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SYNTHESIS OF HEXAMINE LIGANDS BY USING TRITYL AS AN N-BLOCKING GROUP

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Abstract: The amino-groups of diethylenetriamine were regioselectively protected by trityl groups and then reacted with dihalogenated alkylane to give the terminal N-blocked hexamine derivatives, from which a series of hexamine ligands ($\mathbf{5}_{a-f}$) were obtained by removing the trityl groups with 5.0 M HCl solution. Alternatively, the hexamine ligands could be also prepared via amidation and reduction reactions. The synthetic routes described here are mild, efficient and easy to handle.

Polyamines and their analogues are important in view of biological interest in their potent antibiotic and antineoplastic properties. In particular they are currently being used as non-leaving groups in anticancer platinum complexes.[1-5] Bifunctional bis(platinum) complexes such as $[\{trans\text{-}PtCl(NH_3)_2\}_2\mu\text{-}\{NH_2(CH_2)_nNH_2\}](NO_3)_2$ (1,1/t,t; n=4, 6) have been found to be highly effective against cisplatin-resistant cells and show clinical promise.[5,6] To study further this type of anti-cancer complex, we decided to prepare a series of hexamine ligands with the general formula $(NH_2CH_2CH_2)_2N\text{-}R\text{-}N(CH_2CH_2NH_2)_2$, where R is alkyl and aryl. Such ligands are also likely to be of wide use in coordination chemistry, for example in studies of metal-metal interactions,[7,8] small molecule binding,[9,10] and catalytic reactions.[11]

Only two synthetic routes for the preparation of this type of hexamine ligands appear to have been reported by Moser and Schwarzenbach.[12] One route involves alkylation of bis(phathalimidoethyl)amine with dibromoalkylane, in which

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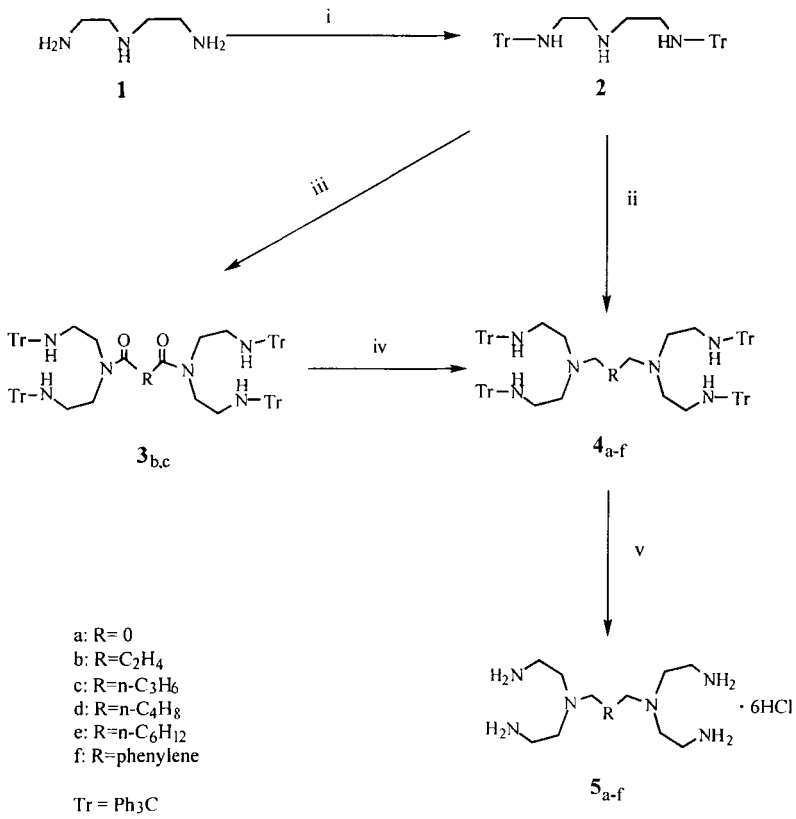

Scheme : i) TrCl, diethylamine, $CHCl_3$, r.t.; ii) dihalogenated alkylane, K_2CO_3, acetonitrile, reflux; iii) glutary dichloride or succinyl chloride, triethylamine, $CHCl_3$; iv) $LiAlH_4$, diethyl ether, reflux; v) 5.0M HCl, reflux.

phthaloyl is used as N-blocking group, and the other route involves the condensation of benzenesulfoethylene-imide with alkyldiamine and then saponification in H_2SO_4. Since the first route provides a very low chemical yield, for the preparation of these ligands even though it is inconvenent to remove the benzenesulfate salt, formed during saponification, from the desired products.[13] In our experiments we have synthesized a series of hexamine ligands by using trityl as the N-blocking group with satisfactory chemical yields, and the synthetic routes are now described.

