HETEROCYCLES, Vol. 79, 2009, pp. 609 - 616. © The Japan Institute of Heterocyclic Chemistry
Received, 17th September, 2008, Accepted, 27th November, 2008, Published online, 1st December, 2008.
DOI: 10.3987/COM-08-S(D)24

SYNTHESIS OF AZA-BRIDGED CALIX(4-METHOXY)TRIAZINES TOWARD FLATTENED π-CONJUGATED MACROCYCLES

Hiroyuki Tanaka,[1] Ayako Wada,[2] Motoo Shiro,[4] Kazuhito Hioki,[2,3] Daiki Morisaki, [1] and Munetaka Kunishima[1,3*]

[1]Faculty of Pharmaceutical Sciences, Institute of Medical, Pharmaceutical, and Health Sciences, Kanazawa University, Kakuma-machi, Kanazawa 920-1192, Japan. [2]Faculty of Pharmaceutical Sciences, Kobe Gakuin University, 1-1-3 Minatojima Chuo-ku, Kobe 655-8586, Japan. [3]Life Science Center, Kobe Gakuin University, 1-1-3 Minatojima Chuo-ku, Kobe 655-8586, Japan. [4]Rigaku Corporation, 3-9-12 Matsubara, Akishima, Tokyo 196-8666, Japan. E-mail: kunisima@p.kanazawa-u.ac.jp

Abstract – Calixtriazines containing a 4-alkoxy-1,3,5-triazine backbone were efficiently synthesized by sequential fragment coupling started from 4-alkoxy-2,6-dichrolo-1,3,5-triazine. These macrocycles tend to form flattened conformations, leading to a stable π-conjugated system, presumably due to the electronic features of the alkoxy-substituent on the triazine rings.

INTRODUCTION

Calixarenes are metacyclophane-type cyclic oligomers formed by condensation between formaldehyde and phenol. They present a unique cavity depending on their specific conformations (cone, partial cone, and alternates), which recognizes various guests in specific ways.[1] To improve selectivity for the wide variety of guests, an array of calixarene analogues have been developed in supramolecular chemistry. In the process of evolution, calixfurans,[2] calixpyrrols,[3] calixindoles,[4] and calixpyridines,[5] which consist of heteroaromatics instead of phenols, and aza-,[6] oxo-,[7] and thia-[8] calixarenes, in which the carbon linkage between aromatic rings are replaced by heteroatoms, have been synthesized.

1,3,5-Triazines have been thoroughly studied and have resulted in extensive applications as pharmaceuticals, polymers, and other chemicals. Recent applications include proton acceptors[9] and metal ligands[10] that act as building blocks in the field of supramolecular chemistry and condensation reagents for organic synthesis.[11,12]

In terms of the synthesis of the calixtriazines, which consisted of 1,3,5-triazines as aromatic backbones, thiacalix[3]triazine **1**[13] (in 1966) and azacalix[2]arene[2]triazines **2**, **3**[14] (in 1973) were initially reported. However these macrocycles received little attention over the course of two decades despite the electronic feature of π-acidic aromatics, and aromatic nitrogen, which acts as a donor for metal ions and hydrogen bonding as melamine derivatives.[15] Recently, investigation has begun on the synthesis and binding activities of the oxo- or aza-oxo-mixed bridged calix[2]arene[2]triazines[16] and the other macrocycles containing 1,3,5-triazines.[17] We report here the preparation of a variety of azacalixtriazines **4-6** based on the use of 4-methoxy-1,3,5-triazines as a building block, wherein co-planarity between the adjacent triazine and phenyl group, lead to an interconversion to more stable π-conjugated macrocycle.

