds[2~4](Scheme 2.).

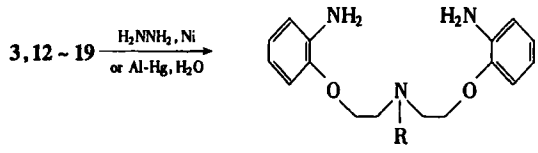


Scheme 2.

We report here the synthesis of a novel type of bis-aminoaromatic ethers containing nitrogen and oxygen donors (**20 ~ 28**). Detosylation of compound (**1**) using 33% HBr-HAc followed by Raney nickel-catalyzed hydrazine or amalgamated aluminum reduction gave 1,5-bis(2-aminophenoxy)-3-azapentane (**20**). Condensation of N-substituted nitrogen mustards with 2-nitrophenol in the presence of potassium carbonate in DMF at 80 ℃ for 6 h afforded 3-substituted 1,5-bis(2-nitrophenoxy)-3-azapentanes (**12 ~ 19**), which were converted to the corresponding diamines (**20 ~ 28**) by reduction using Raney nickel-catalyzed hydrazine or amalgamated aluminum (Scheme 3.).



1 **2** **3** **4 ~ 11** **12 ~ 19**



20 ~ 28

20; R = H

4,12,21; R: $CH_2CH=CH_2$ **5,13,22**; R: C_4H_9-n

6,14,23; R: C_5H_{11}-n **7,15,24**; R: $CH_2CH_2OCH_3$

8,16,25; R: $CH_2CH_2OC_2H_5$ **9,17,26**; R: $CH_2CH_2OC_4H_9$-n

10,18,27; R: $CH_2CH_2OCH_2CH_2OCH_3$ **11,19,28**; R: $CH_2CH_2OCH_2CH_2OC_4H_9$-n

Scheme 3.

Recently, attention has been given to the preparation of this type of diamines and synthesis of novel macrocycles utilizing them. We employed the above-mentioned diamines to synthesize macrocyclic Schiff bases bearing pandent arms[5].

Experimental

Melting points were determined on the microscope melting point apparatus and uncorrected. IR spectra were recorded on an SP 3-100 infrared spectrometer. ^1H NMR spectra were obtained on a Varian XL-200 (200MHz) NMR spectrometer using TMS as internal standard, $CDCl_3$ as a solvent. Mass spectra were carried out on a VG analytical ZAB – 3F – HFHF three-sector tandem mass spectrometer of BEB geometry. Elemental analyses were run on a Perkin-Elmer 204 elemental analyser.

3-Tosyl-1,5-bis(2-nitrophenoxy)-3-azapentane (**1**) was prepared according to the literature[6], yield 71 %, bp 131 ~ 132 ℃. N, N-bis(2-chcloroethyl) amines (**4 ~ 11**) were prepared by the method of Wu Chengtai et al[7]. Aluminum amalgam was prepared by the method described in the reference[8].

***Synthesis of* 1,5-*bis*(2-*nitropheoxy*)-3-*azapentane hydrobromide* (2)**

3-Tosyl-1,5-bis(2-nitrophenoxy)-3-azapentane (**1**)(50 g,0.1 mol) and phenol (47 g,0.5 mol) were placed in a 1000 mL three-necked flask. A solution of HBr-HAc (33 %,400 mL) was added to the mixture, which was stirred under nitrogen. The solid was dissolved over a period of 30 min. The mixture was stirred under reflux for 55 h. The solvent was removed by distillation. Dry toluene (80 mL) was added to the resulting residue and co-distilled to remove the trace acetic acid. Methylene chloride (100 mL) was added to the resulting brown residue. The mixture was stirred and filtered by suction. The crude product was recrystallized from ethanol (1200 mL) to produce light yellow needle crystals 29.4 g, yield 68.7 %, bp 170 ~ 171 ℃.

***Synthesis of* 1,5-*bis*(2-*nitrophenoxy*)-3-*azapentane* (3)**

To a solution of 1,5-bis(2-nitrophenoxy)-3-azapentane hydrobromide (**2**) in DMF was added crushed potassium carbonate. The mixture was stirred for 2 h at room temperature, and poured into ice-water. A light yellow precipitate formed at once and was separated, yield 97 %, bp 60 ~ 61 ℃.

