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A CONVENIENT SYNTHESIS OF MACROCYCLIC LACTAMS

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SUMMARY A facile method is described for the synthesis of macrocyclic lactams using dicarboxylic acids and diamines directly in the presence of diphenylphosphoryl azide.

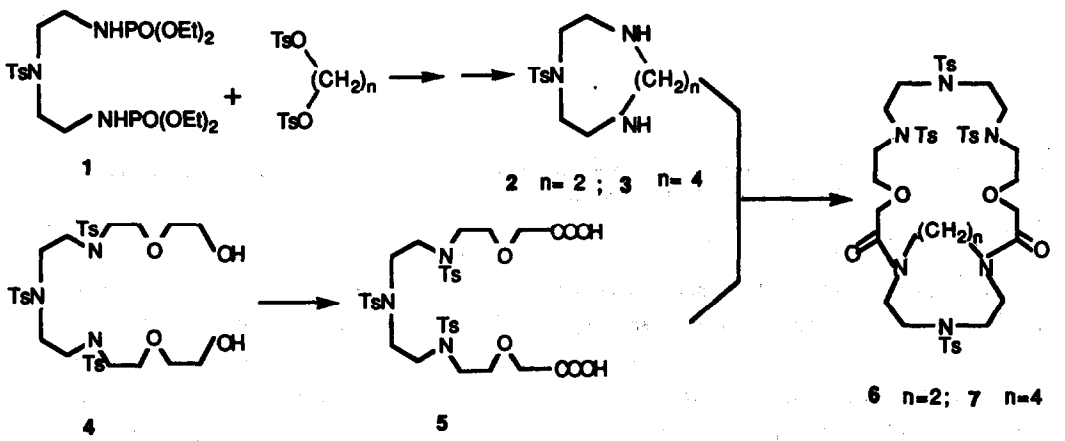
Macrocyclic polyamines have been shown to complex a variety of inorganic and organic ions.[1] Recent developments in anion complexation by synthetic polyammonium molecules have created a new field for the design of molecular receptors capable of selectively and strongly binding anionic substrates, thus extending supramolecular chemistry to anions as well as cations. Advances in the application of these macrocycles in order to study the complexation of cations and anions, however, rely critically on versatile methods of synthesis. Of contemporary interest is the assembly of sophisticated ring systems, such as spherical and cylindrical macrocycles,[2-4] and those with various functional side chains.[5,6] Macrocyclic lactams are some of the most useful precursors for fabricating these macrocycles. Of importance, as a result, are efficient synthetic approaches to macrocyclic lactams. Additionally macrocyclic lactams themselves are of interest for binding metal ions.[7]

One of the most common and conventional methods of constructing macrocyclic lactams is to utilize the reaction of dicarboxylic acid chlorides with diamines. This route is indeed effective especially with simple acyl chlorides that are readily purified and in cases of less reactive amines. Adverse factors, however, arise in the generally low yields and difficulty in purifying larger acyl chlorides. Furthermore, high-dilution techniques are necessary in most cases to perform such reactions, in order to obtain reasonable yields because of a tendency to form linear polyamides. Although a variety of methods of preparing amides by activating carboxylic acids to combine with amines is known, especially in the synthesis of peptides, relatively rare are examples using such techniques to synthesize macrocyclic lactams. One example was highlighted by Cazaux et al[8] who employed 2-mercaptothiazoline and 1,3-dicyclohexylcarbodiimide (DCC) to activate dicarboxylic acids for the formation of macrocyclic lactams. This approach, however, is tedious in the isolation of the activated esters of such difunctional molecules, and the yields are not high.

In search of macrocyclic molecular receptors concerned with biomimetic activities, macrocyclic lactams and cylindrical macrocycles were of interest, which encouraged an investigation into an efficient method for building macrocyclic lactams systematically. This report describes a facile approach found to be very useful in the preparation of macrocyclic lactams using diphenylphosphoryl azide (DPPA) as an

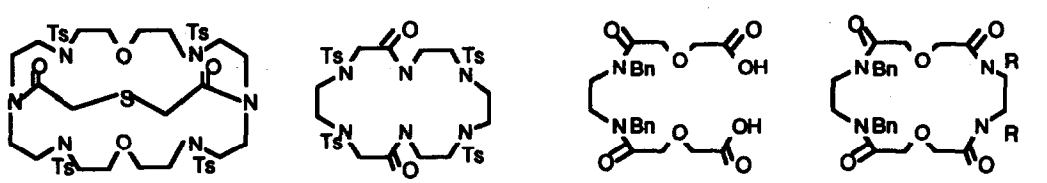
activating reagent of carboxylic acids. DPPA was first introduced by Shioiri et al[9] in the synthesis of amides in peptides.

