



Dendritic *bis*- and *tetrakis*-iminodiacetic acid-boronate complexes in one-pot cross-coupling reactions



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ARTICLE INFO

Article history:

Received 9 March 2016

Received in revised form

20 May 2016

Accepted 24 June 2016

Available online 25 June 2016

Keywords:

Boronates

Cross-coupling reactions

Dendrimers

Hydrolysis

Iminodiacetic acid

Suzuki-Miyaura reaction

ABSTRACT

Iminodiacetic acids are versatile metal chelating ligands. We herein undertook a study of dendritic *bis*- and *tetrakis*-iminodiacetic acids functionalized at the peripheries of branched core moieties. The dendritic iminodiacetic acids are synthesized by *O*- and *N*-alkylations of chosen alcohol and amine reactive sites emanating from a branched core. In order to identify the reactivities of such dendritic iminodiacetic acids, chelation with arylboronates is conducted. An assessment of the hydrolysis under aq. basic condition shows that dendritic boronates hydrolyze to boronic acid significantly slower than monomeric boronates. Slower hydrolysis of dendritic boronates is taken advantage, in order to conduct competitive C–C bond-forming Suzuki-Miyaura cross-coupling reactions. Teraryl synthesis is performed using monomeric and dendritic boronates. The iterative, multiple aryl-aryl bond formation is conducted subsequently, so as to prepare tetraaryls, through consecutive reactions of chosen boronic acid, monomeric boronate, dendritic boronate and aryl bromide, in one-pot. The study shows that slower hydrolysis of dendritic boronate is valuable in order to conduct multiple consecutive aryl-aryl bond formation.

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1. Introduction

Iminodiacetic acid is a versatile chelating ligand for metal ions, aided by additional coordination of the imine moiety of the ligand with the metal ions [1–4]. Ethylenediamine tetraacetic acid is a prime example of the versatility of this ligand to metal ion coordination [5]. Iminodiacetic acid is a valuable ligand for organometallic reactions, for example, the value of this ligand in boronate complex formation and subsequent slow release to boronic acid from the complex in Suzuki-Miyaura cross-coupling reactions has been exploited elegantly by Burke and co-workers [6], as a strategy to mitigate a major undesired homocoupling of boronic acids in the cross-coupling reactions. With innumerable occasions in which iminodiacetic acid ligands are involved, we undertook a study in which this ligand is installed multiply in a dendritic fashion. Dendritic structures are characterized by the presence of building blocks arranged symmetrically around a core atom or moiety. Seminal early reports on the synthesis of cascade molecules by Vögtle [7], poly(amidoamine) series by Tomalia [8], arborals by Newkome [9], poly(benzyl ether) series by Fréchet [10],

poly(propylene imine) series by Meijer [11] and phosphorus dendrimer series by Caminade and Majoral [12] established a new direction to the synthesis and studies of highly branched molecules. Ever since these reports, interest in highly branched and mono-dispersed macromolecules is established thoroughly in multiple directions of studies [13–16], including stabilization of metal catalysts by dendritic ligands [17,18]. With the advancements in dendritic structures, we undertook an effort to study the iminodiacetic acid ligand when arranged in a branched fashion. Dendritic iminodiacetic acids were synthesized, following which, the benefits of the newly formed dendritic iminodiacetic acids were assessed through formation of boronate ester complexes. The dendritic boronates were utilized subsequently in Suzuki-Miyaura iterative cross-coupling reaction, so as to form ter- and tetraaryls in one-pot. Synthesis and studies of new dendritic iminodiacetic acids and their boronate complexes in the cross-coupling reactions are reported herein.

2. Results and discussion

2.1. Synthesis *bis*- and *tetrakis*-iminodiacetic acids

Molecular structures of the target *bis*- (1) and *tetrakis*-iminodiacetic acids (2) containing branched dendritic structures are

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shown in Fig. 1. These dendritic iminodiacetic acids were synthesized, from commercially available monomer building blocks, namely, bromoethyl acetate and bromoacetonitrile.

