Synthesis with Silicon Templates: Preparation of Macrocyclic Amides

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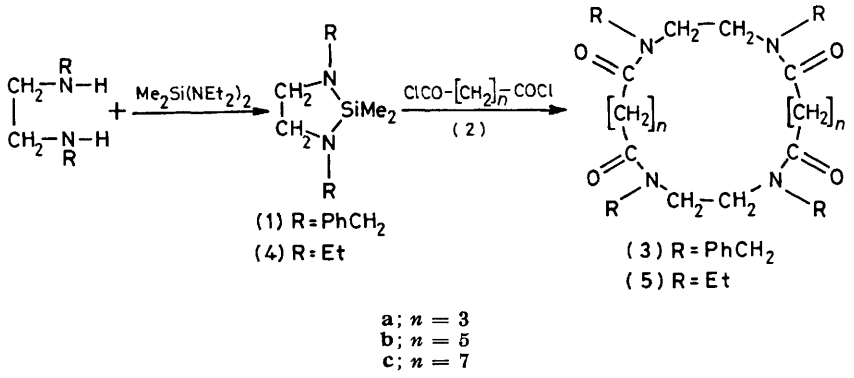
Summary A new method for the preparation of macrocyclic amides *via* the use of 1,3,2-diazasilolidines as covalent templates is reported.

THE preparation of ring compounds *via* amide bond formation represents a major barrier towards the synthesis of many natural products such as cyclic alkaloids[1] 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 the corresponding diazasilolidine[6] and its subsequent condensation with an activated carboxylic acid derivative[7] 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 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-2,4,5-trichlorophenyl pimelate provided the tetramide (**3b**) in 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

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

Compound (% yield)	M.p. (*t*/°C)	I.r. (ν/cm^{-1})[a]	δ[b] MeCH_2N or PhCH_2N	δ[b] CH_2NR	δ[b] CH_2CO	δ[b] [CH_2]	*m/e* (*M*$^+$)
(**3a**) (31)	231—234	1630	4·39(s)	3·38(t)	2·40(t)	2·01(m)	672
		1469	4·47(s)	3·47(t)	2·48(t)		
		1420	4·70(s)	3·57(t)	2·57(t)		
(**3b**) (12)	199—201	1630	4·65(s)	3·59(s)	2·28(m)	1·65(m)	728
		1445	4·42(m)	3·35(m)			
(**3c**) (40)	199—204	1640	4·65(s)	3·58(s)	2·28(m)	1·62(m)	784
		1470	4·45(m)	3·39(m)			
		1420					
(**5a**) (26)	218—221	1625	3·24—3·40(m)		2·36(m)	1·80(m)	424
		1470					
		1420					

[a] The i.r. spectra were recorded in KBr discs. [b] The n.m.r. spectrum of compound (**3a**) was recorded in Me_2SO solution, and those of compounds (**3b**), (**3c**), and (**5a**) in $CDCl_3$ solution on a 90 MHz Bruker instrument. The chemical shifts given are relative to Me_4Si.

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.

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