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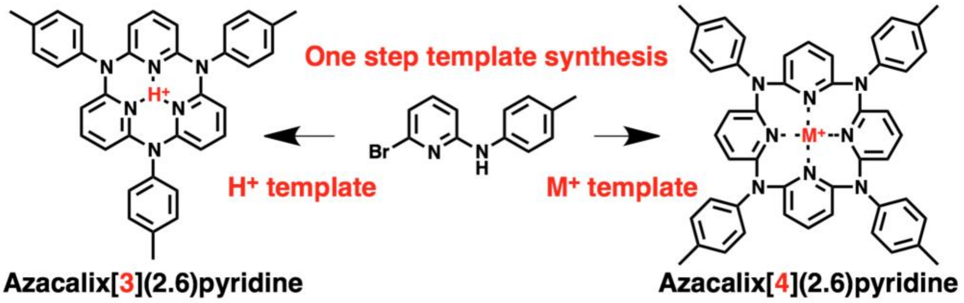

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Template-directed synthesis of macrocyclic aminopyridines: azacalix[*n*](2,6)pyridines (*n* = 3, 4)

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ABSTRACT

Template-induced synthetic routes for azacalix[*n*](2,6)pyridines (*n* = 3, 4) have been elaborated. The proton and nickel ion served as the efficient template for the cyclization reactions, and the presence of the templates preferentially afforded the cyclic trimers and tetramers in moderate to good yields, respectively. The compatibility of the cyclic tetramer with nickel ion was also confirmed by X-ray crystallography.

Synthesis and characterization of new macrocyclic compounds have been a research focus in the fields of host–guest and supramolecular chemistry. Azacalix[*n*](2,6)pyridines and their homologs are among the recent emerging new generation of macrocyclic compounds because they exhibit specific molecular recognition properties owing to their multiple Lewis base points and cavity size.[1] Their complexation properties have been utilized for detecting guests such as Zn^{2+} ion (*n* = 4) and fullerenes (*n* = 4–10).[2] The structure of azacalix[3](2,6)pyridine is also of interest; synergistic hydrogen-bonding ability of the three pyridine nitrogen atoms in its cavity is appropriate for capturing a single proton and works as an efficient organic superbase catalyst.[3] Moreover, azacalix[*n*](2,6)pyridines (*n* = 3, 4) exhibited unique delayed fluorescent behaviors.[4] However, for the synthesis of azacalix[*n*](2,6)pyridines and their homologs, skillful syntheses including step-by-step C–N coupling reactions and/or dilute conditions have generally been adopted.[1-3] A step-economical synthesis method that can produce the macrocyclic compound having a desirable ring size is important for practical applications. Alternatively, the template effect, caused by ions or uncharged organic molecules, is a very useful tool for the synthesis of macrocyclic compounds; the macrocyclic ring size strongly depends on the size of the template.[5] Therefore, the template considerably increases the yield of the macrocyclic product with the desired ring size. We thus envisioned that azacalix[*n*](2,6)pyridines can be synthesized by template-directed synthesis; the use of appropriate templates such as proton and transition-metal ions induce the cyclization reactions. This approach provides an efficient one-step synthesis of the cyclic trimer and tetramer separately from the same starting material. Herein, we report the template-directed synthesis of azacalix[*n*](2,6)pyridines (*n* = 3, 4).

The starting materials (**1a**–**1c**) were synthesized by the aromatic nucleophilic substitution reactions of 2,6-dibromopyridine derivatives with aniline derivatives in high yields (see the supplementary data). First, the Ullmann reaction of each starting material was conducted under the previously reported reaction conditions for the step-wise synthesis.[3b] The reaction of **1a** afforded the corresponding monoprotonated macrocyclic trimer (**2a**H•Br) selectively and in 80% yield; the cyclic trimer (**2a**) was obtained as an inner monoprotonated form (**2a**H•Br) owing to its high basicity (pK_{BH+} = 23.1 in acetonitrile).[3a] The other proton adducts, **2b**−**2c**H•Br, were also obtained in almost excellent yields (Table 1, entries 2 and 3). Notably, only trace amounts of differently sized macrocycles and linear oligomers were observed, as confirmed by the matrix-assisted laser desorption/ionization time-of-flight mass spectrometry (MALDI-TOF-MS); the undesired products could be easily separated by column chromatography. The yields of the azacalix[3](2,6)pyridines did not decrease even under high concentration conditions (entries 5–7). The high yields of **2a**−**2c**H•Br could be attributed to the template effect of proton. The Ullmann reaction produces hydrogen bromide as the by-product, and the proton serves as the template. The captured proton in the intermediate selectively afforded the cyclic trimer, as predicted in the previous report.[3] In contrast, the reaction with