***Synthesis of* 3-*allyl*-1,5-*bis*(2-*nitrophenoxy*)-3-*azapentane* (12) *as a typical procedure for preparation of* 3-*Substituted* 1,5-*bis*(2-*nitrophenoxy*)-3-*azapentanes* (13 ~ 19)**

2-Nitrophenol (9.8 g,0.07 mol), DMF (50 mL) and anhydrous potassium carbonate (9 g) was placed in a three-necked flask and stirred for 30 min at 80 ℃. A solution of N,N-bis(2-chloroethyl) allylamine (6.3 g,0.035 mol) in DMF (10 mL). Stirring was continued for 6 h at the same temperature. After cooling, the reaction mixture was poured into a solution of sodium hydroxide (1 mol/L,800 mL), and stood in a referigerator to form a precipitate which was subsquently crushed and washed with ethanol. After drying over P_2O_5 in vacuo, 9.5 g of pure product was obtained, yield 70 %, bp 48 ~ 49 ℃.

The reaction work-up of nitro-compounds (**13 ~ 19**) is described below.

The reaction mixture was poured into aqueous sodium hydroxide . The lower oganic layer was separated. Water (160 mL) and methylene chloride (100 mL) was added to the separated lower organic layer. The organic layer , which was separated and dried over anhydrous magnesium sulfate, was evaporated to remove the solvent. The resulting residue was purified by column chromatography on silica-gel using methylene chloride as an eluent to give yellow oily product.

***Raney nickel-catalyzed hydrazine reduction of* 1,5-*bis*(2-*nitrophenoxy*)-3-*azapentane* (3) *to* 1,5-*bis*(2-*aminophenoxy*)-3-*azapentane* (20) *as a typical procedure for conversion of nitro-compounds* (12 ~ 19) *to amino-compounds* (21 ~ 28) (*Method A*)**

To a solution of 1,5-bis(2-nitrophenoxy)-3-azapentane (3)(5.0 g,0.014 mol) in anhydrous ethanol (150 mL) was added Raney nickel (0.25 g). The reaction mixture was stirred under reflux and in a nitrogen atmosphere. Hydrazine hydrate (85 %, 10 mL) was added dropwise to the suspension. Stirring was continued until the color of the solution changed from yellow to colorless and hydrogen no longer formed. After cooling, the reaction mixture was filtered under nitrogen. The filtrate was evaporated to give a colorless oil which turned to a solid when refrigerated. The crude product was recrystallized from benzene to produce white needle crystals of the product, yield 85 %, bp 70 ~ 71 ℃.

***Amalgamated aluminum reduction of* 3-*allyl*-1,5-*bis*(2-*nitrophenoxy*)-3-*azapentane* (12) *to* 3-*allyl*-1,5-*bis*(2-*aminophenoxy*)-3-*azapentane* (21) *as a typical procedure for conversion of nitro-compounds* (3, 13 ~ 19) *to amino-compounds* (20, 22 ~ 28)(*Method B*)**

Water (50 mL), aluminum amalgam (5.0 g) and 3-allyl-1,5-bis(2-nitrophenoxy)-3-azapentane (12)(5.8 g,0.015 mol) were placed in a three-necked flask under nitrogen. The reaction mixture was stirred in a cool water bath for 30 min and then

stirred under reflux until the aluminum disappeared. The reaction work-up was similar to the method A, yield 82 %, mp 55 ~ 56 ℃.

Results and discussion

All the nitro-compounds (**3**, **12** ~ **19**) and all the amino-compounds (**20** ~ **28**) were identified by elemental analysis and ^{1}H NMR spectra (Table 1. and Table 2.). Moreover, all the nitro-compounds and amino-compounds were analysed by MS spectra (Table 1.).

Table 1. Data of elemental analysis and MS spectra of nitro-compounds(**3**, **12** ~ **19**) and amino-compounds (**20** ~ **28**)

