Efficient Routes for the Synthesis of 1,4,7,10,13-Pentaazacyclohexadecane-14,16-dione

Chiara Da Pieve,1 Alfredo Medina-Molner, Bernhard Spingler*
University of Zürich, Winterthurerstr. 190, 8057 Zürich, Switzerland
Fax +41(44)6356803; E-mail: spingler@aci.unizh.ch
Received 11 October 2006; revised 24 November 2006

SYNTHESIS 2007, No. 5, pp 0679–0682xx .xx .2 0 07
Advanced online publication: 08.02.2007
© Georg Thieme Verlag Stuttgart · New York

Abstract: The synthetic access to 1,4,7,10,13-pentaazacyclohexadecane-14,16-dione was significantly improved from an overall yield of 1% to 33%. The procedure involved the use of COCF₃ or DDE as highly selective protecting groups for primary amines and of Boc to protect the secondary amine functions. The reaction of a tris-Boc protected tetraethylenepentamine with malonic acid gave the macrocycle in a 44% yield, the same reaction with malonyl chloride, however, yielded only 3.6% of the desired product. Boc deprotection and removal of the trifluoroacetate salts gave access to the final product, 1,4,7,10,13-pentaazacyclohexadecane-14,16-dione, in an overall yield of 33%.

Key words: azamacrocycles, 1,4,7,10,13-pentaazacyclohexadecane-14,16-dione, protecting groups, cyclization, ligands

In recent years there has been a continuing interest in the field of macrocyclic complexes because of their close resemblance with naturally occurring biological systems, their stability (macrocyclic effect), and well-behaved coordination chemistry. A variety of macrocyclic crown ethers, cryptands, and azamacrocycles have been synthesized. The latter have a strong tendency to form stable complexes with transition metals, such as Ni²⁺, Cu²⁺, Co³⁺ and Zn²⁺. These macrocyclic systems can have a varying ring size, number and kind of donor atoms, as well as substituents. Kimura et al. introduced the macrocyclic bisamide copper(II) complexes of α,ω-oligoamines when working on superoxide dismutase model systems.³

It is known that Ni(II) and Cu(II) complexes of 1,4,7,10,13-pentaazacyclohexadecane-14,16-dione (7) are able to promote the conversion of poly d(GC) from B to Z form.⁴ During our studies aimed at a better understanding of the transition metal induced B- to Z-DNA transformation,⁴h,5 we initially synthesized the ligand 1,4,7,10,13-pentaazacyclohexadecane-14,16-dione (7) according to the published procedure.⁶ However, we were not able to reproduce the published yield of 15%. The isolation of the product, in fact, required purification by chromatography on silica gel and preparative HPLC, and yielded only 1% of the desired product. Alternative reaction routes were thus considered. The protection of the three secondary amine groups of the tetraethylenepentamine would leave only its terminal primary amine groups free to react with the diethyl malonate reducing the number of possible side products. In order to selectively protect the secondary amines, one first has to protect the primary amines. Recently there have been several reports about the synthesis of oligoamines with all their secondary amines Boc-protected. One group chose to use trifluoroacetate,⁷ and two others 1-(4,4-dimethyl-2,6-dioxycyclohexylidene)ethyl (DDE)⁸ to yield the linear oligoamines protected at their α- and ω-positions.⁹

Based on these reports, we chose to compare the efficiency of COCF₃ and DDE as protecting groups for the synthesis of tetraethylenepentamine having its primary amine functions protected. The obtained products were then reacted with (Boc)₂O for the protection of the secondary amines. The COCF₃ and DDE protecting groups were selectively removed under mild conditions (Scheme 1), leaving the secondary amines protected by the Boc groups. In effect, the trifluoroacetamide path gave a higher overall yield and in addition did not require any purification by chromatography.