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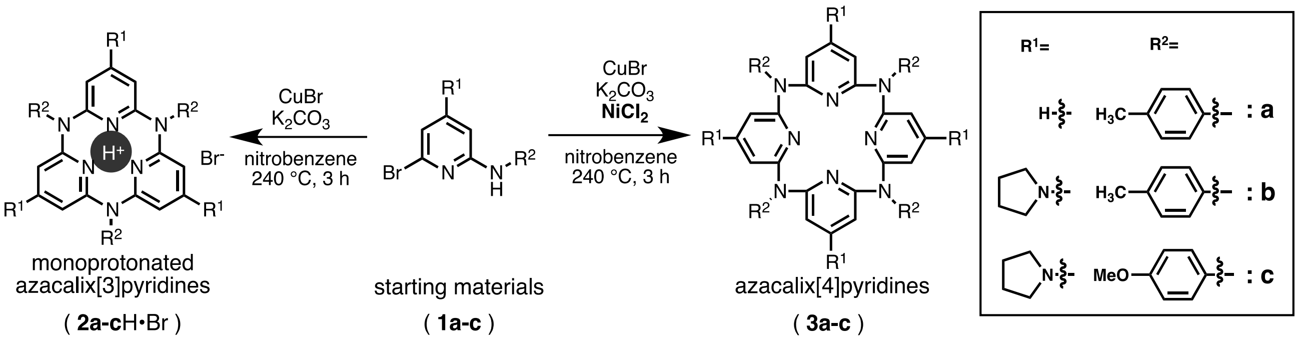

Figure 1. One step synthesis of azacalix[*n*]pyridine derivatives (*n* = 3, 4) in the presence of proton and nickel(II) ion as a template.

Table 1. Synthesis of azacalix[3](2,6)pyridine derivatives in the presence of proton as a template

Entry	R^1	R^2	Product (${}^{MeCN}pK_{BH^+}$ of **2a-c**)[3]	Conc. (M)	Yield (%)[a]
1	H-	tolyl-	**2a**H•Br (23.1)	0.017	80
2	pyrrolidino-	tolyl-	**2b**H•Br (28.1)	0.017	94
3	pyrrolidino-	anisyl-	**2c**H•Br (29.5)	0.017	92
4[c]	H-	tolyl-	**2a**H•Br (23.1)	0.017	-[b]
5	H-	tolyl-	**2a**H•Br (23.1)	0.05	80
6	H-	tolyl-	**2a**H•Br (23.1)	0.1	92
7	H-	tolyl-	**2a**H•Br (23.1)	1	88

[a] Isolated yield. [b] The linear aminopyridine oligomers were obtained.
[c] NaO^{t}Bu was used as a base.

Table 2. Synthesis of azacalix[*n*](2,6)pyridine derivatives (*n* = 3, 4) in the presence of transition-metal ion as a template

Entry	Template	Yield (%)[a]	
		2aH•PF_6	**3a**
1	-	80[d]	0
2	$Zn(COOCH_3)_2$•$6H_2O$	85[d]	trace
3	$CuBr_2$	83[d]	trace
4	$CaCO_3$	82[d]	trace
5	$Mg(O^tBu)_2$	88[d]	trace
6	$NiCl_2$	5	40
7	$NiCl_2$[b]	n. r.	
8	$NiCl_2$[c]	32	30
9	$NiBr_2$	5	43
10	NiI_2	4	41
11	$Ni(acac)_2$	82	4
12	$Ni(cod)_2$	87	2

[a] Isolated yield. [b] No CuBr catalyst.
[c] Using Pd-catalyzed reaction (the details is shown in supplementary data).
[d] The yield of **2a**H•Br.

Table 3. Synthesis of azacalix[4](2,6)pyridine derivatives (**3a**−**3c**) in the presence of nickel(II) ion as a template

Entry	R^1	R^2	Product (cyclic 4mer)	Yield (%)[a]	
				cyclic 3mer[b]	cyclic 4mer
1	H-	tolyl-	**3a**	5	40
2	pyrrolidino-	tolyl-	**3b**	23	57
3	pyrrolidino-	anisyl-	**3c**	16	46

[a] Isolated yield.
[b] The yield means monoprotonated azacalix[3](2,6)prydines (**2a**−**c**H•PF_6).

