Convenient Synthesis of *N,N,N',N'*-Tetrakis(2-pyridylmethyl)-α,ω-alkanediamines Using a Phase-Transfer Catalyst

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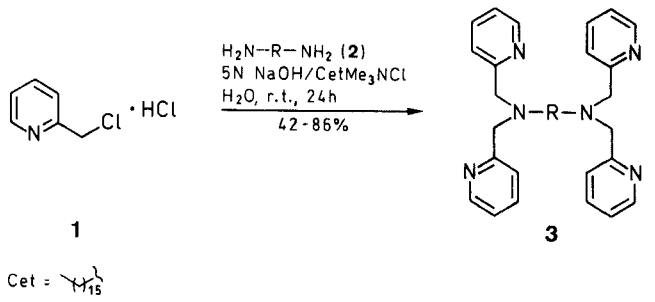
Alkylation of α,ω-alkanediamines and their *N,N'*-disubstituted derivatives with 2-(chloromethyl)pyridinium chloride in the presence of hexadecyltrimethylammonium chloride as a phase-transfer catalyst gave conveniently the corresponding *N,N,N',N'*-tetrakis(2-pyridylmethyl)-α,ω-alkanediamines in good yields. *N,N'*-Bis(2-pyridylmethyl)-*N,N'*-bis(2-thienylmethyl)-1,2-ethanediamine was similarly obtained.

N,N,N',N'-Tetrakis(2-pyridylmethyl)-α,ω-alkanediamines are well known to be excellent multidentate ligands for transition metals.[1,2] It has been also shown recently that the manganese complex of 1,3-bis[bis(2-pyridylmethyl)amino]-2-propanol is a new type of mixed-valence complex[3,4] and the iron complex of *N,N,N',N'*-tetrakis(2-pyridylmethyl)-1,2-ethanediamine has a high SOD-activity.[5] Thus, the complexes of *N,N,N',N'*-tetrakis(2-pyridylmethyl)-α,ω-alkanediamines with transition metals seem to possess a potential functionality. However, the preparation of these ligands needed multiple steps or a long reaction time and a tedious workup. We now report a convenient method for preparing *N,N,N',N'*-tetrakis(2-pyridylmethyl)-α,ω-alkanediamines.

N,N,N',N'-Tetrakis(2-pyridylmethyl)-1,2-ethanediamine (**3a**) was previously prepared by alkylation of 1,2-ethanediamine with 2-(chloromethyl)pyridine under controlled alkali conditions[6] or the condensation of 2-pyridinecarbaldehyde with 1,2-ethanediamine, subsequent reduction of the resulting imine with sodium borohydride, and alkylation with 2-(chloromethyl)pyridine.[2] The former reaction is a one-step synthesis but needs a long reaction time (one week) and tedious workup. We could overcome these problems by using a phase-transfer catalyst. For example, the reaction of 4 equivalents of 2-(chloromethyl)pyridinium chloride (**1**) with 1,2-ethanediamine (**2a**) in the presence of a catalytic amount of hexadecyltrimethylammonium chloride in 5N sodium hydroxide solution gave **3a** in 68% yield after only one day. The product was easily purified by short column chromatography on alumina and subsequent recrystallization from cyclohexane. In a similar manner, the *N,N,N',N'*-tetrasubstituted 1,3-propanediamine **3b**,[2] *trans*-1,2-cyclohexanediamine **3c**,[2] and 1,3-diamino-2-propanol **3e**[7] were obtained from the corresponding alkanediamines in 76, 86, and 85% yield, respectively. The yield of *N,N,N',N'*-tetrakis(2-pyridylmethyl)-1,2-propanediamine (**3d**)[2] could be enhanced from 53% to 77% using dichloromethane as the organic phase.

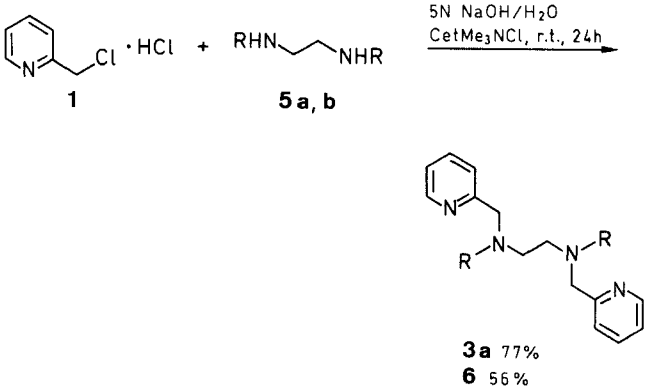
1,2-Phenylenediamine reacted with **1** under similar conditions to give only *N,N,N'*-tris(2-pyridylmethyl)-1,2-phenylenediamine (**4**) in 42% yield as the main product, without the formation of the tetraalkylated product. This seems to be due to an increase in steric hindrance resulting