An example of this technique is shown for the synthesis of the macrobicyclic lactam 6. The starting triazacyclononane 2 was prepared in 29% yield by reacting the disodium salt of the biphosphoramidate 1 with ethyleneglycol ditosylate in DMSO[10], and then removing the phosphoryl group in THF-HCl in high



yield.[11] The triazacycloundecane 3 was made in 39% yield in a similar way to compound 2. The dicarboxylic acid 5 (mp 130-132°C) was readily obtained in 85% yield by oxidation of the diol 4 [12] with Jones' reagent in acetone at room temperature with vigorous stirring. Mixing the dicarboxylic acid 5 and the HCl salt of 2 with DPPA in the presence of triethylamine in DMF gave a clear solution which was stirred at room temperature for several hours. The macrocyclic lactam 6 was obtained in 82% yield after work-up (General Procedure and Table). Using this method, compounds 7 and 8 were also prepared in reasonable yields. The starting macrocycle for lactam 8 was prepared according to the procedure reported by Mertes et al.[5]

In the control experiment, the acid 5 was converted into the acyl chloride by treatment with thionyl chloride at refluxing temperature. The acyl chloride, after thorough removal of excess thionyl chloride



in vacuum, was used directly in cyclization with the amine **2** under high-dilution techniques in benzene in the presence of triethylamine, resulting in 24% yield. Such a yield is reasonable compared to similar examples reported by others,[2] but considerably inferior to the yield obtained by the new method.

Three other macrocyclic lactams were prepared in order to generalize the procedure. Compound **9** was first reported by Lehn et al,[2] and was obtained in 38% yield by reacting the diamine, $H_2NCH_2CH_2NTsCH_2CH_2NTsCH_2CH_2NH_2$, with the dicarboxylic acid chloride, $ClOCCH_2NTsCH_2CH_2NTsCH_2COCl$, under high-dilution techniques and strictly anhydrous conditions. The diamine used in this work was prepared by reacting the dimesylate of the diol, $HOCH_2CH_2NTsCH_2CH_2NTsCH_2CH_2OH$, with potassium phthalimide in DMF, and then hydrazinolysis in ethanol.[13] The acid was made following the procedure reported by Stetter and Mayer.[14] The tetralactams **11** and **12** have been shown to display selectivity in binding metal ions.[8] The diacid **10** was made by reacting N,N'-dibenzylethylenediamine with diglycolic anhydride in the presence of triethylamine in refluxing benzene for 4h. All of these lactams were prepared in excellent yields compared to those reported in the literature,[2,8] even though the yields were not optimized. The solvents used were selected solely on the basis of the solubility of the starting materials. It should be noted that the reaction temperature is of importance because a Curtius' rearrangement may occur at higher temperatures.[9]

The NMR spectra of these macrocyclic lactams appear more complicated than anticipated due to the rigidity of the amides which deters the free inversion of the rings. Compound **2**, for instance, should be highly symmetrical and have relatively simple ^1H and ^{13}C NMR spectra. Instead, four peaks are observed for the carbons connected to the oxygens and six peaks for the small ring carbons.

Table Conditions for the Preparation of Macrocyclic Lactams and Comparison of Yields with Previously Reported Methods

COMPD	REACTION CONDITIONS			YIELD (%)	
	TIME (h)	SOLVENT	SUBSTRATE: DPPA	Current	Previously Reported
6	16	DMF	1:5	82	24 *
7	16	DMF	1:5	40	
8	24	THF	1:2.5	67	
9	30	THF	1:3	70	38 [2]
11	24	DMF	1:3	73	32 [8]
12	36	DMF	1:3	58	27 [8]

* The yield obtained from the acyl chloride of corresponding acid.

General Procedure

To a solution of a diamine (1 mmol) and dicarboxylic acid (1 mmol) in DMF or THF (50-100 mL, over freshly dried 4 Å molecular sieves at 400°C) was added triethylamine (5 mmol) at room temperature with stirring. To this mixture, after 10 min, was added DPPA (2.5-5 mmol). The resulting solution was stirred

at room temperature for several hours. The solvent was removed in vacuo, and the remaining solution was diluted with CH_2Cl_2, washed with 10% aqueous NaOH solution, water, 1 N HCl and saturated NaCl solution. The CH_2Cl_2 layer was dried over anhydrous Na_2SO_4. The residue, after evaporation of the solvent, was chromatographed on a silica gel column eluting with CH_2Cl_2-MeOH to give the pure products.[15]

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13. The diol, recrystallized from ethanol, mp 149-151°C, was prepared in 61% yield by reacting N,N'-ditosylethylenediamine with ethylene carbonate in a catalytic amount of powdered KOH at 160-190°C for 4h. The dimesylate, recrystallized from ethanol, mp 135-136°C, was obtained in 90% yield by treating with methanesulfonyl chloride in CH_2Cl_2 in the presence of triethylamine. The diphthalimide derivative, mp 210°C, was obtained in 90% yield by the reaction of the mesylate with potassium phthalimide in DMF at 80°C overnight. The diamine obtained from hydrazinolysis is a solid, mp138-139°C.
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15. All the compounds in this work were confirmed by ^1H and ^{13}C NMR and MS, and elemental analysis for **2, 3, 5, 6, 7** and **8**.

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