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Straightforward and mild deprotection methods of *N*-mono- and N^1,N^7-functionalised bisaminal cyclens

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ABSTRACT

Strategic removal of the bisaminal bridge of *N*-mono- and N^1,N^7-difunctionalised cyclen glyoxal derivatives was carried out via transamination processes with vicinal diamines. These procedures were found to be particularly well-suited for cyclen targets bearing sensitive groups.

1. Introduction

Cyclen derivatives have been extensively studied in recent years, due to their strong coordination ability towards a wide range of cations, including transition metal ions and lanthanide ions.[1] Their complexes exhibit high thermodynamic stability and kinetic inertness suitable for biomedical applications such as magnetic resonance imaging[2] and radiopharmaceuticals,[3] among others.

Selective *N*-alkylation and/or functionalisation is a crucial step in the preparation of functional or poly-functional cyclen-based macrocyclic ligands bearing one or more chemically reactive functional groups in order to have an effective handle over their behavior and properties.[4] Cyclens bearing one or two soundly placed functionalized pendant arms are able to complete the coordination sphere of specific cations to form stable complexes. As another example, bifunctional ligands provide the requisite for covalent attachment to small molecules or targeting biomolecular vector of interest, such as, peptides,[5] proteins (monoclonal antibodies)[6] or nano-particles,[7] opening a wide range of potential applications including the development of metal-based targeted and responsive agents for diagnostic and molecular imaging (MRI, SPECT, PET),[4,8] tumor therapy[3,9] and luminescent materials.[8,10]

To date, several synthetic routes have been reported for the selective *N*-alkylation of cyclens including synthesis from acyclic precursors, direct alkylation or acylation or protection methodologies.[11] Each methodology presents its own interest, however all are presenting some drawbacks as the need of tricky chromatography purification.

A few years ago, tetraazamacrocyclic bis-aminals appeared to be an excellent tool that give access to both *N*-mono- and N^1,N^7-di-functionalised cyclens.[12] Cyclen was found to react with glyoxal yielding a tetracyclic tetraamine (cyclen glyoxal), which upon treatment with a stoichiometric amount of reactive halides leads to the formation of giving quaternary ammonium salts of *N*-mono-alkylated or N^1,N^7-dialkylated tetrazamacrocycle derivatives respectively. This methodology enables to functionalise by a wide range of pendant arms and to obtain dissymmetrical di-substituted cyclens, which are not accessible otherwise. In a classical procedure, ammonium salts are isolated by taking advantage of their progressive precipitation in the organic reaction medium, with very high yield. This avoids fastidious purifications as chromatography columns. However, the limitation of the bisaminal route is the deprotection of the cyclen glyoxal ammonium derivatives, which is generally achieved by treatment with a large excess of hydrazine monohydrate,[13] aqueous sodium hydroxide,[14] or an ethanolic solution of hydroxylamine,[15] limiting the use of sensitive groups such as esters, amides or phthalimides. Additionally, the deprotected compounds are difficult to extract from the deprotecting agents, which are, especially hydrazine, toxic/carcinogen and are proscribed for uses in an industrial scale/context.

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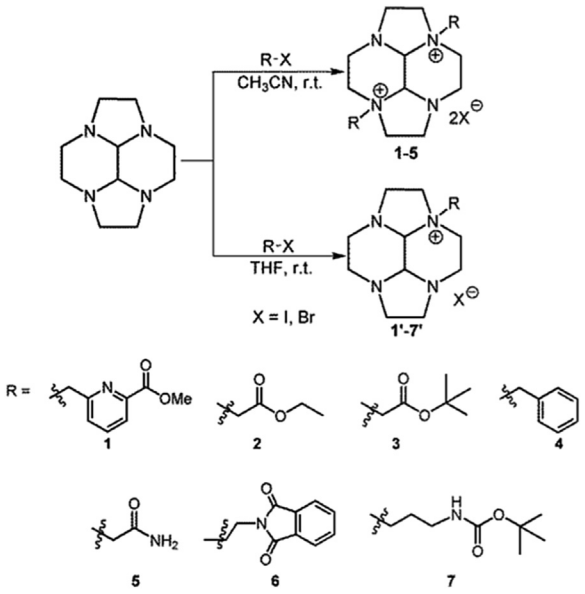
Herein, we wish to extend the scope of the bisaminal strategy to a more general and efficient deprotection approach to bypass its limitations. Thus, we present here novel, safe and clean routes to deprotect the bisaminal bridge in high yields, with respect to sensitive groups, which are usually denatured during this delicate step, offering a direct access to specific *N*-mono- and N^1,N^7-di-functionalised cyclens. The deprotections were carried out via a transamination process with vicinal diamines. These procedures were found to be very versatile, being particularly well-suited for cyclen targets bearing sensitive groups such as esters, amides, carbamates and phthalamides.

2. Results and discussion

Our method is based on the bisaminal template approach in order to achieve selective *N*-mono- and *trans*-N^1,N^7-functionalisation on the cyclen macrocycle.