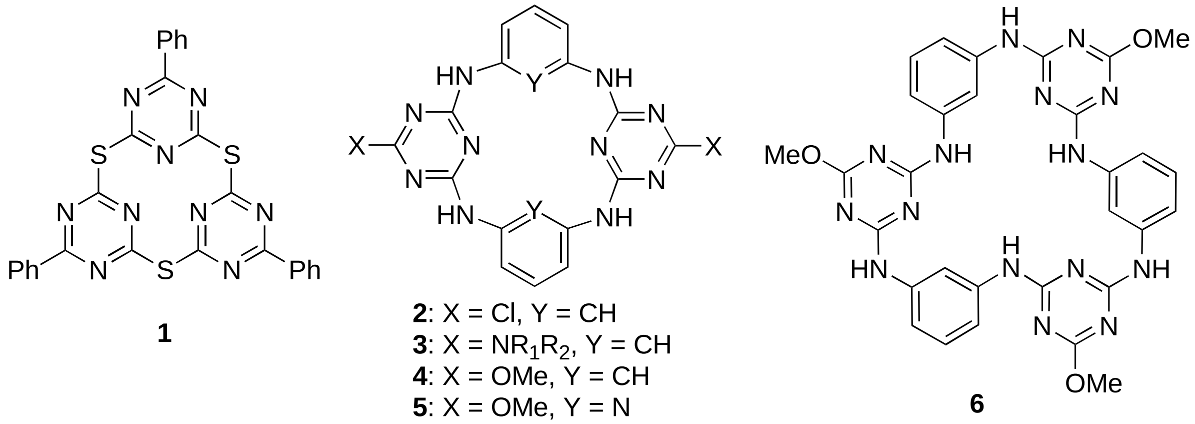
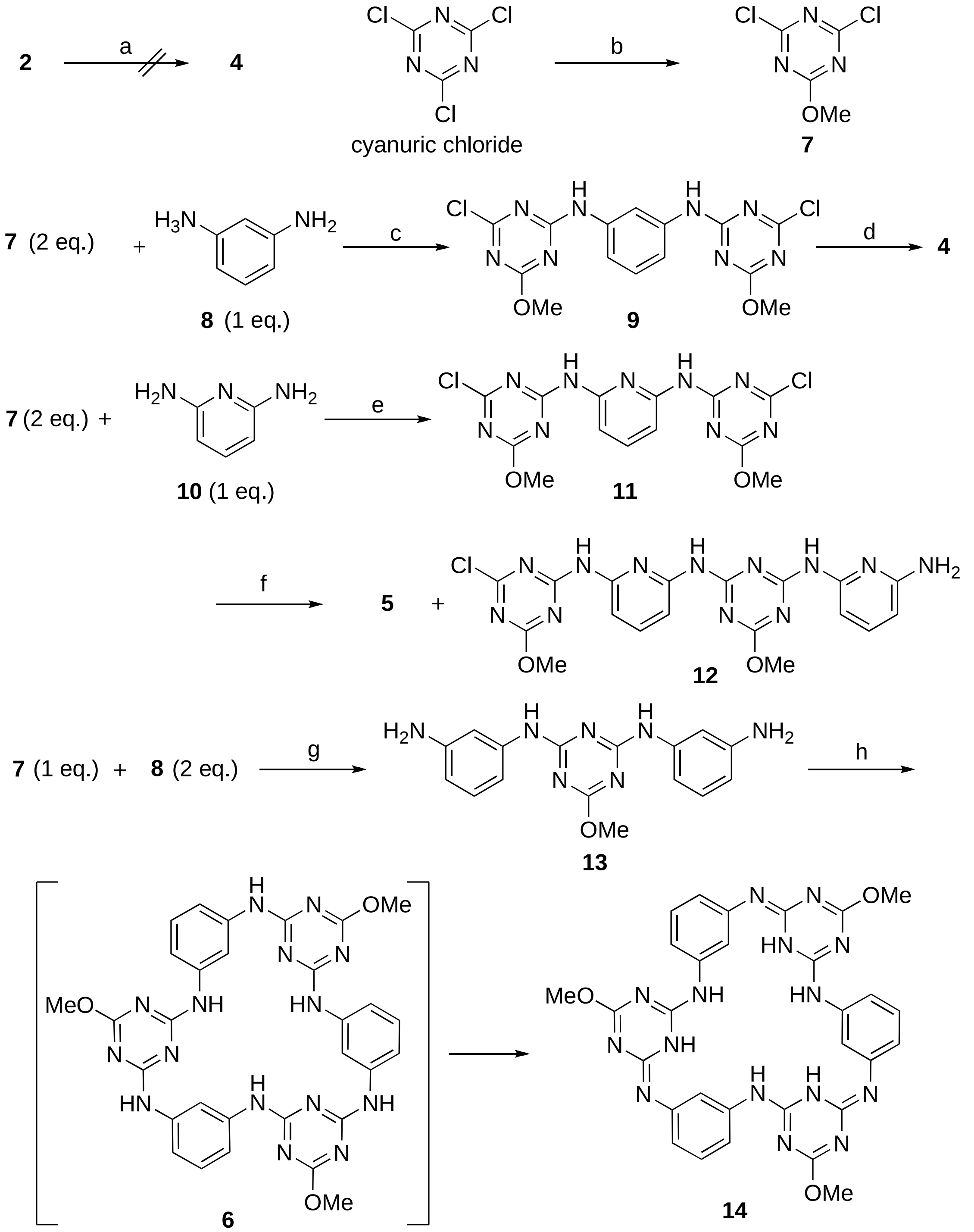


