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Synthons for supramolecular assemblies: Synthesis of new triazine-core polyhydroxylated and multi-*N*-donor compounds

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ABSTRACT

The synthesis of new triazine-core polyhydroxylated and multi-*N*-donor compounds are being reported. The reaction of 2,4,6-*tris*(4-*n*-butylaminophenyl)triazine (1) with cyanuric chloride provided star-shaped fragment (2) with six reactive chloro-substituents. Upon treatment of this fragment with *bis*(2-hydroxyethyl)amine (3a) and *bis*(2-pyridylmethyl)amine (3b), functionalized polyhydroxylated (4a) and multi-*N*-donor compounds (4b) were obtained in high yields through nucleophilic aromatic substitution. These functionalized compounds are expected to have unique applications in supramolecular self-assembly and material chemistry.

1. Introduction

Appropriately designed molecular synthons are very important for the construction of aesthetically appealing abiological three dimensional self-assemblies in a predictive manner. Symmetry, shape and functionality of the synthons have the key influence on the nature and applications of self-assembled architectures [1]. Synthons having *N*-heterocyclic chelating ligands and hydrogen bond donor sites are proved to be an important candidate in the field of supramolecular self-assembly. The availability of various types of chelating ligands and transition metal ions provides numerous possibilities for the preparation of metal-coordinating architectures characterized by different stabilities, geometries and properties [2-5]. Similarly, a variety of stable and functional molecular systems have been constructed using hydrogen bond as a cementing force between molecular subunits [6-8].

The architecture of such self-assembled systems is strongly determined by the nature of molecular synthons. Therefore, the design of novel molecular synthons and their successful synthesis play an important role in supramolecular and material chemistry [9,10]. In the past two decades, a variety of molecular synthons capable of forming hydrogen bond and dative metal-ligand interactions have been synthesized for the construction of supramolecular systems having applications in various fields such as microelectronics [11,12], medicine and biotechnology [13,14], catalysis [15-17], sensors [18,19], and solar/fuel cells [20,21].

In spite of the enormous progress, a variety of abiological systems still need to be explored to fully understand the functions and complexity of the systems created by nature. Therefore, the synthesis of new molecular synthons for creating desired supramolecular architectures for their applications in host-guest chemistry [22,23], self-assembly [24-26] and supramolecular catalysis [27,28] is currently an active area of research. Herein, we report the synthesis of new triazine-core polyhydroxylated and multi-*N*-donor synthons bearing potential sities for hydrogen bonding and metal-ligand interactions. The presence of various triazine moieties in these structures may also provide a route towards medicinal applications of the resulting molecular architectures.

2. Experimental

2.1. Instrumentation

Melting points were recorded using a Gallenkamp (SANYO) model MPD.BM 3.5 and are uncorrected. FT-IR spectra were recorded on Shimadzu FT-IR 8201 PC (4000-400 cm^{-1}). NMR spectra were recorded using Bruker AM-300 spectrometer and chemical shifts are reported in ppm versus tetramethylsilane with either tetramethylsilane or the residual solvent resonance used as an internal standard. Mass spectra were acquired on Bruker Omniflex MALDI-TOF instrument. Elemental analyses were conducted using a LECO-183 CHNS analyzer. Solvents were dried according to standard procedures prior to use. All other major chemicals were obtained from commercial sources and used without further purification.

2.2. Synthesis of 4,4',4''-(1,3,5-triazine-2,4,6-triyl)tris(N-butylaniline) **(1)** [29-31]

In 100 mL round bottom flask, 2,4,6-*tris*(4-aminophenyl)triazine (7.09 g, 20 mmol) and *p*-toluenesulfonyl chloride (TsCl, 12.58 g, 66 mmol) were taken in 25 mL pyridine and heated the reaction mixture with constant stirring at 120 °C for 2 h. Then reaction mixture was cooled to room temperature and added to it 0.1 N HCl with continuous stirring.