Synthesis of zero generation **1** and first generation **2** dendrimers was initiated using 2,2'-diaminoethyl ether (**3**) as the core, by a divergent assembly method. Thus, iterative reactions of *O*- and *N*-alkylations and functional group reductions, in a multistep synthetic sequence, were utilized to prepare **1** and **2** (Scheme 1). The diamine derivative **3**, in turn, was prepared by subjecting diethylene glycol to *bis-O*-tosylation, reaction of the resulting *bis-O*-tosylate with NaN₃ and reduction of the resulting *bis*-azide to *bis*-amine **3**. Reaction of **3** with ethyl bromoacetate afforded *tetrakis*-ester **4**, in 90% yield. *Tetrakis*-ester derivative **4** was subjected to reduction in the presence of LiAlH₄ in THF to the corresponding *tetrakis*-alcohol **5**, in a nearly quantitative yield (Scheme 1).

The progress of reduction of ester functionalities in **4** was monitored by the disappearance of stretching frequency at 1741 cm⁻¹ in the IR spectrum. Upon completion of the reaction, *tetrakis*-alcohol **5** was isolated from inorganic salts through differential solubilisation in MeOH and in CHCl₃. *Tetrakis*-alcohol **5** was reacted subsequently with bromoacetonitrile in THF:DMF (1:1), in the presence of NaH, under reflux. The resulting reaction mixture was purified (SiO₂) to afford *tetrakis*-nitrile **6**, in 56% yield. *Tetrakis*-nitrile **6** was reduced to *tetrakis*-amine **7**, using Raney-Co catalyst and H₂ (50 atm), in a nearly quantitative yield. The progress of the nitrile reduction in **6** to amine was monitored by the disappearance of stretching frequency at ~2209 cm⁻¹ in the IR spectrum. The iterative reaction of *N*-alkylation of *tetrakis*-amine **7** with ethyl bromoacetate and purification of the reaction mixture (SiO₂, CH₂Cl₂/MeOH linear gradient) afforded *octakis*-ester **8**, in 48% yield (Scheme 1). The newly-formed *tetrakis*- (**4**) and *octakis*- (**8**) esters were hydrolysed under aq. alkaline conditions to afford the corresponding *tetrakis*- and *octakis*-acids **1** and **2**, respectively, in quantitative yields. The structural homogeneities of the *bis*- (**1**) and *tetrakis*- (**2**) iminodiacetic acids were verified by physical methods. Changes in the chemical shifts of the -CH₂- group adjacent to the peripheral functionality were observed periodically. Thus, disappearance of the singlet at ~3.59 ppm of -CH₂CO₂Et group and appearance of resonances at ~2.56 and ~3.64 ppm, corresponding to -CH₂CH₂OH, were observed, consistent with the presence of these functional groups. Similarly, disappearance of the signal at 4.29 ppm of -CH₂CN and appearance of resonances at ~3.45 and ~2.74 ppm of -CH₂CH₂NH₂ were observed for the nitrile to amine reaction. Functional group changes at the peripheries were also confirmed by ¹³C NMR spectroscopy. Disappearance of -CN resonance at ~116 ppm and the appearance of carbonyl group resonance of the ester functionality at ~171 ppm confirmed complete conversion of nitrile to amine. Similarly, reduction of ester to alcohol led to the appearance of a signal at ~62 ppm (-CH₂OH). The constitutions of the dendrimers were confirmed further by mass

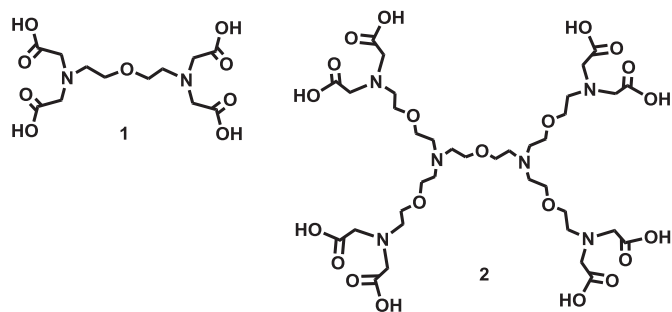


Fig. 1. Molecular structures of the dendritic iminodiacetic acids.

spectrometry in each case. Fig. 2 provides overlay spectra of the conversion of *tetrakis*-ester **4** to *octakis*-ester **8**, involving *tetrakis*-alcohol **5** and *tetrakis*-nitrile **6** intermediates.