The synthetic route is shown in the Scheme. The terminal amino groups in diethylenetriamine (**1**) were protected by trityl groups via reaction with trityl chloride in the presence of diethylamine in chloroforme to afford compound **2**.

The presence of diethylamine in this reaction not only improved the chemical yield but also the regioselectivity of the reaction. Use of triethylamine instead of diethylamine gave rise to diethylenetri(N-tritylamine) as a major by-product. The terminal N-blocked compound **2** reacted with dibromoalkylane or diiodoalkylane to afford the terminal N-blocked compound $\mathbf{4}_{a,d\text{-}f}$, from which the hexamine ligands $\mathbf{5}_{a,d\text{-}f}$ were obtained as hydrochloride salts by removing the trityl group in 5 M HCl. However, unexpectedly heterocycles as quaterammonium salts were obtained as the major products when the linker 1,4-dibromobutane and 1,5-dibromopentane were reacted with compound **2**. Further studies on these heterocyclization reactions will be reported elsewhere.

Acetonitrile and ethanol seemed to be the most suitable solvents for the alkylation reactions. Although DMF can increase the rate of the alkylation more fast, it leads to serious side-reactions as well. On the other hand, it was very easy to obtain pure product **4** if acetonitrile was used as solvent for this alkylation because product **4** precipitated from boiling acetonitrile as soon as formed while reactants did not. Therefore the pure product **4** was obtainable simply by filtration and washing with water.

The hexamine ligands could also be prepared via intermediate diamide **3**, which could be reduced to compound **4** by $LiAlH_4$ in diethyl ether. In this experiment, the ligands $\mathbf{5}_b$ and $\mathbf{5}_c$ were prepared by this synthetic route with reasonable chemical yields. However,in comparison with $\mathbf{5}_c$ the chemical yield of $\mathbf{5}_b$ was lower. The reason for this may be that it is more difficult to reduce $\mathbf{3}_b$ to $\mathbf{4}_b$ in comparison with reduction of $\mathbf{3}_c$ to $\mathbf{4}_c$ because the two carbonyl oxygens in $\mathbf{3}_b$ are so close with each other that the chelation with reducing agent may happen.

Our experiments show that trityl is useful as an N-blocking group and allows facile preparation of polyamine analogues such as hexamine ligands although its application in peptide synthesis has been limited due to its failure (with the exception of tritylalanine and tritylglycine) to couple with other amino acids.[14] Trityl chloride reacts with most amine derivatives in organic solvents with satisfactory yields and selectively protects priminary amines with diethylamine present. Furthermore, unlike phthaloyl[12] and acyl[15] which are often used as N-blocking groups for the synthesis of amine and polyamines, trityl groups are stable to reducing agents such as $LiAlH_4$ and as a result, the synthesis of polyamines can be achieved via amide derivatives as shown in the Scheme.

Experimental:

Melting points were determined on an Electrothermal melting point apparatus (uncorrected). ^1H NMR and ^{13}C NMR spectra were recorded on Bruker AC-200 and AC-250 spectrometers, respectively. All of the chemicals were purchased from Aldrich and used without further purification.

Bis(2-N-tritylaminoethyl)amine (2)

Into a solution of diethylenetriamine (**1**) (2.0 g, 19.4 mmol) and diethylamine (8.0 ml) in chloroform (20.0 ml) was added a soution of trityl chloride (10.0 g, 38.8 mmol) in chloroform (40.0 ml) slowly with stirring at room temperature. After addition, stirring was continued for 5 h. The reaction mixture was washed with water and dried over anhydrous sodium sulphate. Then chloroform was removed by rotary evaporation and the residue was recrystallized from methanol to give product **2** (8.1 g, 71.0% yield): mp 146 °C; ^1H NMR ($CDCl_3$) d: 7.15-7.50 (m, 30H, aromatic-**H**), 2.63 (t, 4H, 2C**H**$_2$), 2.28 (t, 4H, 2C**H**$_2$). Anal. calcd. for $C_{42}H_{41}N_3$: C, 85.82; H, 7.03; N, 7.15. Found: C, 86.10; H, 7.00; N, 7.22.

General procedure for preparation of $4_{a, d-f}$ (Exemplified with 4_e)
A mixture containing compound **2** (1.0 g, 1.7 mmol), 1,8-diiodooctane (0.31 g, 0.85 mmol), anhydrous potassium carbonate (1.0 g, 7.2 mmol), acetonitrile (70.0 ml) and DMF (3 drops) was refluxed under stirring for 50 h. Then the mixture was filtered while it was still hot and the filtered soild washed thoroughly with water and dried to give $\mathbf{4_e}$ (0.99 g, 90.6% yield). mp: 172-174 °C; ^{1}H NMR ($CDCl_3$) δ: 7.10-7.46 (m, 60H, aromatic-**H**), 2.35 (t, 8H, 4C**H**$_2$), 2.15 (t, 8H, 4C**H**$_2$), 1.99 (t, 4H, 2C**H**$_2$), 1.20 (t, 4H, 2C**H**$_2$), 1.0-1.15 (m, 8H, 4C**H**$_2$); Anal. calcd. for $C_{92}H_{96}N_6$: C, 85.93; H, 7.53; N, 6.54. Found: C, 85.85; H, 7.53; N, 6.70.

