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Access to Macrocyclic Lactams. Application to a New Series: the Dibenzotetralactams

Nathalie Arnaud, Claude Picard*, Louis Cazaux, Pierre Tisnès

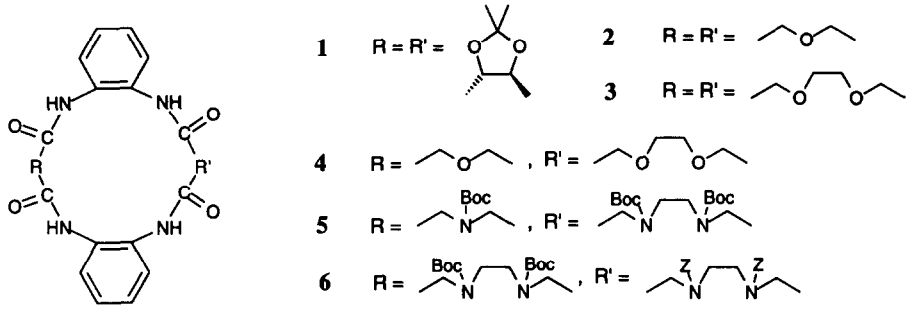
Université Paul Sabatier, Laboratoire de Synthèse et Physicochimie Organique Associé au CNRS
118, Route de Narbonne F-31062 Toulouse Cedex

Abstract: A facile route is described for the synthesis of macrocyclic dibenzotetralactams derived from 1,2-diaminobenzene based on a stepwise approach using diacid dichlorides or mixed pivalic dianhydrides for ring closure. This method is applicable for the preparation of a variety of receptors of various ring size, heteroatom substitution and pendant chains.

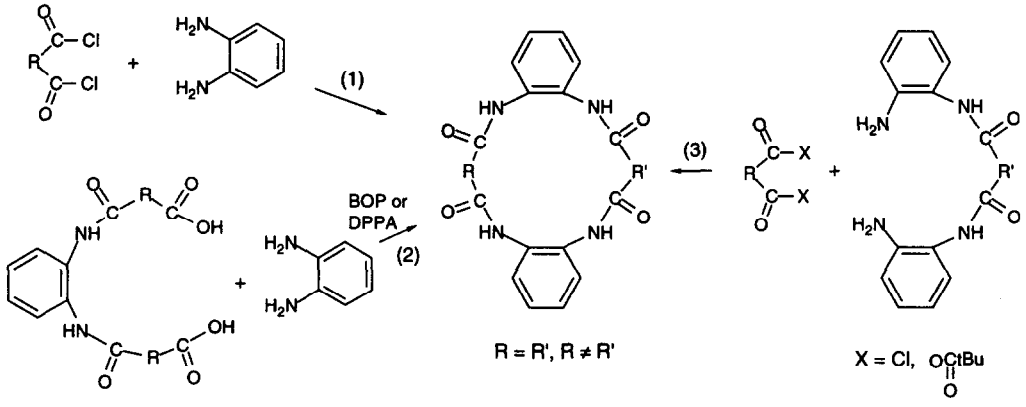
The design and synthesis of new macrocyclic ligands for specific applications is a subject of continuous investigations. Among the macrocyclic compounds, tetralactams are of increasing interest not only as potential precursors which yield by reduction to azacrowns, but also for their specific applications such as the molecular recognition of biologically interesting substrates,[1] the selective alkaline-earth ions extractions,[2] their use in selective electrodes,[3] in luminescent lanthanides probes[4] and the design of ligands for highly oxidizing transition metal complexes.[5] Tetralactams can also be used as macrocyclic backbones allowing a distribution of some donor sets other than amide functions.[6] In addition neutral catenanes with two interlocking tetralactams macrocycles were recently described.[7]

On the other hand benzo groups are often introduced as integral parts of macrocyclic receptors.[8] These aromatic subcyclic units can be expected to reduce the flexibility of the macroring, to enhance the hydrophobicity of the cavity, and can also interact with guest by π-stacking or π-cation interactions. Moreover functional groups can be simply introduced in the benzo moiety to couple the macrocycles or their complexes with carrier molecules.

