Pergamon

Tetrahedron Letters 40 (1999) 381–382

TETRAHEDRON
LETTERS

Simple and High Yielding Regioselective Synthesis of 1,4,8-Tri(carbamoylmethyl)-1,4,8,11-tetraazacyclotetradecane hydroiodide

István Lázár

Lajos Kossuth University, Department of Inorganic and Analytical Chemistry,
Debrecen-10, Pf. 21, Hungary, 4010; e-mail: lazar@tigris.klte.hu

Received 15 September 1998; accepted 26 October 1998

Abstract:

Near quantitative synthesis of 1,4,8-tris(carbamoylmethyl)-1,4,8,11-tetraazacyclotetradecane hydroiodide (**1**) has been achieved by reacting the parent macrocycle 1,4,8,11-tetraazacyclotetradecane (cyclam) with iodoacetamide in acetone in the presence of diisopropylethylamine as a base. The reaction stops at the trisubstituted stage even in the presence of a large excess of the reactants. This process represents the first example of a solubility controlled regioselective synthesis of a polyazamacrocyclic complexing agent; the driving force is the exceptionally low solubility of **1** in the reaction medium. **1** was hydrolyzed in acidic medium to the corresponding acetate derivative 1,4,8-tris(carboxylmethyl)-1,4,8,11-tetraazacyclotetradecane (**2**) in high yield.

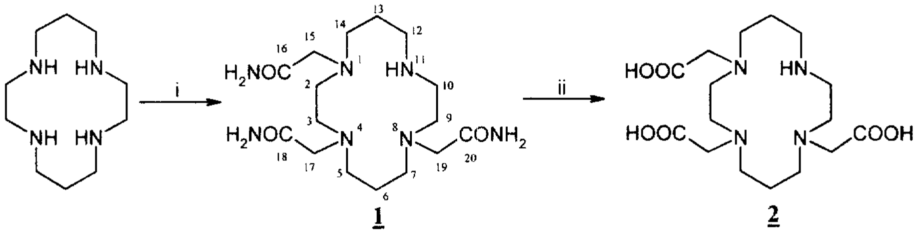
Keywords: Macrocycles; Aza compounds; Regiochemistry; Complexation

Regioselective *N*-substitution of the polyazamacrocycles to create new complexing agents with highly specific characteristics is an important issue. For regioselective syntheses, several approaches have been developed. [1] We now report the selective formation of a new trisubstituted derivative of cyclam.

Reacting cyclam with a large excess of iodoacetamide in acetone over several hours in the presence of diisopropylethylamine (DIPEA) as a base resulted in precipitation of a white powder. This, after washing with water, proved to be the unexpected product pure triamide **1**, which was virtually insoluble both in acetone and water (Scheme 1). Using shorter reaction times and lesser excess of the reactants gave mixtures of partly substituted products. Since the

PII: S0040-4039(98)02317-X

precipitation starts at an early stage of the reaction it seems to be possible that although mono- and disubstituted (carbamoylmethyl)cyclam hydroiodides are poorly soluble, their solubility is high enough to let the third substitution step proceed. The formation of **1** is probably due to the high proton affinity of the cyclam ring and the low solubility of the ion pair formed, which comprises a large-sized macrocyclic cation and the iodide ion. **1** was hydrolyzed into the corresponding acetate derivative **2** in acidic solution. Fractional crystallization of **2** resulted in pure crystalline product in fairly low yield, while evaporation of the hydrolysis mixture gave high yield, but the product was contaminated with ammonium chloride.



Scheme 1 Reagents and conditions: i) ICH_2CONH_2, DIPEA, –DIPEA·HI, in acetone, reflux 8 h, yield > 99 %, [2]; ii) hydrolysis in aprox. 25 % HCl under reflux for 3–4 h.

This synthesis of **1** requires only common glassware and inexpensive reactants and gives practically quantitative yield. So far no other procedure giving a regioselectively substituted macrocyclic derivative in one simple synthetic step and in near quantitative yield has been reported.[3]

Acknowledgement Financial support from the Hungarian National Research Foundation (OTKA No. 23810) is gratefully acknowledged.

References and notes

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[2] *TE3A-AMID·HI* (**1**): Chloroacetamide (1.34 g, 14.25 mmol) and dry sodium iodide (2.24 g, 14.95 mmol) was dissolved in acetone (30 ml) and the solution refluxed for 2.5 hours. To this mixture was added diisopropyl ethylamine (5 ml, 28,6 mmol) and the cyclam (476 mg, 2.376 mmol) in one portion and the reaction mixture was refluxed for 8 hours. The solution was cooled to room temperature and the precipitate was filtered off. The solid was washed with acetone (10 ml), water (2x2.5 ml). acetone (2x10 ml) and ether (2x10 ml) and dried with hot air yielding 1 as a white powder (1.12 g, 2.36 mmol, yield: 99%). ^1H NMR (DCl, ref. TSP): 4.23 (s, 2H, H19), 4.22 (s, 2H, H17), 4.16 (s, 2H, H15), 3.85 (m, 4H, H2+H3), 3.81 (m, 2H, H9), 3.76 (m, 2H, H10), 3.61 (t, 2H, H5), 3.58 (t, 2H, H7), 3.54 (t, 2H, H14), 3.48 (t, 2H, H12), 2.31 (m, 2H, H6), 2.25 (m, 2H, H13). ^{13}C NMR (DCl, ref. MeCN=0.3): 167.44 (C18), 166.71 (C16, C20), 55.62, 55.32, 55.11 (C17, C15, C19), 49.89, 49.50, 49.34 (C5, C7, C14), 46.64, 46.29 (C2,C3, C9), 41.25 (C10), 37.39 (C12), 18.25, 18.07 (C6, C13). Iodide analysis for $C_{16}H_{34}N_7O_3I$, calcd. 25.41 %, found 25.31 %.

[3] According to our preliminary results, 1,4,7,10-tetraazacyclododecane shows similar selectivity for the trisubstituted derivative under identical conditions.