Molecular Catalysis 444 (2018) 70–75

Contents lists available at ScienceDirect

Molecular Catalysis

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

Research Paper

Influence of base additives on the selectivity of palladium-catalysed aminocarbonylation: Highly selective functionalization of a cavitand scaffold

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ARTICLE INFO

Article history:
Received 24 August 2017
Received in revised form 17 October 2017
Accepted 24 October 2017

Keywords:
Cavitand
Aminocarbonylation
Carbon monoxide
Palladium
Carboxamide
Ketocarboxamide

ABSTRACT

Tetracarboxamides and tetrakis(2-ketocarboxamides) of resorcinarene-based cavitands have been synthesised in palladium-catalysed aminocarbonylation of the corresponding tetraiodocavitand. In this way, deepened cavitands with the same functionalities at the upper rim were obtained even in the simultaneous application of two primary amines as *N*-nucleophiles. The influence of base additives on the unexpectedly high chemoselectivity towards tetra-functionalised products, *i.e.* tetrakis(2-ketocarboxamides) and tetracarboxamides, has been investigated in details.

1. Introduction

Among the host molecules used in supramolecular chemistry, resorcinarene-based cavitands [1] play a peculiar role. They possess a fascinating conformationally rigid, bowl-shaped structure. In order to modify the cavity, there are two major possibilities: i) to shape the inner cavity of the rigid bottom part via variation of the methylene bridges, ii) to form 'arms' with appropriate length and polarity connected to the upper (R^2) and bottom rim (R^1) ('embroidering' the bowl) (Fig. 1). The appropriate choice of the shape and functionalities, *i.e.*, the groups to interact with the entering guest molecule, could result in the formation of sensors, nanoreactors and drug delivery systems [2]. In addition to conventional organic reactions [3], homogeneous catalytic reactions as well as the appropriate combination of high-yielding conventional synthetic procedures and highly selective homogeneous catalytic reactions can be used for the synthesis of the basic skeleton and its further functionalization. These approaches are not widely used in the synthesis of functionalised cavitands; there are only sporadic examples for the use of palladium-catalysed cross-coupling reactions [4].

We have been interested in the synthesis of deepened cavitands via benzyl bromination, Williamson etherification using 4-iodophenol. The resulting tetraiodocavitand (**1**) [5] provided easy access to a wide variety of deepened cavitands using its four iodoaryl functionalities.

Among the transition metal catalysed homogeneous reactions, aminocarbonylation, *i.e.*, the formation of carboxamides (single CO insertion) and that of the 2-ketocarboxamides (double CO insertion) play a special role due to the presence of amide functionalities. It has to be added that carboxamide formation was already shown by using aminocavitands and the appropriate acylation agents [6].

Unexpectedly high selectivities towards carboxamides and 2-ketocarboxamides were obtained using tetraiodocavitand substrates in palladium-catalysed aminocarbonylation [5]. As for the aminocarbonylation of simple model substrates, since the early discovery of Heck et al. [7], hundreds of examples have been published on the carbonylation of iodo- and bromoarenes, iodoalkenes as well as their synthetic surrogates, aryl triflates and alkenyl triflates, respectively. The structural variation of both the substrates and the *O*- and *N*-nucleophiles have been reported in several reviews [8]. The wide applicability of aminocarbonylation, due to its high functional group tolerance, was demonstrated also in our group for

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http://dx.doi.org/10.1016/j.mcat.2017.10.031
2468-8231/

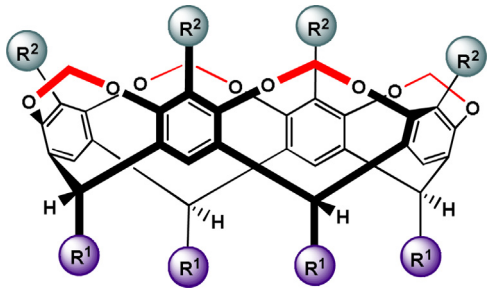

Fig. 1. Options of functionalization at the upper (R^2) and the bottom rims (R^1) of a cavitand.

model compounds [9] and derivatives of practical (pharmacological) importance [10].

In this study, we aimed to broaden the scope of palladium-catalysed homogeneous catalytic reactions on a cavitand scaffold and to investigate the role of bases on chemoselectivity and reaction mechanism explaining 'tetra-functionalization'.