Figure 1. Various types of calixtriazines. R_1 and R_2 indicate alkyl groups or hydrogen.

RESULTS AND DISCUSSION

The synthesis of 4-alkylamino calixtriazines **3** was carried out by the $\mathrm{S_NAr}$ reaction of calixtriazine **2** with primary or secondary amines under basic conditions.[14,16a,16b] Although calix[2]arene[2](4-methoxy)triazine **4** seems to be readily obtained by the substitutions of **2** with methanol under basic conditions, the reaction cannot proceed because of the lower nucleophilicity of alcohols compared with that of amines.[16c] We successfully achieved the synthesis of azacalix(4-methoxy)triazines **4-6** by the macrocyclization based on the sequential $\mathrm{S_NAr}$ reaction of 2,6-dichrolo-4-methoxytriazine (**7**) (Scheme 1).[18]

Mono methoxy substituted triazine **7** was selectively and quantitatively obtained by the treatment of cyanuric chloride with methanol at 0 ˚C. Of the 4-arene derivatives, acyclic trimer **9** was initially synthesized from 1,3-phenylenediamine (**8**) and two equivalent of **7** by the $\mathrm{S_NAr}$ reaction at ambient temperature (98% yield); then azacalix[2]arene[2](4-methoxy)triazines **4** were obtained in 68% yield by heating a 1:1 mixture of **8** and the trimer **9** at 100 ˚C for 72 hrs in a sealed tube. The synthesis of calix[2]pyridine[2](4-methoxy)triazine **5** was carried out the same way as that of **4** except for the use of 2,6-diaminopyridine (**10**) and a trimer **11** instead of **8** and **9**, respectively. The lower nucleophilicity of pyridylamine, however, caused longer reaction time (48 h) and reduction in yield (65%). To make



Scheme 1. Synthesis of aza-calix(4-methoxy)triazines **4**-**6**. (a) MeOH, *i*Pr_2NEt, reflux; (b) MeOH, $NaHCO_3$, H_2O, 0 °C, 2.5 h, 98%; (c) *i*Pr_2NEt, THF, rt, 50 min, 98%; (d) **8**, *i*Pr_2NEt, THF, 100 °C, 72 h, 68%; (e) *i*Pr_2NEt, THF, rt, 48 h, 65%; (f) **10**, *i*Pr_2NEt, THF, 130 °C, 120 h, (g) *i*Pr_2NEt, THF, 60 °C, 48 h, 55%; (h) **9**, *i*Pr_2NEt, THF, 100 °C, 72 h, 57%.

matters worse, only a small amount (less than 7%) of calixpyridyltriazine **5** was obtained as a mixture with acyclic tetramer **12** (determined by ESI-MS and 1H-NMR; data not shown) despite longer reaction time at higher temperature (130 ˚C, 120 h).