2, 3	R	2, 3	R
a	CH_2CH_2	**d**	$CH(CH_3)CH_2$
b	$-(CH_2)_3-$	**e**	$CH_2CH(OH)CH_2$
c	1,2-*c*-C_6H_{10}	**f**	1,2-C_6H_4

Scheme 1

from the imposed planar arrangement of the two amino groups in 1,2-phenylenediamine. The fact that *cis*-1,2-cyclohexanediamine could not be tetraalkylated under similar conditions can be explained by the same reasoning. The structure of **4** was determined by ^1H and ^{13}C NMR spectra and H,H-COSY measurement. Further alkylation of **4** with large excess of **1** afforded a trace amount of *N,N,N',N'*-tetrakis(2-pyridylmethyl)-1,2-phenylenediamine (**3f**), the structure of which was confirmed only by its ^1H NMR spectrum [δ = 8.49 (dd, 4H), 7.42 (dt, 4H), 7.10 (d, 4H), 7.07 (dd, 4H), 6.69 (A_2B_2, 2H), 6.78 (A_2B_2, 2H), 4.74 (s, 8H)]. The reaction of 1,2-ethanediamine with 2 equivalents of **1** gave not *N,N'*-bis(2-pyridylmethyl)-1,2-ethanediamine (**5**) but the tetrasubstituted diamine **3a** in 40% yield. Similarly, 1,3-propanediamine also produced the corresponding tetra-



5a, **3a** R = 2-pyridylmethyl
5b, **6** R = 2-thienylmethyl

Scheme 2

alkylated product under similar conditions. This is probably because the first alkylation increases the nucleophilicity of the nitrogen atom.

N,N'-Bis(2-pyridylmethyl)-1,2-ethanediamine[8] similarly led to the tetrasubstituted diamine **3a** in 77% yield. *N,N'*-Bis(2-thioenylmethyl)-1,2-ethanediamine, which was prepared from the condensation of 2-thiophenecarbaldehyde and 1,2-ethanediamine and subsequent reduction of the resulting imine, was alkylated with **1** in similar manner to give *N,N'*-bis(2-pyridylmethyl)-*N,N'*-bis(2-thienylmethyl)-1,2-ethanediamine **(6)** in 56% yield.

N,N,N',N'-Tetrakis(2-pyridylmethyl)ethanediamine (3a); Typical Procedure:

To a solution of 2-(chloromethyl)pyridinium chloride **(1)** (commercially available, without purification) (1.97 g, 12 mmol) in H_2O (0.5 mL) was added aq 5 N NaOH (3 mL) with stirring under N_2. To the resulting red solution were added 1,2-ethanediamine (0.21 mL, 3 mmol), aq 5 N NaOH (3 mL), and hexadecyltrimethylammonium chloride (20 mg). The mixture was stirred vigorously for 24 h at r.t. The mixture was extracted with CH_2Cl_2, the extract washed with H_2O and dried ($MgSO_4$). After evaporation of the solvent, the residue was chromatographed on alumina by elution with CH_2Cl_2/EtOAc. Compound **3a** (1.1 g, 68%) was obtained as colorless crystals, which were recrystallized from cyclohexane; mp 111–111.5°C, (Lit.[6] mp 110–111.5°C).

1,3-Bis[bis(2-pyridylmethyl)amino]-2-propanol **(3e)**:

This compound was eluted with EtOAc and was found to be unstable on standing in air. Pale yellow oil (73%).

^{1}H NMR ($CDCl_3$/TMS): δ = 1.67 (br s, 1 H, OH), 2.61 (dd, J = 7.9, 13.3 Hz, 2 H, CH_2), 2.69 (dd, J = 4.1, 13.3 Hz, 2 H, CH_2), 3.85 (d, J = 14.7 Hz, 4 H, CH_2), 3.90 (d, J = 14.7 Hz, 4 H, CH_2), 3.97 (m, 1 H, CH), 7.10 (m, 4 H, H_5), 7.36 (d, J = 7.8, 4 H, H_3), 7.58 (td, J = 7.6, 1.7 Hz, 4 H, H_4), 8.50 (dd, J = 4.8, 1.1 Hz, 4 H, H_6).