2. Experimental

2.1. General procedures

All reagents were purchased from Aldrich and used as received. THF was dried using conventional methods. ^{1}H and ^{13}C NMR spectra were recorded in $CDCl_3$ on a Bruker Avance III 500 spectrometer at 500 and 125.7 MHz, respectively. ^{1}H chemical shifts (δ), reported in parts per million (ppm) downfield, are referenced to the residual protons of $CDCl_3$ at 7.26 ppm. The ^{13}C chemical shifts are referenced to the carbon resonance of $CDCl_3$ at 77.0 ppm. MALDI-TOF MS spectra were obtained on an Autoflex II TOF/TOF spectrometer (Bruker Daltonics) in positive ion modes, using a 337 nm pulsed nitrogen laser (accelerating voltage: 20.0 kV, matrix: 2,5-dihydroxybenzoic acid). Cavitand **1** was prepared as previously described [5]. Full characterization of **2a** and **3a** has already been reported elsewhere [11].

2.2. A typical procedure for aminocarbonylation experiments

2.2.1. Method A

In a parent experiment (Table 1, entry 1) cavitand **1** (150 mg, 0.1 mmol), $Pd(OAc)_2$ (5.6 mg, 0.025 mmol) and PPh_3 (13.1 mg, 0.05 mmol) were weighed into a 100 mL flask equipped with a gas-inlet, and a reflux condenser with a balloon at the top of it and placed under an inert atmosphere. Dry DMF (15 mL), Et_3N (0.11 mL, 0.8 mmol) (the corresponding amount of base is given in Table 1) and *n*-propylamine (0.041 mL, 0.5 mmol) (and/or *n*-decylamine (0.100 mL, 0.5 mmol)) were added, and then the reaction mixture was placed under atmospheric CO pressure. The reaction mixture was stirred at 60 °C for 48 h. The Pd metal traces were filtered, and the filtrate was evaporated to dryness. The residue was dissolved in chloroform (20 mL), washed with 5% hydrochloric acid (20 mL), brine (20 mL) and water (20 mL). The organic phase was dried over Na_2SO_4. The drying agent was filtered, the chloroform was partially evaporated (to a volume of 5 mL) and treated with *n*-hexane. The off-white precipitate was filtered, dried and analysed by ^{1}H NMR spectroscopy to determine the composition of the reaction mixture.

2.2.2. Method B

In those experiments where solid base (K_2CO_3) was used, cavitand **1** (150 mg, 0.1 mmol), $Pd(OAc)_2$ (5.6 mg, 0.025 mmol), PPh_3 (13.1 mg, 0.05 mmol) and K_2CO_3 (327 mg, 2.4 mmol) were weighed into a 100 mL flask equipped with a gas-inlet, and a reflux condenser with a balloon at the top of it and placed under an inert atmosphere. DMF (15 mL), *n*-propylamine (0.041 mL, 0.5 mmol) (and/or *n*-decylamine (0.100 mL, 0.5 mmol)) were added and then the reaction mixture was placed under atmospheric CO pressure. As above, the reaction was carried out under the conditions indicated in Table 1. The work-up of the reaction mixture was identical to that above.

2.3. Characterizations of the novel products

Cavitand **2b** ('*N*-Decylcarboxamide cavitand): Pale yellow powder (114 mg, 66%), m.p. 220–224 °C; [Found: C, 74.22; H, 8.25; N, 3.03%, $C_{108}H_{140}N_4O_{16}$ requires C, 74.11; H, 8.06, N, 3.20%]; IR (KBr, ν (cm^{-1})) 973, 1245, 1425, 1642, 1665, 1716, 3034; δ_H (500.1 MHz, $CDCl_3$): 0.90 (t, *J* 6.88 Hz, 12H, CH_3CH_2), 1.20-1.45 (m, 56H, CH_3CH_2), 1.59-1.74 (m, 8H, $NHCH_2CH_2$), 1.85 (d, *J* 7.3 Hz, 12H, CH_3CH), 3.45 (q, *J* 6.5 Hz, 8H, CH_2NH), 4.67 (d, *J* 7.3 Hz, 4H, inner of OCH_2O), 5.00 (s, 8H, $ArCH_2O$), 5.10 (q, *J* 7.0 Hz, 4H, $CHCH_3$), 5.73 (d, *J* 7.3 Hz, 4H, outer of OCH_2O), 6.57 (m, 4H, NH), 6.85 (d, *J* 8.4 Hz, 8H, Ar), 7.41 (s, 4H, Ar), 7.75 (d, *J* 8.4 Hz, 8H, Ar). δ_C (125.1 MHz, $CDCl_3$): 14.1, 16.2 (CH_3CH), 22.7, 27.1, 29.3, 29.4, 29.6, 29.6, 30.1, 31.2 (CH_3CH), 31.9, 40.2, 60.5 ($ArCH_2O$), 100.2 (OCH_2O), 114.2, 120.8, 122.5, 127.7, 128.9, 138.9, 154.0, 160.8, 166.8 (NHC=O). MALDI-TOF *m*/*z*: 1751.19 $[M+H]^+$.