Toward the synthesis of aza-calix[3]arene[3](4-methoxy)triazine **6**, bis-phenylenediamine inverse trimer **13** was prepared by substitution of **7** with two equivalents of **8** at 60 ˚C for 48 h. Even for a large macrocycle, cyclocoupling between the trimers **11** and **13** produced a satisfactory high yield (57%) under the same conditions as those employed for **4**. Surprisingly, in the NMR spectrum of the obtained macrocycle, there were two pairs of dissymmetrical NH groups and aromatic protons equally separated. This spectrum suggested three pairs of adjacent triazine-phenol rings in **6** were converted to π-conjugated isomer, which led to a more stable conjugated macrocycle **14**. Thermal interconversion between **14** and **6** was not observed at temperatures up to 100 ˚C in DMSO-d_6 on an NMR analysis. Since this type of conjugation was not observed on either calix[2]arene[2]triazines **2-4** or aza-calix[3]arene[3](4- alkylamino)triazines,[17c] this isomerization probably arose not only from the larger ring size of the 6-arene compared to that of the 4-arenes, which allows it to form the conjugated structure without increase in the ring strain, but also from an electronic feature of the alkoxy group at the 4-position of 1,3,5-triazine rings.

In solid state, **4** forms 1,3-altanate in a relatively flattened conformation as compared with 4-chloro or 4-amino calixtriazines (Figure 2 and Table 1).[16a,19] In the crystal structure, hydrogen bonding between oxygen in THF and hydrogen of the bridged NH groups was observed (distances between O3-N13 is 2.98 Å, and O4-N8 is 2.89 Å in Figure 2). By contrast, an absolutely flat conformation of the macrocycle **14** was observed in the crystallographic structure, which supports the existence of a π-conjugated macrocycle as noted above (Figure 3).[20] Regardless of the flat conjugated system of **14**, neither stacking between calixtriazines nor a layered structure was observed since solvent molecules (acetone and hexane, which were omitted from the figure) were packed between the macrocycles.

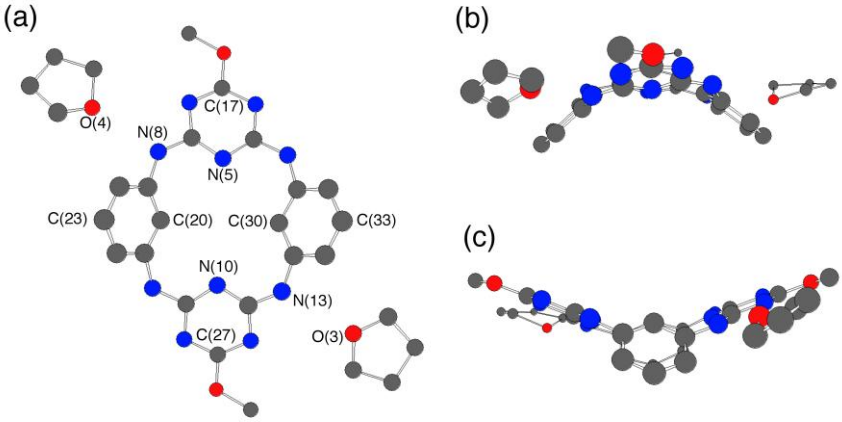


Figure 2. Crystal structure of **4**·2THF: top view (a) and side views (b and c). Hydrogen atoms are excluded for clarity.

	Distances for **4**	Distances for **2**[a]
N5-N10	4.577	4.648
C17-C27	9.612	9.035
C20-C30	4.255	4.217
C23-C33	8.572	7.392

Table 1. Distances between atoms on upper/lower rims in aromatic rings. [a]The data was cited from ref 16a.