Cyclen glyoxal[13] was selectively *N*-mono or *trans*-N^1,N^7-dialkylated by condensation with the appropriate halide alkyl/derivative/moiety, leading to the quaternary mono- or di-ammonium bisaminals in excellent yields depending on solvent and stoichiometry used (Scheme 1).[12] However, it must be mentioned that the di-alkylation with carbamates or phthamilides moieties didn't occur. Even with a high excess of the alkylating agent and in a polar solvent, the isolated compound is the mono-alkylated bisaminal salt respectively **6′** or **7′**. Compound **6′** was obtained as a salt insoluble in any organic media even in MeOH. In compound **7′**, the bulky Boc group may hinder the availability of the lone pair of N^7.



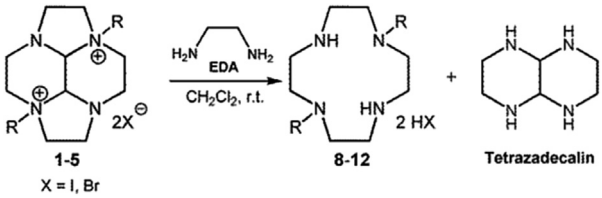
Scheme 1. General route for *N*-mono- and N^1,N^7-di-alkylation of cyclen glyoxal.

As stated above, the bisaminal bridge of *N*-mono- or N^1,N^7-functionalised macrocyclic derivatives is commonly removed using hydrazine monohydrate, sodium hydroxide or hydroxylamine. Most of the prepared derivatives reported in this paper are bearing sensitive functions, namely methyl (**1** and **1′**), ethyl (**2** and **2′**) and *t*-butyl esters (**3** and **3′**), amide (**5** and **5′**), phthalimide (**6′**) or Boc-protected amine (**7′**) to these classical methods and can thus not be obtained in these drastic conditions. However, these derivatives represent important key compounds in the synthesis of cyclen-based macrocyclic ligands.

To achieve the strategic deprotection, vicinal diamines, namely 1,2-ethylenediamine (EDA) and 1,2-phenylenediamine (*o*-PDA) were used to readily remove the bisaminal bridge.

2.1. Deprotection of *trans*-N^1,N^7-dialkylated cyclen glyoxal derivatives

In a first attempt, *trans*-N^1,N^7-dialkylated cyclen glyoxal derivatives were reacted with 1,2-ethylenediamine (Scheme 2). In a typical procedure (Method A), 1 equiv of quaternary salt (**1**–**5**) and approximately 2.2 equiv of EDA were stirred for 1–4 h at room temperature in dichloromethane leading to the formation of a white precipitate, which was isolated, structurally characterised and revealed to be a mixture of *trans*- and *cis*-1,4,5,8-tetraazadecalin (TAD).[16] This result is not surprising since TAD derivatives have been intended to act as stable 'cores' of cyclen, homocyclen and cyclam synthesis.[17] After removal of the TAD by filtration, the desired product was simply obtained by evaporating the solvent.



Scheme 2. Method A: Deprotection of di-substituted cyclen glyoxal derivatives with 1,2-ethylenediamine.

Different organic solvents were attempted namely acetonitrile, chloroform, toluene and THF. Even though the starting quaternary ammonium is not soluble in all these solvents, the reaction proceeds to completion within hours under the same conditions. Still, it was noted that the reaction is much faster in dichloromethane. The insolubility of TAD in these organic solvents favors a smooth separation of the aza-macrocycles by a mere filtration. It was also found that when a polar solvent (methanol or ethanol) is used, the esters **1**–**3** undergo an aminolysis with EDA at room temperature.

In most cases, the deprotected functionalised-cyclen derivatives were isolated in a protonated form. A deprotonation procedure was subsequently carried out on the salts to neutralize the hydrogen halides by cesium carbonate to give N^1,N^7-difunctionalized cyclen derivatives **8**–**12** (Table 1, method A). Analytically pure compounds were obtained with good to quantitative yields.

Based on the above, we had foreseen the replacement of EDA with 1,2-phenylendiamine (*o*-PDA). The resulting aromatic tetrazadecalin byproduct, being even more stable, should also favor the removal of the bisaminal bridge and therefore the release of quaternary ammoniums.

The N^1,N^7-functiontionalised bisaminal derivatives **1**–**5** were thus submitted to *o*-PDA (3 equiv) After less than 4 h, all the compounds could be fully deprotected in THF or MeOH. The resulting compounds **8**–**12** precipitated and could be recovered by simple filtration. Contrary to our original expectations, the tetrazadecaline, 5,11-dihydroquinoxalino[2,3-*b*]quinoxaline, was not formed as by-product. NMR and mass analysis showed that 1,4-benzodiazine (quinoxaline) was instead formed,[18] suggesting that only 1 equiv of *o*-PDA is needed to achieve complete deprotection (Scheme 3). In fact, the corresponding N^1,N^7-difunctionalised cyclen macrocyles **8**–**12** were isolated in form of salts with high yields and excellent purity in the presence of only 1.1 equiv of *o*-PDA (Table 1, method B).

However, the reactions need to be carried out at ambient temperature in a dry solvent and inert atmosphere due to the sensitivity of the reaction to moisture and oxygen. Actually, when in solution, phenylenediamines are known to be particularly prone to auto-oxidation by air oxygen.[19]