Cavitand **3b** ('*N*-Decylketocarboxamide cavitand'): White powder (133 mg, 72%), m.p. 198–202 °C; [Found: C, 72.03; H, 7.76; N, 2.89%, $C_{112}H_{140}N_4O_{20}$ requires C, 72.23; H, 7.58; N, 3.01%]; IR ($CHCl_3$, ν (cm^{-1})) IR (KBr, ν (cm^{-1})) 970, 1251, 1435, 1572, 1649, 2851, 2953; δ_H (500.1 MHz, $CDCl_3$): 0.90 (t, *J* 6.88 Hz, 12H, CH_3CH_2), 1.10-1.45 (m, 56H, CH_3CH_2), 1.52-1.72 (m, 8H, $NHCH_2CH_2$), 1.85 (d, *J* 7.3 Hz, 12H, CH_3CH), 3.46 (q, *J* 6.5 Hz, 8H, CH_2NH), 4.67 (d, *J* 7.3 Hz, 4H, inner of OCH_2O), 5.00 (s, 8H, $ArCH_2O$), 5.09 (q, *J* 7.0 Hz, 4H, $CHCH_3$), 5.74 (d, *J* 7.3 Hz, 4H, outer of OCH_2O), 6.57 (m, 4H, NH), 6.84 (d, *J* 8.4 Hz, 8H, Ar), 7.41 (s, 4H, Ar), 8.38 (d, *J* 8.4 Hz, 8H, Ar). δ_C (125.1 MHz, $CDCl_3$): 14.1, 16.2 (CH_3CH), 22.7, 27.1, 29.3, 29.4, 29.6, 29.6, 30.1, 31.2 (CH_3CH), 31.9, 40.2, 60.5 ($ArCH_2O$), 100.2 (OCH_2O), 114.2, 120.8, 122.5, 127.7, 128.9, 138.9, 154.0, 162.5, 162.9 (NHC=O), 186.2 (C=O). MALDI-TOF *m*/*z*: 1884.89 $[M+Na]^+$.

3. Results and discussion

Aminocarbonylation of tetraiodocavitand (**1**) as model substrate of supramolecular importance, synthesised by an improved methodology in a high-yielding reaction sequence [5], was carried out in the presence of *in situ* formed palladium(0) catalytic system (Scheme 1). The use of $Pd(OAc)_2$ precursor and two eq. of PPh_3, acting as both ligand and reducing agent, to form coordinatively highly unsaturated reactive catalyst has been already discussed in details [12]. Two primary amines of different sizes, *n*-propylamine (**a**) and *n*-decylamine (**b**) were chosen as *N*-nucleophiles in the presence of various base additives in order to shed some light on the fine details of the mechanism of aminocarbonylation providing unexpected chemoselectivity.

In perfect agreement with our recent report [11], the product distribution was surprisingly simple. Using the above two amines (**a** and **b**) in aminocarbonylation, either separately or together, four products were obtained only: the carboxamide type products (**2a** and **2b**) and the 2-ketocarboxamide type products (**3a** and **3b**) bearing four identical functionalities at the upper rim. That is, no 'mixed' products were formed in detectable amount (by ^{1}H NMR) and the reaction has to be considered as 'highly selective' in two contexts: *i)* either four carboxamide or four ketocarboxamide groups, formed via simple or double carbon monoxide insertion, respectively, can only be found in the tetra-functionalised compounds; *ii)* the use of both nucleophiles (**a** and **b**) at the same time resulted in the formation of compounds holding either four *n*Pr or