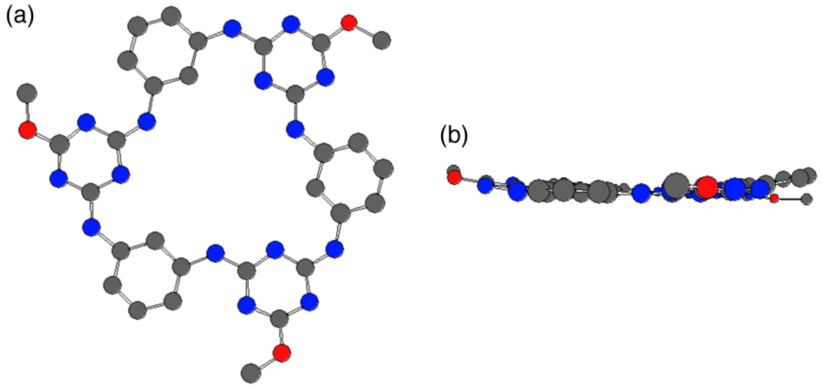


Figure 3. Crystal structure of **14**: (a) top view and (b) side views. Hydrogen atoms and solvents are excluded for clarity.

In conclusion, we were able to develop an efficient and convenient preparation of 4-alkoxy-1,3,5-triazines-based calixtriazines by application of sequential S_NAr reactions on triazine rings without any protection on the nitrogen linker. Although the final step for the construction of macrocycles **4** or **6** may involve macrocyclization of the linear tetramer or hexamer, the reactions proceeded with satisfactory yields. A chief characteristic of our calixtriazines is their flattened conformation compared to that of others reported previously; indicating that the nature of substituents at the 4-position of 1,3,5-triazine is an important factor determining the conformational structure of calixtriazines.

EXPERIMENTAL

General

All melting points were measured by Yanagimoto melting point apparatus and the temperatures were uncorrected. NMR spectra were recorded using BRUKER DPX400 spectrometers (δ given in ppm, internal Me_4Si). IR spectra on JEOL JIR-100 FT-IR spectrometer, EI-MS spectra on HITACHI M-2000 Mass spectrometer, and ESI-MS were taken on Micromass ZQ2000 spectrometer. TLC and chromatography was performed on silica gel (Kieselgel 60 F_{254} for TLC, Wakogel 75-150 mesh for column chromatography). Solvents and reagents were purchased from Aldrich, Nacalai Tesque, and Wako Chemicals and dried according to usual procedures.

2,4-Dichloro-6-methoxy-1,3,5-triazine 7.

Cyanuric chloride (300 g, 1.63 mol) was added to a mixture of MeOH (1.6 L), water (156 mL) and $NaHCO_3$ (273 g, 3.25 mol) at 0 °C. After stirring for 2.5 h, iced water (1.5 L) was added, then the resulting precipitate was collected by filtration. The solid was washed with water followed by lyophilyzation to give **7** (287 g, 98%) as a white solid, mp 88-89 °C; IR (KBr) 1545, 1486, 1391, 847 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 4.13 (s, 3H).

Compound 9.

A solution of 1,3-phenylenediamine **8** (3.00 g, 27.8 mmol) in THF (30 mL) was slowly added to a solution of **7** (10.0 g, 55.6 mmol) and *i*Pr_2NEt (10.8 g, 83.4 mmol) in THF (70 mL) at 0 °C, then stirred at rt for 50 min. The solvents were removed *in vacuo*, and the residue was separated between EtOAc (200 mL) and 0.1 N HCl (150 mL). The organic layer was washed with water (100 mL x 2), dried over $MgSO_4$, filtrated and evaporated to give **9** (10.8 g, 98%) as a white solid, mp 179-182°C; IR (KBr) 3353, 1565, 1483, 1366 cm^{-1}; ^1H NMR (CD_3OD) δ 4.02 (s, 6H), 7.32 (t, J = 8.0 Hz, 1H), 7.40 (d, J = 8.0 Hz, 2H), 8.07 (brs, 1H); ESIMS [MeOH/H_2O (1/1)] *m/z* 395 ($M+H^+$), 417 ($M+Na^+$); Anal. Calcd for $C_{14}H_{12}C_{l2}N_8O_2$: C, 42.55; H, 3.06; N, 28.35. Found: C 42.64; H, 3.29; N, 28.13.