$\mathbf{4_a}$: 1.35 g (66.0% yield) from **2** (2.0 g, 3.40 mmol) and 1,2-dibromoethylane (0.32 g, 1.7 mmol). mp: 194-196 °C; ^{1}H NMR ($CDCl_3$) δ: 7.1-7.40 (m, 60H, aromatic-**H**), 2.24 (t, 8H, 4C**H**$_2$), 2.07 (t, 8H, 4C**H**$_2$), 1.96 (s, 4H, 2C**H**$_2$); Anal. calcd. for $C_{86}H_{84}N_6$: C, 85.96; H, 7.05; N, 6.99. Found: C, 86.12; H, 7.18; N, 7.04.

$\mathbf{4_d}$: 1.14 g (71.1% yield) from **2** (1.50 g, 2.55 mmol) and 1,6-diiodohexane (0.43 g, 1.27 mmol). mp: 165-167 °C; ^{1}H NMR ($CDCl_3$) δ: 7.10-7.48 (m, 60H, aromatic-**H**), 2.35 (t, 8H, 4C**H**$_2$), 2.15 (t, 8H, 4C**H**$_2$), 1.97 (t, 4H, 2C**H**$_2$), 1.16 (t, 4H, 2C**H**$_2$), 0.97 (t, 4H, 2C**H**$_2$); Anal. calcd. for $C_{90}H_{92}N_6$: C, 85.95; H, 7.37; N, 6.68. Found: C,86.10; H, 7.24; N, 6.78

$\mathbf{4_f}$: 1.60 g (98.6% yield) from **2** (1.50 g, 2.55 mmol) and a, a'-dibromo-p-xylene (0.335 g, 1.27 mmol). mp: 195-197 °C; ^{1}H NMR ($CDCl_3$) δ: 7.10-7.50 (m, 60H, aromatic-**H**), 6.95 (s, 4H, aromatic-**H**), 3.15 (s, 4H, 2C**H**$_2$Ph), 2.40 (t, 8H, 4C**H**$_2$), 2.22 (t, 8H, 4C**H**$_2$); Anal. calcd. for $C_{92}H_{88}N_6$: C, 86.48; H, 6.94; N,6.58. Found: C, 86.61; H, 7.02; N, 6.50.

General procedure for preparation of 4_b and 4_c (Exemplified with 4_c)

Compound **2** (2.0 g, 3.4 mmol) and triethylamine (0.51 g, 5.0 mmol) were dissolved in chloroform (30 ml) and cooled by an ice bath. To this solution was added glutary dichloride (0.29 g, 1.72 mmol) in chloroform (10.0 ml) slowly with stirring. After the addition, the mixture was refluxed for 1 h and then washed with water and dried over anhydrous sodium sulphate. The solvent was removed by rotary evaporation and the residue was purified by recrystalization from ethanol to give amide $\mathbf{3_c}$ (1.80 g, 1.39 mmol)). This was then added to a suspension of $LiAlH_4$ (0.50 g, 13.06 mmol) in dry diethyl ether (20 ml) under nitrogen with stirring, and the mixture was refluxed for 48 h and stirred at room temperature for 24 h. To this mixture chloroform (30.0 ml) was added and then the reaction product and excess of hydride were decomposed by the dropwise addition of H_2O (0.50 ml), followed by 15%(w/v) NaOH solution (0.50 ml) and H_2O (1.50 ml) in succession. After vigorous stirring for 20 minutes, the mixture was filtered by suction and the filtered precipitate was washed thoroughly with chloroform. Evaporation of the combined chloroforme solutions afforded 4_C (1.52 g, 71.0% yield based on glutary dichloride). mp: 166-168 °C; ^{1}H NMR ($CDCl_3$) δ: 7.1-7.49 (m, 60H, aromatic-**H**), 2.35 (t, 8H, 4C**H**$_2$), 2.14 (t, 8H, 4C**H**$_2$), 1.92 (t, 4H, 2C**H**$_2$), 1.10 (m, 4H, 2C**H**$_2$), 0.84 (m, 2H, C**H**$_2$); Anal. calcd. for $C_{89}H_{90}N_6$: C, 85.95; H, 7.29; N, 6.76. Found: C, 85.71; H, 7.40; N, 6.69.