In order to gain access to the macrocycle 7, we performed various cyclization reactions of malonic acid derivatives.
with 4,7,10-tris(Boc)tetraethylenepentamine (5). As already mentioned in the introduction, direct condensation of tetraethylenepentamine with diethyl malonate gave completely unsatisfactory results. The reaction of 5 with malonic acid under standard peptide coupling conditions gave the highest yield (44%) of the desired product 6. On the other hand, when the protected pentamine 5 was reacted with malonyl dichloride, only 3.6% of 6 could be isolated (Scheme 2). This result is in line with a publication from the group of Picard, who cyclized Boc-protected amines only with the help of anhydride activated diacids, but not with the corresponding diacid dichlorides. Bradshaw et al., however, reported a relatively high yield for the azamacrocycle formation with the help of a diacid chloride. After deprotection of the Boc groups of 6 and removal of the trifluoroacetate salts, we obtained the macrocycle 1,4,7,10,13-pentaazacyclohexadecane-14,16-dione (7) in an overall yield of 33% starting from tetraethylenepentamine.

All chemicals were purchased from Aldrich or Fluka (Buchs, Switzerland) and used without further purification. Tetraethylenepentamine was obtained as a free base according to the literature. A modification of the procedure described in literature was performed under N₂. The reactions were monitored by HPLC or TLC. TLC were carried out on Merck-Hitachi M-8000 spectrometer. NMR spectra were recorded on a Varian Mercury 200 MHz, Gemini 300 MHz, or Bruker DRX 500 MHz spectrometer. The chemical shifts are relative to residual solvent protons as reference. Elemental analyses were performed on a Leco CHNS-932 elemental analyzer.

1,13-Di(DDE)tetraethylenepentamine (1)

Tetraethylenepentamine (1 g, 5.3 mmol) was dissolved in anhyd EtOH (30 mL). The mixture was stirred at r.t. for 24 h. The solvent was then removed under vacuum to yield a yellow oil; yield: 1.84 g (98%); HPLC: t₁₈ = 18.3 min.

1H NMR (500 MHz, DMSO-d₆): δ = 0.92 (s, 12 H), 2.23 (s, 8 H), 2.46 (s, 6 H), 2.56 (t, J = 5.2 Hz, 4 H), 2.59 (t, J = 5.4 Hz, 4 H), 2.73 (t, J = 5.9 Hz, 4 H), 3.43 (t, J = 5.9 Hz, 4 H).

13C NMR (125 MHz, DMSO-d₆): δ = 17.69, 27.90, 29.75, 42.90, 47.37, 48.52, 48.98, 52.40, 106.92, 127.31, 196.20.


1,13-Di(DDE)-4,7,10-tris(Boc)tetraethylenepentamine (2)

A solution of (Boc)₂O (3.23 g, 18.5 mmol) in MeOH (15 mL) was added dropwise over 10 min at 0°C to a solution of 1 (1.90 g, 3.68 mmol) in MeOH (30 mL). The mixture was stirred at r.t. for 24 h. H₂O (15 mL) was added to the solution and the stirring continued at 40°C for 2 h. The solvent was removed in vacuo and the residue was purified by chromatography on silica gel. Elution was started with 1:1 EtOAc–hexane. The polarity of the eluent was gradually increased to 100% EtOAc. The product was obtained as a white solid; mp 77–80°C; yield: 2.37 g (79% based on 1); Rf = 0.15 (100% EtOAc); HPLC: t₁₈ = 24.2 min.

1H NMR (500 MHz, MeOH-d₄): δ = 1.01 (s, 12 H), 1.42–1.45 (m, 25 H, CH₂), 2.34 (s, 8 H), 2.55 (s, 6 H), 3.35 (br t, 8 H), 3.48 (br t, 4 H), 3.68 (br t, 4 H).

13C NMR (125 MHz, MeOH-d₄): δ = 18.45, 28.56, 28.88, 31.18, 42.36, 46.36, 47.55, 53.64, 81.73, 109.09, 156.89, 176.03, 199.97.

MS (ESI): m/z = 817 (100%, [M]+).

Anal. Calcd for C₃₄H₅₃N₇O₁₆: C, 63.11; H, 8.75; N, 8.56. Found: C, 63.33; H, 8.92; N, 8.62.

1,13-Di(trifluoroacetyl)tetraethylenepentamine (3)⁷

Ethyl trifluoroacetate (1.38 mL, 22.6 mmol) was added dropwise to a solution of tetraethylenepentamine (1.0 g, 5.3 mmol) in MeOH (25 mL) at –78°C. The mixture was stirred for 1 h at –78°C and then at r.t. for 24 h. The solvent was removed under vacuum to yield a yellowish oil; yield: 2.02 g (quant).