Tetraaza-calix[2]arene[2](4-methoxy)triazine 4.

A solution of 1,3-phenylenediamine **8** (0.54 g, 5.00 mmol), **9** (1.98 g, 5.00 mmol) and *i*Pr_2NEt (1.62 g, 12.5 mmol) in THF (100 mL) was stirred for 72 h under N_2 at 100 °C in sealed tube. After removal of the solvents, the residue was suspended in 1N HCl (50 mL), then filtrated, and dried to give **4** (1.46 g, 68%) as a white powder, mp >280 ° C; IR (KBr) 1592, 1468, 1358 cm^{-1}; ^1H NMR (DMSO-*d*$_6$) δ 3.88 (s, 6H), 6.75 (dd, J = 8.0, 2.0 Hz, 4H), 7.16 (t, J = 8.0 Hz, 2H), 7.76 (t, J = 2.0 Hz, 2H), 9.41 (s, 4H); ESIMS [MeOH/H_2O (1/1)] *m/z* 431 ($M+H^+$), 453 ($M+Na^+$); Anal. Calcd for $C_{20}H_{18}N_{10}O_2 \cdot 1/2H_2O$: C, 54.67; H, 4.36; N, 31.87. Found: C 54.40; H, 4.19; N, 31.83.

Synthesis of 11.

A solution of 2,6-diaminopyridine **10** (1.52 g, 13.9 mmol) in THF (20 mL) was slowly added to a solution of **7** (5.00 g, 27.8 mmol) and *i*Pr_2NEt (5.39 g, 41.7 mmol) in THF (30 mL), then the mixture was stirred for 48 h at rt. After removal of the solvents, the residue was separated between EtOAc (200 mL) and 0.1 N HCl (150 mL). The organic layer was washed with water (150 mL x 3), dried over $MgSO_4$, filtrated and concentrated. The crude residue was purified by a column chromatography [SiO_2, $CHCl_3$/MeOH (98/2)] to give **11** (3.58 g, 65%) as a white solid, mp 188-191° C; IR (KBr) 1592, 1462, 1353, 1284 cm^{-1}; ^1H NMR ($CDCl_3$) δ 4.07 (s, 6H), 7.84 (t, J = 8.1 Hz 2H), 8.04 (d, J = 8.1 Hz, 2H), 8.88 (brs, 2H); ESIMS [MeOH/H_2O(1/1)] *m/z* 396 ($M+H^+$), 418 ($M+Na^+$); Anal. Calcd for $C_{13}H_{11}Cl_2N_9O_2 \cdot 1/2H_2O$: C, 38.53; H, 2.99; N, 31.11. Found: C, 38.51; H, 3.15; N, 30.98.

Compound 13.

A solution of 1,3-phenylenediamine **8** (1.32 g, 12.2 mmol) in THF (20 mL) was slowly added to a solution of **7** (1.00 g, 5.56 mmol) and *i*Pr_2NEt (2.15 g, 16.7 mmol) in THF (60 mL), then stirred at 60 °C for 48 h. The reaction mixture was poured into EtOAc (150 mL) and water (100 mL). The organic layer was washed with water (100 mL x 2), dried over $MgSO_4$, filtrated and evaporated. The residue was purified by a column chromatography [SiO_2, hexane/EtOAc (8/2)] to give **13** (0.99 g, 55%) as a white solid; mp 143-146 ° C; IR (KBr) 3370, 1582, 1453, 1382, 1356 cm^{-1}; ^1H NMR (CD_3OD) δ 3.96 (s, 3H), 6.45 (ddd, *J* = 7.9, 2.2, 1.0 Hz, 2H), 6.85 (brs, 2H), 7.03 (t, *J* = 8.0 Hz, 2H), 7.27 (brs, 2H); HRMS (EI) calcd for $C_{16}H_{17}N_7O$ 323.1495; found 323.1515.; Anal. Calcd for $C_{16}H_{17}N_7O$· 1/4AcOEt: C, 59.12; H, 5.54; N, 28.39; found C, 58.76; H, 5.43; N, 28.55.