As part of a general program, aimed at synthesis and study of macrocyclic tetralactams,[2-4,9,10] we considered various strategies for the obtention of dibenzotetralactams derived from diaminobenzene compounds. To the best of our knowledge, no preparation of these materials has been described so far in macrocyclic chemistry. We report here the synthesis of a series of symmetrical or unsymmetrical dibenzotetralactams, **1-6**, derived from 1,2-diaminobenzene and tartaric acid, (poly)oxa or (poly)aza dicarboxylic acids and ranging in size from 16- to 24-membered rings.



Three different routes for the preparation of these macrocycles were investigated (scheme 1). The simple one step and most popular method for the synthesis of tetralactams containing identical bridges and aromatic groups requires the reaction of diacid dichlorides with diamines (path 1).[11] The two stepwise methods investigated in this report involve either an intermediate diamide diacid (path 2) or diamide diamine (path 3) and can lead to symmetrical or unsymmetrical molecules.

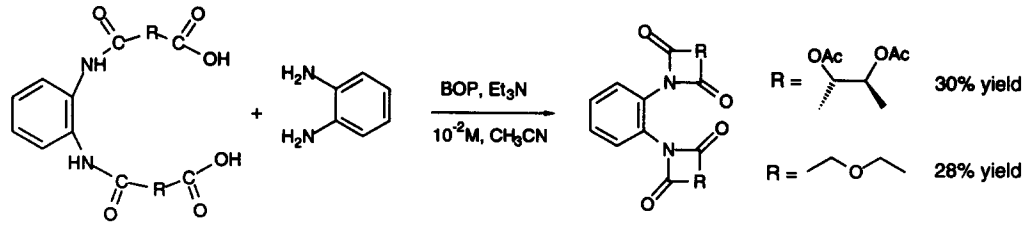


Scheme 1

Path 1: High-dilution coupling of 1,2-diaminobenzene with 2,3-o-isopropylidene-L-tartaric acid dichloride or di- and triglycolic acid dichloride (CH_3CN, Et_3N) gave macrocyclic tetramides **1-3** in very poor yields (<5%). Monomeric dilactam (30% yield for 12-membered dilactam corresponding to **3**) and(or) polymeric materials were essentially obtained.[12]

Path2: This stepwise approach is attractive owing to its successful use with secondary aliphatic diamines[4,10] and to the easy availability of the intermediate diamide-diacid derived from γ or δ diacids. In this way the condensation of diglycolic or diacetyl-L-tartaric anhydride with 1,2-diaminobenzene afforded the corresponding diamide diacids in 90% yield. The subsequent macrocyclization reaction was conducted by using BOP reagent as *in situ* activating-coupling agent. In both cases our attempts were unsuccessful. No amount of the cyclization products (16- or 18-membered ring) was detectable owing to preferential intracyclization of activated diamid diacids to give imide derivatives (scheme 2).

Similar results were obtained by using diphenylphosphoryl azide (DPPA) coupling reagent following the procedure described by L. Qian et al[13] for the synthesis of macrocyclic lactams.

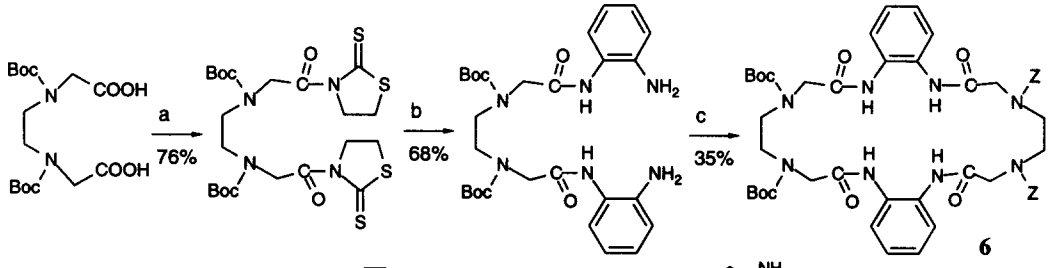


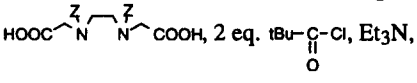
Scheme 2

Path3: this strategy was successful. Our recently published procedure[14] involving the use of bis(thiazolidine-2-thione) derivatives of dicarboxylic acids allows the obtention of the intermediate diamide diamine in good yields (45-80%) and without requiring a time-consuming protection-coupling-deprotection sequence or an excess of 1,2-diaminobenzene.