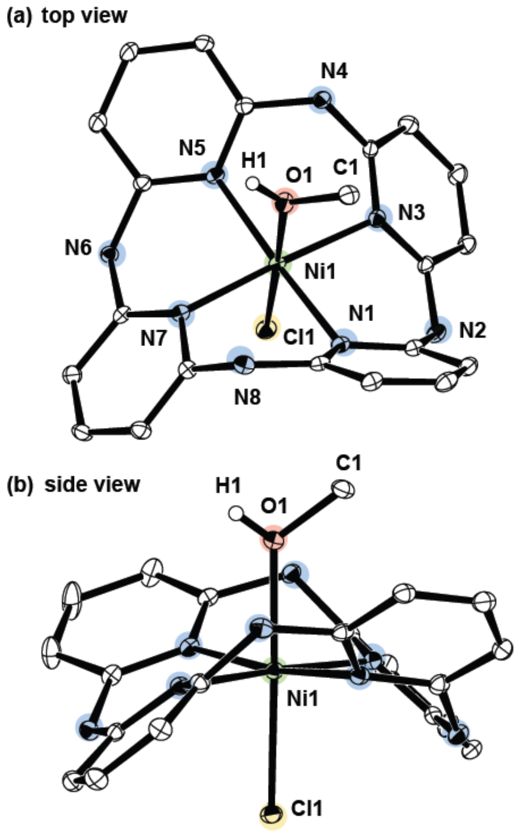

Figure 2. ORTEP drawing of **3a**•Ni with thermal ellipsoids shown at the 30% probability level. Hydrogen atoms except for the proton of the methanol (H1), the four tolyl groups, a Cl anion, a solvated methanol molecule, and a $NiCl_2(CH_3OH)_4$ molecule are omitted for clarity. (a) Top view of **3a**•Ni and (b) side view of **3a**•Ni.

sodium *tert*-butoxide instead of K_2CO_3 did not afford the corresponding macrocyclic trimer; however, it did afford linear aminopyridine oligomers and other sizes of macrocyclic compounds, indicating that a strong base inhibits the template effect of a proton (entry 4).

Alternatively, the effect of metal-salt addition was examined for the template-directed synthesis of macrocyclic tetramer, azacalix[4](2,6)pyridine (**3a**) (Table 2). Copper(II) bromide, zinc diacetate hexahydrate, calcium carbonate, and magnesium bis-*tert*-butoxide were selected as the candidates for the template, because the van der Waals radius of the metal ions were expected to fit the macrocyclic cavity of **3a**.[6] However, the additives did not show a clear template effect (entries 2–5). In contrast, when nickel(II) chloride ($NiCl_2$) was added to the reaction as the template, the yield of **3a** considerably increased than those in the presence of other additives and no additive (entry 6). Other nickel(II)halides also afforded **3a** in almost same yields as $NiCl_2$ (entries 9 and 10), whereas bis(1,5-cyclooctadiene) nickel(0) and nickel(II) acetylacetonato failed to produce **3a** (entries 11 and 12). No template effect of $Ni(acac)_2$ might be caused by stronger bidentate coordination of the acetylacetonato ligands. The nickel-catalyzed arylamination of aryl halides with aryl amines has been reported;[7] however, $NiCl_2$ did not exhibit any catalytic activity in this study (entry 7). Thus, nickel(II) ion served as a template in the reaction mixture. Stability constants of Ni^{2+} and Cu^{2+} complexes with 2,2'-dipyridylamine are much higher than the other metal ions such as Zn^{2+} and Co^{2+},[8] and there is an example on the thermal stability of the metal complexes with 2,2'-dipyridylamine increases in the order Co < Cu < Ni:[9] These facts would be associated with the template effect of Ni^{2+} in the reaction conditions. In the Buchwald−Hartwig reaction of **1a**, a C–N bond-forming reaction, $NiCl_2$ did not show any template effect even under diluted conditions (entry 8, see the supplementary data). The added phosphine ligand for the Pd catalyst may coordinate to a nickel center and inhibit the template effect. Starting materials with electron-donating groups (**1b** and **1c**) also afforded the desired tetramers, **3b** and **3c** in the presence of NiCl$_2$ (Table 3).

To explain the template effect of Ni^{2+} ion, the complexation of **3a** with Ni^{2+} was confirmed by X-ray crystallography. A single crystal of **3a** with Ni^{2+} (**3a**•Ni) was obtained by the crystallization from a mixture of **3a** and NiCl$_2$ in dichloromethane/methanol. The ORTEP drawing is shown in Figure 2. The structure of the **3a**•Ni complex has a nickel ion in the cavity of **3a**.[10] The nickel center has a slightly distorted octahedral geometry. The complex is a cation with Cl^{-} as the counter anion; the nickel center is coordinated to the four pyridyl nitrogen atoms of **3a**, a chloride, and one methanol molecule. The distance between the coordinating pyridyl nitrogen atoms and the nickel center, Ni1, is in the range 2.047−2.087 Å (Table S2); these distances are similar to the average Ni–N distance of 2.073−2.100 Å in *cis*-bis(bipyridine)nickel(II) dichloride.[11] The crystal structure shows that the nickel center fits the cavity of azacalix[4](2,6)pyridine framework with a reasonable geometry and bond distances. These results are consistent with the fact that a Ni^{2+} ion serves as the template for preferentially affording azacalix[4](2,6)pyridines.

In summary, we demonstrated the one-step synthesis of azacalix[4](2,6)pyridines and azacalix[3](2,6)pyridines from the same starting material separately using Ni^{2+} and a proton as the templates, respectively. This is the first example of the template-directed synthesis of azacalix[*n*](2,6)pyridines (*n* = 3, 4) with improved overall yields than the step-by-step methodologies reported previously.

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Supplementary Material

Supplementary data (general experimental information, experimental detail, characterization data) associated with this article can be found, in the online version, at doi.

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