Macrocycle 14.

A solution of **9** (198 mg, 0.50 mmol), **13** (162 mg, 0.50 mmol) and *i*Pr_2NEt (162 mg, 1.25 mmol) in THF (10 mL) was stirred for 72 h under N_2 at 100 °C in sealed tube. After cooling, the precipitate was collected to give product **14** (184.1 mg, 57%) as a pale yellow powder; mp >280 ° C; IR (KBr) 1620, 1561, 1482, 1446, 1407, 1342 cm^{-1}; ^1H NMR (DMSO-d_6) δ 3.98 (s, 9H), 6.94 (dd, *J* = 8.2, 1.2 Hz, 3H), 7.28 (t, *J* = 8.2 Hz, 3H), 8.29 (dd, *J* = 8.2, 1.4 Hz, 3H), 8.51 (s, 3H), 8.77 (s, 3H), 9.94 (s, 3H); ESIMS [MeOH/H_2O (1/1)] m/z 646 ($M+H^+$), 668 ($M+Na^+$).

REFERENCES AND NOTES

1. Recent reviews for calixarenes: (a) S. Shinkai, *Tetrahedron,* 1993, **40**, 8933; (b) V. Böhmer, *Angew. Chem., Int. Ed. Engl.,* 1995, **34**, 713; (c) M. Takeshita and S. Shinkai, *Bull. Chem. Soc. Jpn*., 1995, **68**, 1088; (d) A. Ikeda and S. Shinkai, *Chem. Rev.,* 1997, **97**, 1713; (e) C. D. Gutsche, '*Calixarenes: Monographs in Supramolecular Chemistry*', ed. by J. F. Stoddart, The Royal Society of Chemistry: Cambridge, 1989.
2. R. M. Musau and A. Whiting, *J. Chem. Soc., Perkin Trans. 1,* 1994, 2881.
3. P. A. Gale, J. L. Sessler, V. Král, and V. Lynch, *J. Am. Chem. Soc.,* 1996, **118**, 5140.
4. D. StC. Black, D. C. Craig, N. Kumar, and D. B. McConnell, *Tetrahedron Lett.,* 1996, **37**, 241.
5. V. Král, P. A. Gale, P. Jr. Anzenbacher, K. Jursíková, V. Lynch, and J. L. Sessler, *Chem. Commun.,* 1998, 9.
6. H. Takemura, K. Yoshimura, I. U. Khan, T. Shinmyozu, and T. Inazu, *Tetrahedron Lett.,* 1992, **33**, 5775.
7. B. Dhawan and C. D. Gutsche, *J. Org. Chem.,* 1983, **48**, 1536.
8. T. Sone, Y. Ohba, K. Moriya, H. Kumada, and K. Ito, *Tetrahedron,* 1997, **53**, 10689.
9. V. Paraschiv, M. Crego-Calama, R. H. Fokkens, C. J. Padberg, P. Timmerman, and D. N. Reinhoudt, *J. Org. Chem.,* 2001, **66**, 8297.
10. M. Fujita, K. Umemoto, M. Yoshizawa, N. Fujita, T. Kusukawa, and K. Biradha, *Chem. Commun.,* 2001, 509.
11. M. Kunishima, C. Kawachi, F. Iwasaki, K. Terao, and S. Tani, *Tetrahedron Lett.,* 1999, **40**, 5327.
12. For a recent review of applications of 2,4,6-trichloro-1,3,5-triazine and its derivatives in organic synthesis, see G. Blotny, *Tetrahedron,* 2006, **62**, 9507.
13. G. A. Loughran, G. F. L. Ehlers, and J. L. Burkett, *J. Heterocycl. Chem.,* 1966, **3**, 143.

