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High-yielding synthesis of deepened cavitands bearing picolyl moieties on the upper rim

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ABSTRACT

Conventional high-yielding reactions (such as etherification, condensation reactions) and palladium-catalysed aminocarbonylation served as highly efficient synthetic tools for the synthesis of novel cavitands bearing Schiff-base and carboxamide/2-ketocarboxamide functionalities, respectively. In this way, two families of deepened cavitands with related structures possessing 2-, 3- and 4-picolylamine moieties on the upper rim have been synthesised. Unexpectedly high chemoselectivities towards tetracarboxamides and tetrakis(2-ketocarboxamides) have been observed. The aminocarbonylation of tetraiodocavitand as an iodoaromatic substrate proved to be highly selective in two aspects: (i) no substantial formation of either the mono-, di- or trifunctionalized products was observed and (ii) no 'mixed' products possessing both carboxamide and 2-ketocarboxamide fragments, due to selective simple and double carbon monoxide insertion, were detected.

1. Introduction

2-Methylresorcine-based cavitands[1] with a conformationally rigid, bowl-shaped macrocyclic structure have been generating tremendous interest in the supramolecular community. In addition to cyclodextrins,[2] calixarenes,[3] calix-resorcinarenes[4] and cucurbiturils,[5] the well-known families of molecular hosts with exceptional molecular recognition ability, cavitands have also gained wide applications in 'host–guest' chemistry.

The size and shape of the cavitands are essential considering their potential applications as sensors, nanoreactors and drug delivery systems. Especially the peculiarities of the upper rim, i.e., that of the upper inlet of such molecular containers was brought into focus.[6] Although deepening and enlarging the molecular pocket of cavitands was principally accomplished mainly by conventional organic reactions;[7] some homogeneous catalytic reactions were sparsely employed.[8] In one of our previous papers we described the upper rim functionalisation of a tetraidocavitand by various homogeneous catalytic reactions such as cross-coupling (Suzuki, Sonogashira, Stille) reactions and aminocarbonylation.[9]

Since the latter carboxamide-forming reaction serves as a key-reaction in the present work, it should be mentioned that carboxamide functionalities were previously introduced into the cavitand skeleton by acylation of the corresponding aminocavitands.[10] Palladium-catalysed carbonylations have become indispensable tools in organic chemistry.[11] Among them, palladium-catalysed aminocarbonylation of organohalides (preferably iodoalkenes and iodoarenes) proved to be of high synthetic importance. The facile conversion of iodoalkenes or iodoarenes (as synthetic surrogates of the corresponding enol triflates and aryl triflates, respectively) to carboxamides by using carbon monoxide and various amines as N-nucleophiles, made these reactions of high synthetic importance.[12] Various 'preformed' or in situ generated palladium(0) catalysts were used.[13]

As a part of our on-going research in the carbonylation reactions of iodoarenes and iodoalkenes, we turned our attention towards the systematic variation of the N-nucleophiles. It has to be added that in the case of various compounds with practical interest, the above catalytic reactions provide synthetic methods superior to conventional ones. Since several amines with picolyl substituents (especially 2-picolylamine (*pam*) and di-(2-picolyl)amine (*dpa*)) are favoured ligands in coordination chemistry (vide infra) their attachment to a cavitand backbone with potential host properties was considered.

A wide application of *pam* as ligand in transition metal complexes such as Ir(III),[14] Cu(II),[15–17] Fe(II),[18–21] Pd(II) and Pt(II),[22] Cr(III)[23–25] and Ni(II)[26] has been described. 2-Picolylamine-based multidentate ligands have also been also used in Zn(II),[27,28] Pt(II),[29] Cu(II) and Mn(II)[16,30] complexes. The coordination of the

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potentially *N,N′,N″*-tridentate ligand *dpa* to Cu(II),[31,32] Zn(II)[33,34] and Ir(III)[35] was also reported. The catalytic application of Ir-*pam* complexes[36] and Os- and Ru-*pam*[37] systems has been reported in C–H borylation and transfer hydrogenation, respectively.

The high potential of picolyl moieties in binding properties as well as the molecular recognition properties of cavitands prompted us to combine the two functions in a family of novel cavitands, which proved to be available in high-yielding, facile reactions.

2. Results and discussion

To synthesise multi-level ('deepened') cavitands with pyridyl groups on the upper rim, the tetrabromocavitand (**1**)[38] was reacted with 4-hydroxybenzaldehyde under conventional etherification conditions in the first step yielding the tetraformyl derivative (**2**) in 87% yield. The condensation reaction of **2** with 2-, 3- or 4-picolylamine (**a**–**c**, respectively, Fig. 1) resulted in the high-yielding formation (62–83%) of the corresponding Schiff-bases (**3a**–**3c**) (Scheme 1).

