J.C.S. Снем. Сомм., 1981

Synthesis with Silicon Templates: Preparation of Macrocyclic Amides

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Summary A new method for the preparation of macrocyclic amides via the use of 1,3,2-diazasilolidines as covalent templates is reported.

The preparation of ring compounds via amide bond formation represents a major barrier towards the synthesis of many natural products such as cyclic alkaloids¹ and peptides.² In an attempt to overcome this barrier extensive efforts have been devoted towards the development of appropriate cyclization procedures such as high-dilution techniques,³ various activation methods,⁴ and 'zipper-type' reactions.⁵ We now report an alternative approach which is based on the use of silicon as a covalent template, and which does not necessitate the use of high-dilution conditions. The method involves conversion of a diamine into reaction mixture was then concentrated *in vacuo* to half of its original volume and washed with aqueous 5% sodium hydrogen carbonate solution. Alternatively, the reaction mixture could be treated with 2 ml of pyridine for 30 min at room temperature and subsequently concentrated. Chromatographic separation of the residue provided 452 mg (30.6%) of the macrocyclic tetramide (**3a**). Analogous treatment of (**1**) with pimeloyl dichloride (**2b**) or azelaoyl dichloride (**2c**) provided the corresponding amides (**3b**) and (**3c**) respectively; treatment of compound (**4**) with (**2a**) gave the macrocyclic tetramide (**5a**).

The preparation of macrocyclic amides from diazasilolidines could also be achived by the use of activated esters instead of acyl halides. Condensation of (1) with di-2,4,5trichlorophenyl pimelate provided the tetramide (3b) in



the corresponding diazasilolidine⁶ and its subsequent condensation with an activated carboxylic acid derivative⁷ to provide tetramides as the sole cyclic products. The detailed experimental procedure is illustrated by the preparation of the macrocyclic glutaryl diamide (3a).

A solution of the diazasilolidine (1) (4·42 mmol) in 20 ml of tetrachloroethane, and a solution of glutaryl dichloride (2a) (4·42 mmol) in 20 ml of tetrachloroethane were added simultaneously to 70 ml of refluxing tetrachloroethane. The

25% yield. The isolated yields and spectroscopic properties of the new compounds are summarized in the Table.

Of particular interest are the multiple signals in the n.m.r. spectrum for the methylene groups adjacent to the amide nitrogen, which are indicative of the presence of both *transoid* and *cisoid* arrangements.⁸ Heating of the n.m.r. sample solutions to 80 °C caused these signals to coalesce to broad singlets. X-Ray diffraction analysis of the tetramide (**3a**) established the presence of both geometries also

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TABLE. Yields and spectroscopic properties of the macrocyclic amides (3a-c) and (5a).

Compound (% yield)	M .p. (t/°C)	I.r. (v/cm ⁻¹) ^a	δъ				
			$\overbrace{ \begin{array}{c} \text{MeC}H_2\text{N or} \\ \text{PhC}H_2\text{N} \end{array} }^{\text{MeC}H_2\text{N}}$	CH2NR	CH ₂ CO	[CH ₂]	$m/e (M^+)$
(3a) (31)	231-234	$1630 \\ 1469 \\ 1420$	4·39(s) 4·47(s) 4·70(s)	3.38(t) 3.47(t) 3.57(t)	$2 \cdot 40(t)$ $2 \cdot 48(t)$ $2 \cdot 57(t)$	2 ·01(m)	672
(3b) (12)	199201	$1630 \\1445$	4.65(s) 4.42(m)	3.59(s) 3.35(m)	2.28(m)	1.65(m)	728
(3c) (40)	199204	$1640 \\ 1470 \\ 1420$	4.65(s) 4.45(m)	3.58(s) 3.39(m)	2·28(m)	1•62(m)	784
(5a) (26)	218-221	$1625 \\ 1470 \\ 1420$	3·24—3·40 (m)		2·36(m)	1·80(m)	424

^a The i.r. spectra were recorded in KBr discs. ^b The n.m.r. spectrum of compound (3a) was recorded in Me₂SO solution, and those of compounds (3b), (3c), and (5a) in CDCl₃ solution on a 90 MHz Bruker instrument. The chemical shifts given are relative to Me₄Si.

in the solid state, where cisoid and transoid amide bonds were found to alternate along the ring's periphery.[†]

Evidence for the template effect of the silicon was obtained by reference experiments. Condensation of the free diamine NN'-dibenzylethylenediamine with azelaoyl dichloride (2c) under high-dilution conditions according to a procedure reported by Stetter et al.3 provided the corresponding

macrocyclic diamide and none of the tetramide. Experiments to establish the mechanistic aspects of this template reaction are in progress.

The authors thank the Israel Academy for Sciences and Humanities for support.

(Received, 6th April 1981; Com. 395.)

[†] We thank Dr. F. Frolow for the X-ray analysis which will be described in detail in the full report.

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