14. V. F. Borodkin, V. A. Gnedina, and I. A. Grukova, *Izv. Vyssh. Uchebn. Zaved., Khim. Khim. Tekhnol.,* 1973, **16**, 1722.

15. (a) H. Graubaum, G. Lutze, F. Tittelbach, and M. Bartoszek, *J. prakt. Chem.,* 1995, **337**, 401; (b) M. Mascal, J. L. Richardson, A. J. Blake, and W.-S. Li, *Tetrahedron Lett.,* 1997, **43**, 7639; (c) H. Graubaum, B. Costisella, and R. Dambowsky, *J. prakt. Chem.*, 1998, **340**, 165.

16. (a) M.-X. Wang and H.-B. Yang, *J. Am. Chem. Soc.,* 2004, **126**, 15412; (b) Q.-Q. Wang, D.-X. Wang, H.-W. Ma, and M.-X. Wang, *Org. Lett.,* 2006, **8**, 5967; (c) H.-B. Yang, D.-X. Wang, Q.-Q. Wang, and M.-X. Wang, *J. Org. Chem.,* 2007, **72**, 3757; (d) Q.-Q. Wang, D.-X. Wang, Q.-Y. Zheng, and M.-X. Wang, *Org. Lett.,* 2007, **9**, 2847; (e) B.-Y. Hou, Q.-Y. Zheng, D.-X. Wang, and M.-X. Wang, *Tetrahedron,* 2007, **63**, 10801.

17. (a) D. W. P. M. Löwik and C. R. Lowe, *Tetrahedron Lett.,* 2000, **41**, 1837; (b) D. W. P. M. Löwik and C. R. Lowe, *Eur. J. Org. Chem.,* 2001, 2825; (c) X. Yang and C. R. Lowe, *Tetrahedron Lett.,* 2003, **44**, 1359; (d) C. Zhang and C.-F. Chen, *J. Org. Chem.,* 2007, **72**, 3880.

18. P. de Hoog, P. Gamez, W. L. Driessen, and J. Reedijk, *Tetrahedron Lett.,* 2002, **43**, 6783.

19. *Crystal data* for tetraaza-calix[2]arene[2](4-methoxy)triazine **4**·2THF crystallized from a tetrahydrofurane-acetone-hexane mixed solvent: colorless platelets of $C_{28}H_{34}N_{10}O_4$, dimensions 0.15 x 0.10 x 0.03 mm^3, orthorhombic, space group *P*bca (# 61), a = 7.815(5), b = 21.28(1), c = 33.31(2) Å, V = 5539 (5) Å^3, Z = 8, D_{calcd} = 1.378 g/cm^3. Data collected on a Rigaku RAXIS-RAPID diffractometer with MoKα radiation (λ = 0.71075 Å) at T = -180±1 ºC, $2\theta_{\max}$ = 60.1°, R_{int} = 0.076, μ (MoKα) = 0.97 cm^{-1}. R_1 = 0.045, wR_2 = 0.117.

20. *Crystal data* for macrocycle **14**·acetone·hexane crystallized from a tetrahydrofurane-acetone-hexane mixed solvent: colorless block of $C_{39}H_{47}N_{15}O_4$, dimensions 0.15 x 0.12 x 0.07 mm^3, triclinic, space group *P*-1 (# 2), a = 12.95 (2), b = 14.77 (2), c = 21.46 (2) Å, V = 3902 (9) Å^3, Z = 4, D_{calcd} = 1.344 g/cm^3. Data collected on a Rigaku RAXIS-RAPID diffractometer with MoKα radiation (λ = 0.7107 Å) at T = -180±1ºC, $2\theta_{\max}$ = 26.0°, R_{int} = 0.074, μ (MoKα) = 0.99 cm^{-1}. R_1 = 0.077, wR_2 = 0.196.