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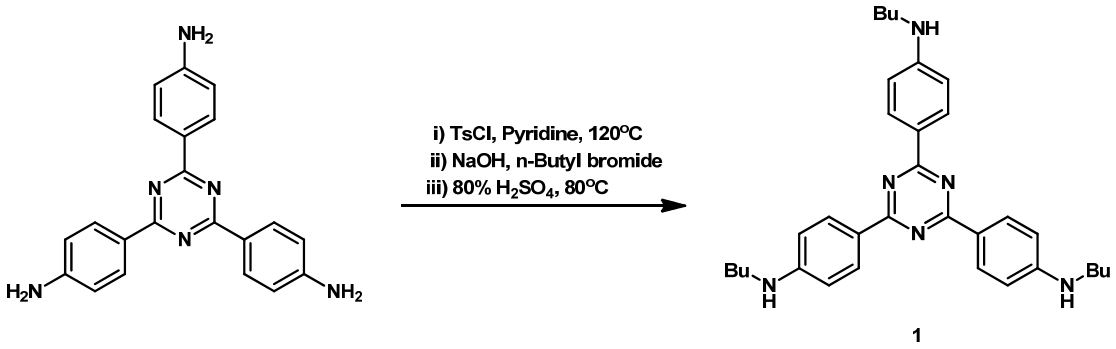
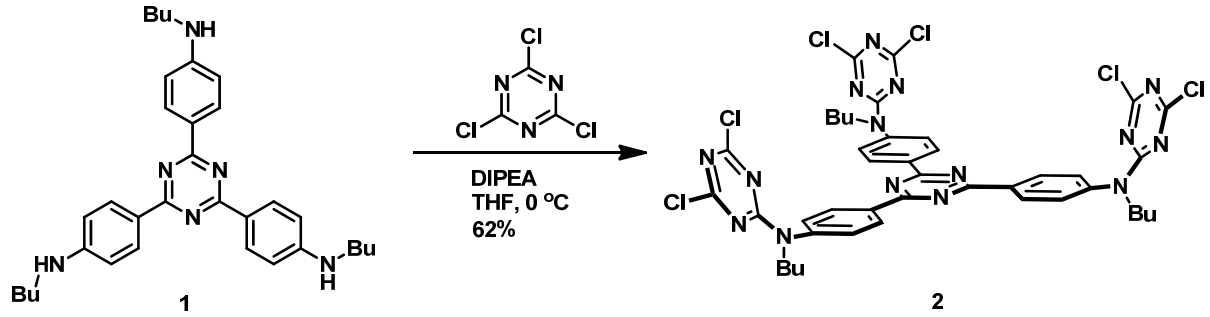


Scheme 1



Scheme 2

Precipitates thus formed were filtered and washed thoroughly with water and dried. The product was further purified by silica gel (100-200) column chromatography by using a mixture of petroleum ether and acetone (2:1) as the mobile phase to give offwhite solid product, 14.70 g, 18 mmol of which was then taken in a 500 mL round bottom flask along with acetone (200 mL):water (100 mL) mixture as solvent and added to it NaOH (4.32 g, 108 mmol) with constant stirring at room temperature. The temperature was gradually increased to 80 °C and *n*-butyl bromide (22.2 g, 17.3 mL, 162 mmol) was then added dropwise to the reaction mixture, which was further stirred at 80 °C for 8 h. The reaction mixture was cooled at room temperature and the precipitates were filtered and washed thoroughly with water. The product was further purified by silica gel (100-200) column chromatography by using a mixture of petroleum ether and chloroform (3:1) as the mobile phase to give pure light yellow solid. This solid (12.8 g, 13 mmol) was taken in 100 mL round bottom flask, and added to it 15 mL 80% H_2SO_4 with constant stirring at room temperature. The temperature was increased to 80 °C and reaction mixture was further stirred for 4 h. It was then cooled to room temperature and slowly added to it saturated solution of NaOH till the pH was basic. The precipitates thus formed were filtered and washed thoroughly with water. The product was further purified by silica gel (100-200) column chromatography by using a mixture of petroleum ether and acetone (1:3) as the mobile phase to give pure compound **1** as light yellow solid (Scheme 1).

4,4′,4′′-(1,3,5-Triazine-2,4,6-triyl)tris(N-butylaniline) (**1**): Yield: 6.55 g, 96%. M.p.: 118-119 °C. IR (KBr, ν, cm^{-1}): 3406, 2928, 1607, 1509, 1468, 1365, 811. ^{1}H NMR (300 MHz, $CDCl_3$, δ, ppm): 8.57 (d, *J* = 8.7 Hz, 6H), 6.66 (d, *J* = 8.7 Hz, 6H), 4.01 (br, s, 3H), 3.19 (t, *J* = 7.0 Hz, 6H), 1.72 – 1.54 (m, 6H), 1.52 – 1.35 (m, 6H), 0.96 (t, *J* = 7.3 Hz, 9H). ^{13}C NMR (75 MHz, $CDCl_3$, δ, ppm): 170.3, 151.5, 130.4, 125.4, 111.7, 43.2, 31.5, 20.2, 13.8.

2.3. Synthesis of N,N′,N′′-((1,3,5-triazine-2,4,6-triyl)tris (benzene-4,1-diyl))tris(N-butyl-4,6-dichloro-1,3,5-triazin-2-amine) (**2**) [31]

To an ice-bath cooled solution of cyanuric chloride (12.45 g, 67.5 mmol) in THF (150 mL) was added dropwise a mixture of compound **1** (7.84 g, 15 mmol) and diisopropylethylamine (7.56 g, 9.67 mL, 58.5 mmol) in THF (100 mL) during 2 h. The reaction mixture was stirred for another 5 h. After removal of diisopropylethylamine hydrochloride salt through filtration, the filtrate was concentrated and chromatographed on a silica gel column (100-200) with a mixture of petroleum ether and chloroform as the mobile phase to give pure compound **2** as a white solid (Scheme 2).