IR (KBr): 1709 cm⁻¹ (C=O).

1H NMR (300 MHz, MeOH-d₄): δ = 2.79–2.99 (m, 16 H).

13C NMR (75 MHz, D2O): δ = 34.01, 41.15, 41.32, 45.05, 113.61 (g, J = 284.1 Hz), 174.21.


1,13-Di(trifluoroacetyl)-4,7,10-tris(Boc)tetraethylenepentamine (4)⁷

A solution of (Boc)₂O (4.29 g, 19.68 mmol) in MeOH (15 mL) was added dropwise, over a period of 10 min, to a solution of 3 (1.5 g, 3.93 mmol) in MeOH (25 mL) at 0°C. The solution was stirred at r.t. for 2 d. The excess of (Boc)₂O was quenched with H₂O (2 mL). The solvent was then removed under vacuum and the residue was purified by chromatography on silica gel. The elution was started with 100% CH₂Cl₂ and then changed to 30:1 CH₂Cl₂–MeOH; yield: 2.4 g (90%); Rf = 0.5 (20:1 CH₂Cl₂–MeOH); HPLC: t₁₈ = 22.4 min.

Scheme 2 Reagents and conditions: (a) malonyl dichloride, Et₃N, CH₂Cl₂, r.t., 12 h, 3.6% yield; (b) malonic acid, HOBr, DCC, CH₂Cl₂, 4 mM soln of 5, r.t., 12 h, 44% yield; (c) TFA, CH₂Cl₂, r.t., 24 h, quantitative yield, (d) anion-exchange column, 83% yield.  

The solvent was then removed under vacuum and the residue was purified by chromatography on silica gel. Elution was started with 1:1 EtOAc–hexane. The polarity of the eluent was gradually increased to 100% EtOAc. The product was obtained as a white solid; mp 77–80°C; yield: 2.37 g (79% based on 1); Rf = 0.15 (100% EtOAc); HPLC: t₁₈ = 24.2 min.

1H NMR (500 MHz, MeOH-d₄): δ = 1.01 (s, 12 H), 1.42–1.45 (m, 25 H, CH₂), 2.34 (s, 8 H), 2.55 (s, 6 H), 3.35 (br t, 8 H), 3.48 (br t, 4 H), 3.68 (br t, 4 H).

13C NMR (125 MHz, MeOH-d₄): δ = 18.45, 28.56, 28.88, 31.18, 42.36, 46.36, 47.55, 53.64, 81.73, 109.09, 156.89, 176.03, 199.97.
NH₂NH₂ (10 mL) were stirred together at r.t. for one day. The com-

4,7,10-Tris(Boc)-14,16-dioxo-1,4,7,10,13-pentaazacyclohexa-

48.16, 81.63, 117.62 (q, J = 285.5 Hz), 154.68, 156.34 (q, J = 24.5 Hz).

4,7,10-Tris(Boc)tetraethylenepentamine (5) by DDE Deprotection

A solution of 2 (505 mg, 0.618 mmol) in EtOH (9 mL) and 25% aq

NH₂NH₂ (10 mL) were stirred together at r.t. for one day. The com-

pletion of the reaction was checked by TLC (eluent = 9:1:0.1

CH₂Cl₂–MeOH–concd soln of NH₄OH). The solvent was removed under vacuum to afford a colorless oil that was further purified by chromatography on silica gel (eluent: 9:1 CH₂Cl₂–MeOH); yield: 1.6 g (quant).

Acknowledgment

This research was supported by the Swiss National Science Foundation and the Forschungskredit of the University of Zürich. We thank Prof. Dr. R. Alberto, Dres J. K. Pak and Ph. Kurz for valuable discussions. We further thank B. and H. Spring for performing the elemental analyses and Dr T. Fox and P. Ruiz-Sánchez for NMR measurements.

References

(1) Current address: The Open University, Milton Keynes, UK.


In ref. 6, compound 7 has been described as a solid. However, following the synthetic pathways in ref. 6, we have previously found that it is extremely difficult to completely remove all the hydrochlorides from tetraethylenepentamine. Therefore derivatives of 1,4,7,10,13-pentaazacyclohexadecane-14,16-dione are frequently isolated as their hydrochloride salts and purified.