Acetate: Nearly colorless oil.

^{1}H NMR ($CDCl_3$): δ = 1.99 (s, 3 H, $COCH_3$).

HRMS: *m/z*, $C_{29}H_{32}N_6O_2$ calc.: 496.6140; found: 496.6100.

Reaction of 1,2-Phenylenediamine with 1:

1,2-Phenylenediamine (0.32 g, 3 mmol) was allowed to react with 2-(chloromethyl)pyridinium chloride (**1**; 1.97 g, 12 mmol) according to the method described above. After separation with column chromatography on alumina, *N,N,N'*-tris(2-pyridylmethyl)-1,2-phenylenediamine (0.48 g, 42%) was obtained as yellow oil.

^{1}H NMR ($CDCl_3$/TMS): δ = 4.32 (s, 4 H, CH_2), 4.59 (s, 2 H, CH_2), 6.51 (d, J = 8.0 Hz, 1 H, C_6H_4), 6.56 (t, J = 7.7 Hz, 1 H, C_6H_4), 6.90 (t, J = 7.7 Hz, 1 H, C_6H_4), 7.07 (dd, J = 5.0, 7.4 Hz, 2 H, Py-5 H), 7.11 (d, J = 7.7 Hz, 1 H, C_6H_4), 7.16 (br s, 1 H, NH), 7.17 (m, 1 H, Py-5 H), 7.29 (d, J = 7.7 Hz, 1 H, Py-3 H), 7.31 (d, J = 7.7 Hz, 2 H, Py-3 H), 7.50 (t, J = 7.6 Hz, 2 H, Py-4 H), 7.59 (t, J = 7.6 H, 1 H, Py-4 H), 8.47 (d, J = 4.8 Hz, 2 H, Py-6 H), 8.59 (d, J = 4.8 H, 1 H, Py-6 H).

Acetamide: Nearly colorless oil.

$C_{26}H_{25}N_5O$	calc.	C 73.74	H 5.94	N 16.54
(423.5)	found	73.43	6.12	16.23

N,N'-Bis(2-pyridylmethyl)-N,N'-bis(2-thienylmethyl)-1,2-ethanediamine (6):

To a vigorously stirred solution of 1,2-ethanediamine (0.30 mL, 3.0 Hz) in abs. EtOH (1 mL), a solution of 2-thiophenecarbaldehyde (0.56 mL, 6.0 mmol) in abs. EtOH (2 mL) was slowly added over a period for 1 h under N_2. The mixture was then refluxed for 1 h. After evaporation of the solvent, the residues was dissolved in abs. EtOH (15 mL). Excess $NaBH_4$ (0.38 g, 10 mmol) was added and the mixture was refluxed for 24 h with stirring. After evaporation, the residue was extracted with CH_2Cl_2 (5 × 10 mL). The organic layer was washed with H_2O (3 × 10 mL) and dried (Na_2SO_4). A light yellow oil (0.72 g) was obtained after evaporation. To a mixed solution of 2-(chloromethyl)pyridinium chloride (0.98 g, 6 mmol) in H_2O (0.25 mL) and 5 N NaOH (2.2 mL) were added a solution of the light yellow oil obtained above in benzene (1 mL) and hexadecyltrimethylammonium chloride (30 mg) under N_2. The mixture was stirred vigorously for 24 h at r.t. and extracted with CH_2Cl_2. The extract was washed with H_2O and dried (Na_2SO_4). After evaporation, the residue was chromatographed on alumina by elution with CH_2Cl_2/EtOAc to give **6** (0.73 g, 56%) as pale yellow crystals, which were recrystallized from hexane/cyclohexane; mp 80.5–81.2°C.

$C_{24}H_{26}N_4S_2$	calc.	C 66.32	H 6.03	N 12.89
(434.6)	found	66.34	6.06	13.08

^{1}H NMR (400 MHz, $CDCl_3$/TMS): δ = 2.72 (s, 4 H), 3.75 (s, 4 H), 3.80 (s, 4 H), 6.85 (dd, 2 H), 6.91 (dd, 2 H), 7.11 (t, 2 H), 7.18 (dd, 2 H), 7.52 (d, 2 H), 7.60 (dt, 2 H), and 8.48 (d, 2 H).

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