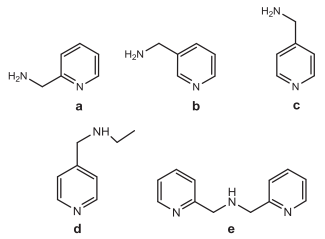


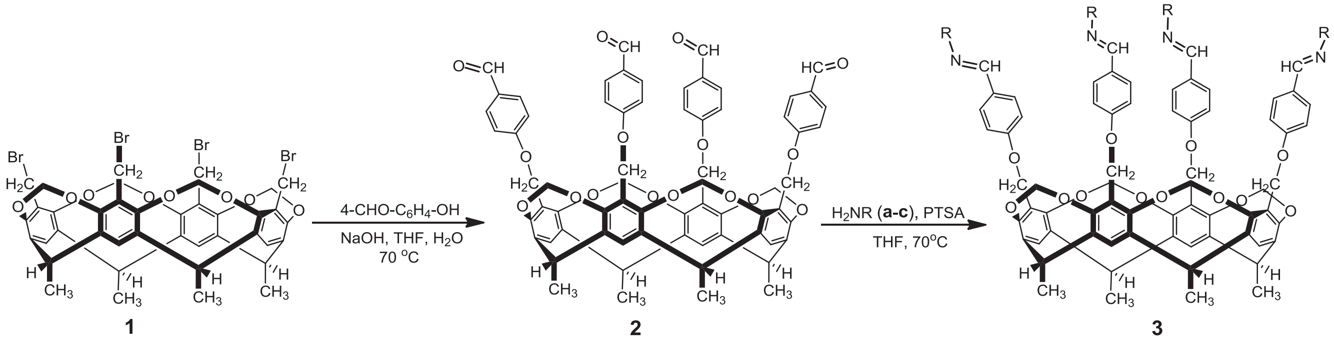
Fig. 1. Amines with pyridyl moieties used in this work.

To synthesise cavitands with similar structures, the aminocarbonylation reaction was chosen to introduce primary and secondary amines on the upper rim of the cavitand scaffold in the presence of $Pd(OAc)_2$+2PPh_3 in situ catalytic systems (Scheme 2). Under the reaction conditions used, highly reactive, coordinatively unsaturated Pd(0) intermediates are formed[39] enabling facile activation of the iodoaromatic substrate, carbon monoxide and amine nucleophile.

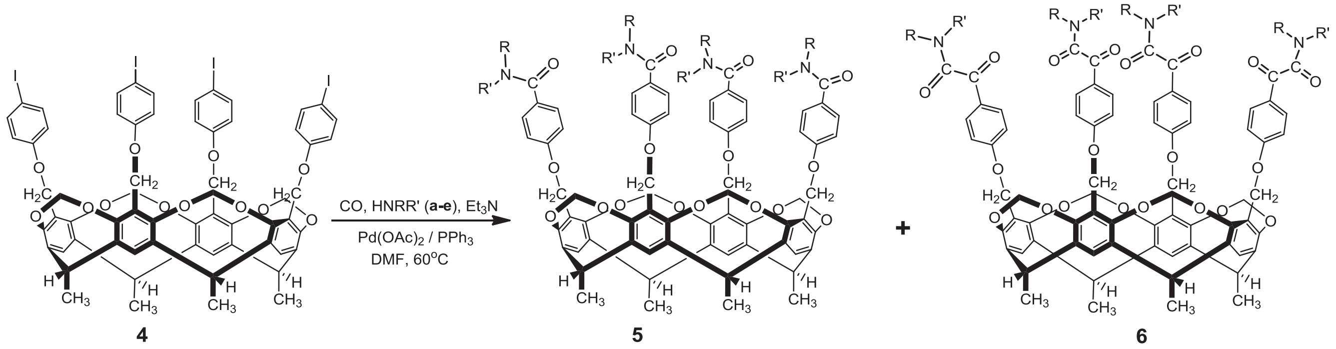
Tetraiodocavitand (**4**), bearing four excellent leaving groups, served as a substrate for further extension of the cavitand structure as demonstrated in various coupling reactions before.[9] In this study, we aimed to extend the scope of palladium-catalysed carbonylations using **4** as key-intermediate in this family of cavitands. The tetraiodocavitand (**4**) was synthesised from tetrabromocavitand (**1**) and 4-iodophenol by an improved methodology.[9]

Primary picolylamines (2-picolylamine (**a**), 3-picolylamine (**b**) and 4-picolylamine (**c**)) as well as secondary amines possessing picolyl substituent (4-(ethylaminomethyl)pyridine (**d**), di-(2-picolyl)amine (**e**)) were employed as N-nucleophiles for the preparation of both novel carboxamidocavitands (**5a**–**5d**) and 2-ketocarboxamides (**6a**–**6e**) in aminocarbonylation. That is, depending on the reaction conditions, the selective synthesis of carboxamides (**5**) and ketocarboxamides (**6**) can be accomplished (vide infra) via simple and double carbon monoxide insertion, respectively.

Under ambient conditions (1 bar CO, 50 °C) the formation of tetracarboxamides is highly favoured (Table 1, *entries 1, 4, 8*) when primary amines were used as N-nucleophiles. However, the use of secondary amine **d** provided a carboxamide/ketocarboxamide mixture of 40:60 (*entry 11*). The secondary amine **e** possessing two 4-pycolyl moieties, has shown decreased reactivity under 1 bar CO and no compound in isolable amount was formed (*entry 13*). It is



Scheme 1. Synthesis of cavitands with Schiff-base moieties on the upper rim.



Scheme 2. Synthesis of tetracarboxamidocavitands (**5**) and tetrakis(2-ketocarboxamido)cavitands (**6**) in palladium-catalysed aminocarbonylation.