Tetrahedron Letters 56 (2015) 759–765

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

Digest Paper

Synthetic strategies for preparation of cyclen-based MRI contrast agents

Nevenka Cakić, Serhat Gündüz, Rathikrishnan Rengarasu, Goran Angelovski *

MR Neuroimaging Agents Group, Max Planck Institute for Biological Cybernetics, Spemannstr. 41, 72076 Tübingen, Germany

ARTICLE INFO

Article history:
Received 28 October 2014
Revised 12 November 2014
Accepted 5 December 2014
Available online 19 December 2014

Keywords:
Cyclen
Macrocyclic ligands
Magnetic resonance imaging
Lanthanide complexes

ABSTRACT

Cyclen-based macrocyclic ligands have an essential role in the development of contrast agents for magnetic resonance imaging (MRI). A prevailing need for preparation of multifunctional probes triggered a number of attempts to synthesize and derivatize ligands which efficiently chelate lanthanide ions and have advantageous MRI properties. This digest Letter summarizes the most common synthetic approaches for the preparation of macrocyclic ligands based on cyclen depending on the desired application.

© 2014 Published by Elsevier Ltd. This is an open access article under the CC BY license (http://creativecommons.org/licenses/by/4.0/).

Contents

Introduction

Magnetic resonance imaging (MRI) has become an important tool in biomedical research and is an essential diagnostic method in clinical radiology today. Moreover, the existence of different types of MRI contrast mechanisms in tissues provides for continuous development of this method.[1] MRI enables tracking of physiological changes noninvasively, allowing imaging of specific biological processes at the molecular or cellular level. To further improve the specificity of MRI, a number of contrast agents have been developed and employed to date. According to their mechanism of action, contrast agents suitable for ^{1}H MRI can be classified as T_1- and T_2-shortening agents or CEST agents.[2] The vast majority of them are based on lanthanide complexes with polyamino polycarboxylic ligands. Due to better thermodynamic and kinetic stability properties that reduce the potential toxicity of the MRI agents in vivo, multidentate macrocyclic chelators based on 1,4,7,10-tetra-azacyclododecane (cyclen) are the most commonly used chelating agents nowadays,[2] although their role in preparing contrast agents for positron emission tomography (PET), single photon emission computed tomography (SPECT), or optical imaging is also very important.[3,4]

The extensive use of cyclen-based contrast agents demands continuous improvements in derivatization and preparation of novel macrocyclic molecules with various chelating and functional groups. Synthetic changes aim to improve specific physicochemical or biological properties of the contrast agents thereby enabling their binding to particular macromolecules, localization to a specific organ or receptor and hence expanding the scope of their application.[5–7] To obtain various products with diverse desired structures and properties, an awareness of the synthetic chemistry

* Corresponding author. Tel.: +49 7071 601 916; fax: +49 7071 601 919.
E-mail address: goran.angelovski@tuebingen.mpg.de (G. Angelovski).

http://dx.doi.org/10.1016/j.tetlet.2014.12.087
0040-4039/© 2014 Published by Elsevier Ltd.
This is an open access article under the CC BY license (http://creativecommons.org/licenses/by/4.0/).

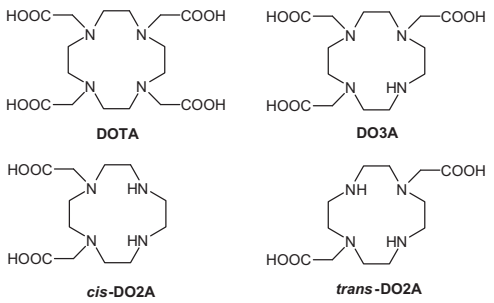


Figure 1. Structures of principal chelators described in this work.

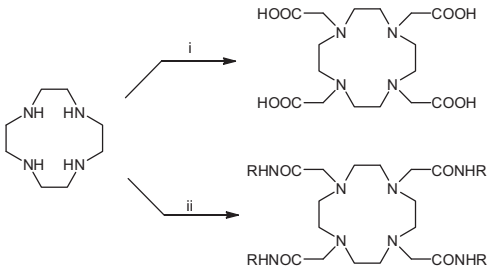
of these systems is required, especially of the numerous *C*- and *N*-functionalization procedures of cyclen.

To this end, a number of review articles and books focused on preparation, general chemical properties, or application of contrast agents have been already published.[1,2,8–13] In the present work, we concisely summarize existing methodologies for the synthesis of the most common macrocyclic chelators (cyclen-1,4,7,10-tetraacetic acid – DOTA, cyclen-1,4,7-triacetic acid – DO3A and cyclen-1,4- or 1,7-diacetic acid – *cis*- or *trans*-DO2A, respectively, Fig. 1) and their derivatives, emphasizing the most straightforward synthetic pathways for their preparation. Furthermore, we discuss different methodologies that lead to functionalization of the cyclen pendant arms. Finally, we briefly list some recent examples of contrast agents that were prepared according to such procedures, finding useful applications.