Entry	Formula	Found(Calcd.)(%)			Yield(%) (A/B)	FAB-MS (m/z)
		C	H	N		
3	$C_{16}H_{17}N_3O_6$	55.18(55.32)	4.80(4.94)	11.82(12.10)	97	[a]346, [a]347
12	$C_{19}H_{21}N_3O_6$	58.93(58.90)	5.52(5.47)	10.57(10.85)	85	[a]386, [b]387
13	$C_{20}H_{23}N_3O_6$	59.60(59.83)	5.10(5.28)	10.21(10.47)	76	[a]402, [b]403
14	$C_{21}H_{27}N_3O_6$	60.50(60.70)	6.12(6.08)	9.87(10.12)	74	[a]416, [b]417
15	$C_{19}H_{23}N_3O_7$	56.05(56.28)	5.98(5.73)	10.12(10.37)	72	[a]404, [b]405
16	$C_{20}H_{25}N_3O_7$	57.30(57.26)	6.27(6.55)	9.75(10.02)	71	[a]418, [b]419
17	$C_{22}H_{29}N_3O_7$	58.86(59.04)	6.27(6.55)	9.20(9.38)	73	[a]446, [b]447
18	$C_{21}H_{27}N_3O_8$	56.34(56.11)	6.18(6.07)	9.18(9.35)	70	[a]448, [b]449
19	$C_{24}H_{33}N_3O_8$	58.34(58.63)	6.84(6.78)	8.32(8.55)	68	[a]490, [b]491
20	$C_{16}H_{21}N_3O_2$	66.92(66.86)	7.56(7.83)	14.24(14.63)	81/78	[c]288
21	$C_{19}H_{25}N_3O_2$	69.82(69.68)	7.92(7.71)	11.58(11.83)	85/82	[c]328
22	$C_{20}H_{29}N_3O_2$	69.70(69.92)	8.70(8.53)	11.98(12.24)	87/81	[c]344
23	$C_{21}H_{31}N_3O_2$	70.22(70.54)	8.54(8.76)	11.50(11.76)	89/86	[c]358
24	$C_{19}H_{27}N_3O_3$	66.31(66.05)	7.65(7.89)	11.94(12.17)	84/80	[c]346
25	$C_{20}H_{29}N_3O_3$	66.54(66.82)	8.30(8.15)	11.42(11.69)	88/85	[c]360
26	$C_{22}H_{33}N_3O_3$	68.34(68.19)	8.82(8.58)	10.67(10.84)	90/88	[c]388
27	$C_{21}H_{31}N_3O_4$	65.02(64.74)	8.18(8.04)	10.58(10.79)	84/79	[c]390
28	$C_{24}H_{37}N_3O_4$	66.61(66.78)	8.43(8.66)	9.56(9.74)	87/85	[c]432

[a] $[M-1]^+$. [b] $[M]^+$. [c] $[M+1]^+$.

Table 2. Data of ^{1} NMR spectra
of nitro-compounds (3, 12 ~ 19) and amino-compounds (20 ~ 28)