2.2. Studies of boronate complexes of **1** and **2**

Following synthesis of *bis*- (**1**) and *tetrakis*-iminodiacetic acids (**2**), their complexation with boronic acid and subsequent reactions of boronates were investigated. Iminodiacetic acid forms the corresponding boronate upon reaction with a boronic acid. Additional coordination of imine moiety to boron centre in the boronate complex provides stability to the complex, and thus, iminodiacetic acid boronate complexes are considered orthogonal to the reactivity of boronic acids. Facile hydrolysis of iminodiacetic acid-boronate complex releases the reactive boronic acid. Such a stability of a boronate and its lability under hydrolytic condition to form boronic acid is exploited elegantly in the particular class of boronic acid mediated reactions, namely, the Suzuki-Miyaura cross-coupling reactions [19–21]. The boronate mediated Suzuki-Miyaura cross-coupling reactions are developed immensely in order to overcome pertinent difficulties of protodeboronation, oxidation and homocoupling competing reactions [22], as demonstrated by Lloyd-Jones and co-workers. Important to sustained developments in Suzuki-Miyaura C–C bond forming reactions are: (i) the discovery of ‘slow-release’ methodology, in which the reactive boronic acid is generated *in situ* through controlled basic hydrolysis of a boronate ester, developed by Burke and co-workers [23–26]; (ii) the development of 1,8-diaminonaphthalene as the protecting group of boronic acids, the deprotection to the reactive boronic acid implemented through an acid treatment, reported by Sugimoto and co-workers [27,28] and (iii) the development of organotrifluoroborate as a robust surrogate of boronic acid, which hydrolyzes in protic media to generate the boronic acid [29–32]. We followed these developments in order to identify the reactivities of dendritic *bis*- and *tetrakis*-iminodiacetic acids.

Syntheses of *bis*- and *tetrakis*-boronates **9** and **10** were conducted upon reaction of arylboronic acids with dendritic iminodiacetic acids **1** and **2** in DMF or DMSO-PhMe (1:5) for ~24–48 h, with azeotropic removal of water from the reaction mixture (Scheme 2) [33].

The formation of the phenyl *bis*-boronate ester (**9a**) was ascertained from ¹H NMR spectrum, following the early report of iminodiacetic acid-boronate complexes studied by Wrackmeyer and co-workers [34]. The diastereotopic methylene protons of iminodiacetic portion in dendritic phenyl *bis*-boronates appeared as a well-resolved pair of doublets at δ 4.39 and 4.22, with a geminal coupling constant of 17.1 Hz. Aromatic protons appeared as a set of multiplets between δ 7.49 and 7.35 ppm. Internal methylene protons adjacent to ether and tertiary nitrogen moieties resonated as triplets at δ 3.89 and 3.07 ppm, respectively. In ¹³C NMR spectrum, the diastereotopic methylene carbon resonated at δ 59.2 ppm, whereas carbons adjacent to tertiary nitrogen and ether moieties appeared at δ 57.8 and 66.3 ppm, respectively. Carbonyl carbon of the ester moiety appeared at δ 168.5 ppm. ¹¹B NMR spectrum of dendritic phenyl *bis*-boronate showed chemical shift at δ 11.9, as compared to phenyl boronic acid δ value 29.5. Composition of the phenyl *bis*-boronate (**9a**) was also confirmed by mass spectrometry, which showed molecular ion peak at m/z 531.1716, corresponding to the sodium adduct. *Tetrakis*-boronates (**10**) followed a similar trend as that of *bis*-boronates. In ¹H NMR spectrum of **10a**, the diastereotopic methylene protons appeared as a pair of doublets at δ 4.45 and 4.26, with geminal coupling constant of 17.2 Hz, whereas the aromatic protons resonated as two multiplets between δ 7.53 and 7.36 ppm. The methylene protons of ether moiety of the

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