Ligands based on DOTA

DOTA is an octadentate ligand with four carboxylate and four amino groups which coordinate with lanthanide ions. Consequently, their complexes with DOTA possess high thermodynamic stability and kinetic inertness, making these compounds useful in MRI as contrast agents. DOTA can be easily prepared by tetra N-alkylation of cyclen with chloroacetic acid. This synthetic procedure was reported almost four decades ago and is still an acceptable method for DOTA preparation (Scheme 1).[14] Other haloacetic acid derivatives (bromo- or iodo-) can also be used as alkylating agents, and such a procedure is especially useful for the preparation of the tetraamide (DOTAM) chelators. Here the common precursor is chloroacetyl chloride which is first converted to the desired chloroacetamide; subsequently the conversion of chloro- to iodoacetamide is done prior to alkylation (Scheme 1),[15] resulting in numerous compounds that are suitable for use as contrast agents for CEST MRI.[16,17]

A number of procedures for preparation of DOTA derivatives exist to date, resulting in products that can be divided into two general groups: (a) *N*-functionalized and (b) *C*-functionalized

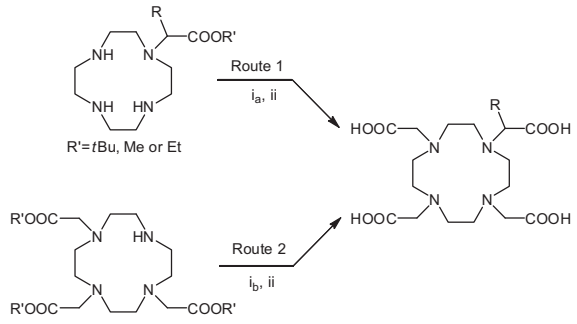


Scheme 1. General synthetic scheme for the preparation of DOTA (top) and DOTAM-type chelators (bottom) from cyclen. The most common conditions are: (i) XCH_2COOH or (ii) XCH_2CONHR (X = Cl, Br, I), DIPEA or K_2CO_3, MeCN or DMF. R stands for hydrogen, an alkyl or an aryl group.

DOTA-type ligands. The former can be prepared starting from the monoalkylation of cyclen with one group, followed by the alkylation of the remaining three secondary amine positions with another group (Scheme 2, route 1). The second approach for *N*-functionalized DOTA ligand synthesis includes alkylation of the remaining amine on the ester-protected DO3A-type ligand (Scheme 2, route 2), which easily reacts with various alkyl halides in aprotic solvents. These two procedures will be described in more detail in the next section (see below). Older procedures to prepare *N*-functionalized DOTA derivatives involve the use of acyclic precursors and 2+2, 3+1 or 4+0 cyclization processes.[11] However, these procedures are no longer the most convenient, given the wide commercial availability of cyclen as the essential starting material in all procedures.

C-functionalized DOTA-type ligands can be prepared by intramolecular or intermolecular cyclization methods using appropriate scaffolds. For instance, the intramolecular cyclization of tosyl amide (prepared from tetrapeptide followed by borane reduction and tosylation) at high dilution and subsequent detosylation with a concentrated strong acid results in *C*-functionalized cyclen.[18] Its alkylation with *tert*-butyl bromoacetate, followed by hydrolysis yields a *C*-functionalized DOTA-type ligand **1** (Scheme 3, route 1). This synthesis has been improved by initiating the cyclization of diamine with carbamate-protected disuccinimido ester at high-dilution at a higher temperature (90 °C) (Scheme 3, route 2).[19] Using these synthetic approaches, a number of different *C*-functionalized DOTA can be prepared by a simple variation of side arm (R′).

In general, because preparation of *N*-functionalized DOTA derivatives is much more convenient, they are the more frequently used ligands. One of the first DOTA bifunctional chelators **2** was developed for protein and antibody labeling (Fig. 2). The synthetic approach to obtain **2** includes side arm transformation following the strategy from Scheme 2 (route 1). The initial precursor contains a *p*-nitrophenyl group, which is then transformed to isothiocyanate, allowing further synthetic transformations and coupling reactions with primary amines.[20] Following a similar synthetic strategy, *N*-functionalized DOTA derivatives with self-immolative arms as potential enzyme-responsive MRI contrast agents were reported (**3**, Fig. 2).[21] Recently, a range of building blocks for the preparation of DOTA-like chelating agents was also prepared. The procedure starts from DOTAGA-anhydride (GA = glutaric acid) which can be selectively opened with different nucleophiles, resulting in a variety of bifunctionalized DOTA derivatives of type **4** (Fig. 2).[22] This kind of ligand is useful for both in vitro and in vivo applications. For instance, the reactive moiety of these DOTA-type chelators allows further coupling procedures and



Scheme 2. Synthetic routes for the preparation of *N*-functionalized DOTA ligands. The most common reagents: (i_a) $BrCH_2COOR'$, K_2CO_3/MeCN; (i_b) $RCH(X)COOR'$, K_2CO_3 or Et_3N/MeCN or DMF; (ii) HCl/MeOH, HCOOH or TFA (for R′ = *t*Bu), or LiOH, NaOH or KOH, EtOH/H_2O (for R′ = Me or Et). R stands for a number of diverse substituents, R′ = *t*Bu, Me or Et and X = Cl or Br.

Download English Version:

https://daneshyari.com/en/article/5268388

Download Persian Version:

https://daneshyari.com/article/5268388

Daneshyari.com