Entry	^{1}H NMR(δppm, $CDCl_3$, TMS)
3	2.05(1H, s, NH); 3.16[4H, t, $N(CH_2)_2$]; 4.22(4H, t, CH_2O); 6.96 ~ 7.84(8H, m, aromatic)
12	3.07[4H, t, $N(CH_2)_2$]; 3.31, 3.35(2H, d, $NCH_2CH=CH_2$); 4.18(4H, t, CH_2O); 5.11 ~ 5.25 (2H, m, $=CH_2$); 5.75 ~ 5.92(1H, m, CH); 7.01 ~ 7.81(8H, m, aromatic)
13	0.83(3H, t, CH_3); 1.18 ~ 1.44(4H, m, $CH_2CH_2CH_3$); 2.59(2H, t, NCH_2); 2.98[4H, t, N $(CH_2)_2$]; 4.12(4H, t, CH_2O); 6.88 ~ 7.74(8H, m, aromatic)
14	0.83(3H, t, CH_3); 1.20 ~ 1.48(6H, m, $CH_2CH_2CH_2CH_3$); 2.63(2H, t, NCH_2); 3.04[4H, t, N $(CH_2)_2$]; 4.16(4H, t, CH_2O); 6.93 ~ 7.80(8H, m, aromatic)
15	2.88(2H, t, NCH_2); 3.10[4H, t, $N(CH_2)_2$]; 3.27(3H, s, CH_3); 3.45(2H, t, CH_2OCH_3); 4.15 (4H, t, CH_2O); 6.89 ~ 7.76(8H, m, aromatic)
16	1.14(3H, t, CH_3); 2.91(2H, t, NCH_2); 3.13[4H, t, $N(CH_2)_2$]; 3.40 ~ 3.55(4H, m, CH_2OCH^2); 4.17(4H, t, CH_2O); 6.92 ~ 7.88(8H, m, aromatic)
17	0.85(3H, t, CH_3); 1.24 ~ 1.52(4H, m, $CH_2CH_2CH_3$); 2.91(2H, t, NCH_2); 3.13[4H, t, N $(CH_2)_2$]; 3.38(2H, t, $OCH_2CH_2CH_2$)3.52(2H, t, OCH_2CH_2N); 4.17(4H, t, CH_2O); 6.92 ~ 7.79 (8H, m, aromatic)
18	2.95(2H, t, NCH_2); 3.15[4H, t, $N(CH_2)_2$]; 3.32(3H, s, CH_3); 3.45 ~ 3.62(6H, m, $CH_2OCH_2CH_2O$); 4.19(4H, t, CH_2O); 6.93 ~ 7.80(8H, m, aromatic)
19	0.82(3H, t, CH_3); 1.20 ~ 1.51(4H, m, $CH_2CH_2CH_3$); 2.90(2H, t, NCH_2); 3.10[4H, t, N $(CH_2)_2$]; 3.27(2H, t, $OCH_2CH_2CH_2$); 3.40 ~ 3.57(6H, m, $CH_2OCH_2CH_2O$); 4.14(4H, t, CH_2O); 6.89 ~ 7.75(8H, m, aromatic)
20	2.15(1H, s, NH); 3.15[4H, t, $N(CH_2)_2$]; 3.28(4H, s, NH_2); 4.19(4H, t, CH_2O); 6.63 ~ 7.28 (8H, m, aromatic)
21	3.36[4H, t, $N(CH_2)_2$]; 3.58(2H, d, NCH_2CH); 3.84(4H, s, NH_2); 4.10(4H, t, CH_2O); 5.16 ~ 5. 29(2H, m, $=CH_2$); 5.86 ~ 6.00(1H, m, CH); 6.68 ~ 7.24(8H, m, aromatic)
22	0.91(3H, t, CH_3); 1.30 ~ 1.50(4H, m, $CH_2CH_2CH_3$); 2.64(2H, t, NCH_2); 3.00[4H, t, N $(CH_2)_2$]; 3.51(4H, s, NH_2); 4.08(4H, t, CH_2O); 6.66 ~ 6.82(8H, m, aromatic)
23	0.90(3H, t, CH_3); 1.26 ~ 1.56(6H, m, $CH_2CH_2CH_2CH_3$); 2.64(2H, t, NCH_2); 3.00[4H, t, N $(CH_2)_2$]; 3.78(4H, s, NH_2); 4.08(4H, t, CH_2O); 6.65 ~ 6.84(8H, m, aromatic)
24	2.90(2H, t, NCH_2); 3.07[4H, t, $N(CH_2)_2$]; 3.33(3H, s, CH_3); 3.48(2H, t, CH_2OCH_3); 4.16 (4H, t, CH_2O); 3.58(4H, s, NH_2); 4.09(4H, t, CH_2O); 6.64 ~ 6.83(8H, m, aromatic)
25	1.18(3H, t, CH_3); 2.90(2H, t, NCH_2); 3.07[4H, t, $N(CH_2)_2$]; 3.35 ~ 3.74(4H, m, CH_2OCH_2); 3.83(4H, s, NH_2); 4.09(4H, t, CH_2O); 6.68 ~ 7.87(8H, m, aromatic)
26	0.91(3H, t, CH_3); 1.30 ~ 1.58(4H, m, $CH_2CH_2CH_3$); 2.91(2H, t, NCH_2); 3.08[4H, t, N $(CH_2)_2$]; 3.42(2H, t, $OCH_2CH_2CH_2$); 3.56(2H, t, OCH_2CH_2N); 3.80(4H, s, NH_2); 4.17(4H, t, CH_2O); 6.64 ~ 6.84(8H, m, aromatic)
27	2.91(2H, t, NCH_2); 3.06[4H, t, $N(CH_2)_2$]; 3.34(3H, s, CH_3); 3.49 ~ 3.58(6H, m, $CH_2OCH_2CH_2O$); 3.60(4H, s, NH_2); 4.08(4H, t, CH_2O); 6.66 ~ 6.80(8H, m, aromatic)
28	0.91(3H, t, CH_3); 1.27 ~ 1.60(4H, m, $CH_2CH_2CH_3$); 2.92(2H, t, NCH_2); 3.07[4H, t, N $(CH_2)_2$]; 3.44(2H, t, $OCH_2CH_2CH_2$); 3.47 ~ 3.72(6H, m, $CH_2OCH_2CH_2O$); 3.82(4H, s, NH_2); 4.09(4H, t, CH_2O); 6.63 ~ 6.81(8H, m, aromatic)

1,5-Bis(2-nitrophenoxy)-3-azapentane (**3**) was prepared by detosylation of the corresponding N-tosylsubstituted compound instead of reaction of nitrogen mustard with 2-nitrophenol. Here a simplification of the former reaction was considered. 3-Substituted 1,5-bis(2-nitrophenoxy)-3-azapentanes (**12 ~ 19**) were prepared by condensation of the corresponding N-substituted nitrogen mustards (**4 ~ 11**) with 2-nitrophenol rather than by substitution reaction of 1, 5-bis (2-nitrophenoxy)-3-azapentane (**3**) and halides, because the yield of the former reaction was higher.

Either Raney nickel-catalyzed hydrazine or amalgamated aluminum reduction of nitro-compounds to amino-compounds was efficient. These aromatic diamines are subject to oxidization when they are exposed to air. The obtained aromatic diamines by the above-mentioned procedures met the standard of purity required for the next reaction without needing further purification.

Acknowledgements

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