Macrocyclization reactions were carried out with diacid dichlorides in high dilution conditions for the preparation of polyoxa tetralactams **1-4**. Yields of 60-70% were obtained for ring closure reaction except for **4** (15%).

For the synthesis of polyaza tetralactams **5, 6**, the preparation of diacid dichlorides derivatives was not easy, so we employed mixed pivalic anhydride activation.[15] This new procedure for the formation of macrocyclic lactams, adapted of a method from peptide synthesis[16] yield the expected compounds in satisfactory yields (30-35%) without the use of high dilution techniques. This strategy is illustrated in scheme 3 for the synthesis of the unsymmetrical compound **6**.



Scheme 3. Conditions a) DCC,  , EtOAc, r.t., 48 h, b) 2 eq.  , CH_2Cl_2, r.t., 4 days, c)  , 2 eq. , Et_3N, THF, 60°C, 12 hrs, reagent concentrations 0.01 M.

All compounds showed the expected spectroscopic properties and satisfactory elemental analysis and mass spectra.[17]

A study of the complexing properties of tetralactams **1-4** is in progress and will be reported elsewhere. On the other hand, compounds **5-6** are versatile precursors for polyazamacrocycles or macrocyclic receptors with pendant chains. The 24-membered amide derivative **6** is of special interest to us as a precursor for a variety of dinucleating ligands bearing two binding moieties displaying different coordination features.[18]

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    1; 15%; ^{1}H-NMR: δ = 1.55 (s, 12H), 4.85 (s, 4H), 7.22-7.26 (m, 4H), 7.49-7.54 (m, 4H), 9.76 (s, 4H); MS (DCI/NH_3): m/z = 542 (100%, $[M+NH_4^+]$), 525 (40%, $[M+H]^+$).

    2: 68%; ^{1}H-NMR: δ = 4.29 (s, 8H), 7.23-7.28 (m, 4H), 7.63-7.68 (m, 4H), 9.50 (s, 4H); MS (DCI/NH3): m/z = 413 (100%, $[M+H]^+$).

    3: 72%; ^{1}H-NMR: δ = 3.81 (s, 8H), 4.18 (s, 8H), 7.20-7.25 (m, 4H), 7.56-7.61 (m, 4H), 9.44 (s, 4H); MS (DCI/NH_3): m/z = 518 (87.5%, $[M+NH_4^+]$), 501 (100%, $[M+H]^+$).

    4: triglycolic acid dichloride was used for cyclization step, 63%; ^{1}H-NMR: δ = 3.81 (s, 4H), 4.14 (s, 4H), 4.34 (s, 4H), 7.17-7.32 (m, 4H), 7.42-7.47 (m, 2H), 7.75-7.80 (m, 2H), 9.23 (s, 2H), 9.75 (s, 2H); MS (DCI/NH_3): m/z = 474 (100%, $[M+NH_4^+]$), 457 (34%, $[M+H]^+$).

    5: mixed pivalic anhydride of N,N'-Bis(tert-butoxycarbonyl)ethylenediamine-N,N'-diacetic acid was used for cyclization step, 30%; ^{1}H-NMR: δ = 1.33, 1.38 (2s, total 27H), 3.38-3.59 (m, 4H), 3.91-4.26 (m, 8H), 7.16-7.28 (m, 4H), 7.33-7.47 (m, 2H), 7.51-7.74 (m, 2H), 9.56 (s, 4H); MS (FAB): m/z = 886 (37%, $[M+Cs]^+$), 776 (11%, $[M+Na]^+$), 754 (100%, $[M+H]^+$), 654 (53%, $[M-Boc+2H]^+$), 454 (80%, $[M-2Boc+3H]^+$).

    6: See scheme 3 for cyclization step, 35%; ^{1}H-NMR: δ = 1.27-1.53 (m, 18H), 3.35-3.51 (m, 4H), 3.54-3.67 (m, 4H), 3.87-4.26 (m, 8H), 4.98-5.16 (m, 4H), 7.09-7.56 (m, 18H), 9.44 (s, 4H); MS (FAB): m/z = 965 (44%, $[M+H]^+$), 865 (100%, $[M-Boc+2H]^+$), 765 (25%, $[M-2Boc+3H]^+$), 623 (55%, $[M-2Z-OtBu+2H]^+$).
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