$\mathbf{4_b}$: 0.72 g (55.0% yield) from **2** (1.25 g, 2.13 mmol) and succinyl chloride (0.167g, 1.06 mmol). mp: 164-167 °C; ^{1}H NMR ($CDCl_3$) δ: 7.10-7.50 (m, 60H, aromatic-

H), 2.35 (t, 8H, 4C**H**$_2$), 2.14 (t, 8H, 4C**H**$_2$), 1.94 (t, 4H, 2C**H**$_2$), 1.11 (t, 4H, 2C**H**$_2$). Anal. calcd. for $C_{88}H_{88}N_6$: C, 85.95; H, 7.21; N, 6.83. Found: C, 86.15; H, 7.30; N, 6.77.

General procedure for the preparation of $5_{a\text{-}f}$ (Exemplified with 5_e)
A mixture of 4_e (0.80 g, 0.622 mmol) and 5 M HCl (30 ml) was refluxed for 4 h. Then the mixture was filtered and the filtrate was concentrated to about 4 ml by rotary evaporation. Addition of ethanol into the concentrated solution afforded product 5_e (0.32 g, 96.1% yield). ^{1}H NMR (D_2O) δ: 3.3(m, 16H, 8C**H**$_2$), 2.80(t, 4H, 2C**H**$_2$), 1.55(m, 4H, 2C**H**$_2$), 1.30(m, 8H, 4C**H**$_2$); ^{13}C NMR(D_2O) δ: 54, 49.5, 34, 27.5, 25.5, 23; Anal. calcd. for $C_{16}H_{40}N_6$·6HCl: C, 35.90; H, 8.66; N, 15.70. Found: C, 36.10; H, 8.61; N, 15.84.

5_a: 0.15 g (95.0% yield) from 4_a (0.42 g, 0.35 mmol). ^{1}H NMR (D_2O) δ: 3.45 (m, 16H, 8C**H**$_2$), 3.31(s, 4H, 2C**H**$_2$); ^{13}C NMR (D_2O) δ: 54.2, 50, 34; Anal. calcd. for $C_{10}H_{28}N_6$·6HCl: C, 26.62; H, 7.60; N, 18.63. Found: C, 26.84; H, 7.69; N, 18.64.

5_b: 0.253 (90.1% yield) from 4_b (0.72 g, 0.586 mmol). ^{1}H NMR (D_2O) δ: 3.50 (m, 16H, 8C**H**$_2$), 3.32 (m, 4H, 2C**H**$_2$), 1.84 (m, 4H, 2C**H**$_2$); ^{13}C NMR (D_2O) δ: 53, 50, 34, 22; Anal. calcd. for $C_{12}H_{32}N_6$·6HCl: C, 30.08; H, 7.99; N, 17.54. Found: C, 30.20; H, 8.12; N, 17.43.

5_c: 0.15 g (92.1% yield) from 4_c (0.41 g, 0.33 mmol). ^{1}H NMR (D_2O) δ: 3.50 (m, 16H, 8C**H**$_2$), 3.26 (m, 4H, 2C**H**$_2$), 1.83 (m, 4H, 2C**H**$_2$), 1.47 (m, 2H, C**H**$_2$); ^{13}C NMR (D_2O) δ: 53, 50, 34, 23, 22.8; Anal. calcd. for $C_{13}H_{34}N_6$·6HCl: C, 31.66; H, 8.17; N, 17.04. Found: C, 31.76; H, 8.16; N, 17.23.

5_d: 0.36 g (93.4% yield) from 4_d (0.96 g, 0.76 mmol). ^{1}H NMR (D_2O) δ: 3.42 (m, 16H, 8C**H**$_2$), 3.10 (m, 4H, 2C**H**$_2$), 1.68 (m, 4H, 2C**H**$_2$), 1.38 (m, 4H, 2C**H**$_2$); ^{13}C NMR (D_2O) δ: 54, 49.5, 34, 26, 23; Anal. calcd. for $C_{14}H_{36}N_6$·6HCl: C, 33.15; H, 8.35; N, 16.57. Found: C, 33.16; H, 8.40; N, 16.65.

5_f: 0.56 g (96.4% yield) from 4_f (1.40 g, 1.10 mmol). ^{1}H NMR (D_2O) δ: 7.61(d, 4H, aromatic-**H**), 4.32 (s, 4H, 2C**H**$_2$-Ph), 3.38 (m, 16H, 8C**H**$_2$); ^{13}C NMR (D_2O) δ: 135.56, 134.4, 60.49, 52.62, 37.74; Anal. calcd. for $C_{16}H_{32}N_6$·6HCl: C, 36.45; H, 7.26; N, 15.94. Found: C, 36.60; H, 7.30; N, 15.90.

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