N,*N*′,*N*′′-((1,3,5-Triazine-2,4,6-triyl)*tris*(benzene-4,1-diyl)) *tris*(*N*-butyl-4,6-dichloro-1,3,5-triazin-2-amine) (**2**): Yield: 9 g, 62%. M.p.: 272-273 °C. IR (KBr, ν, cm^{-1}): 2959, 1555, 1509, 1479, 1236, 845. ^{1}H NMR (300 MHz, $CDCl_3$, δ, ppm): 8.83 (d, *J* = 8.6 Hz, 6H), 7.44 (d, *J* = 8.5 Hz, 6H), 4.09 (t, 7.3Hz, 6H), 1.75 – 1.59 (m, 6H), 1.48 – 1.31 (m, 6H), 0.94 (t, *J* = 7.3 Hz, 9H). ^{13}C NMR (75 MHz, $CDCl_3$, δ, ppm): 170.8, 170.6, 165.1, 144.6, 135.2, 130.3, 127.3, 50.9, 29.4, 19.8, 13.7.

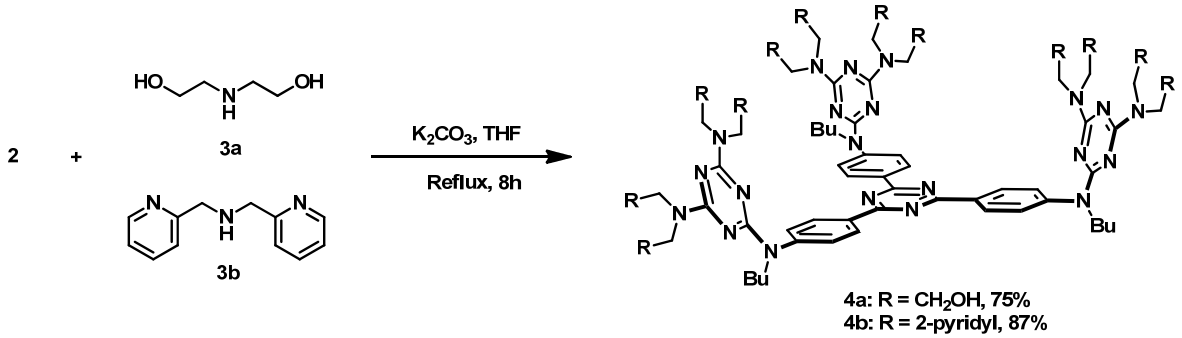
2.4. General procedure for the synthesis of molecular synthons (**4**)

To a solution of compound **2** (0.48 g, 0.5 mmol) in THF (25 mL) was added K_2CO_3 (finely ground) (0.28 g, 2 mmol) and respective nucleophile (**3**) (2 mmol) with constant stirring. The reaction mixture was heated under reflux for 8 h. After cooling to room temperature, the mixture was filtered and solvent was removed. The residue was chromatographed on a silica gel column (100-200) with a mixture of acetone and methanol as the mobile phase to give pure products as white solids (Scheme 3).

Table 1. Optimization of base and solvent for the synthesis of **4a** and **4b** [a].

No	Solvent	Temperature (°C)	Time (hours)	Base	4a [b]	4b [b]
1	THF	Reflux	14	Na_2CO_3	40	45
2	THF	Reflux	12	K_2CO_3	71	81
3	THF	Reflux	09	Cs_2CO_3	70	78
4	THF	Reflux	16	DIPEA	57	60
5	THF	Reflux	15	Et_3N	33	44
6	1,4-Dioxane	Reflux	09	K_2CO_3	44	50
7	DME	Reflux	10	K_2CO_3	19	23
8	Acetone	Reflux	10	K_2CO_3	55	63
9	$CHCl_3$	Reflux	24	K_2CO_3	10	28
10	CH_3CN	Reflux	07	K_2CO_3	66	72
11 [c]	THF	Reflux	08	K_2CO_3	75	87
12 [d]	THF	Reflux	07	K_2CO_3	73	84

[a] **2** (0.5 mmol), **3** (2.0 mmol).
[b] Isolated yields, base (1.5 mmol).
[c] Base (2.0 mmol).
[d] Base (2.5 mmol).



Scheme 3

2,2',2'',2''',2'''',2''''',2'''''',2''''''',2'''''''',2''''''''',2'''''''''',2''''''''''-((6,6',6''-(((1,3,5-Triazine-2,4,6-triyl)tris(benzene-4,1-diyl)) tris(butylazanediyl))tris(1,3,5-triazine-6,4,2-triyl))hexakis(azanetriyl))dodecaethanol (**4a**): Yield: 0.52 g, 75%. M.p.: 290-292 °C. IR (KBr, ν, cm^{-1}): 3409, 1571, 1478, 1363, 1211, 1159. ^1H NMR (300 MHz, DMSO-d_6, δ, ppm): 8.36 (d, *J* = 8.2 Hz, 6H), 6.96 (d, *J* = 8.2 Hz, 6H), 3.93 (t, *J* = 6 Hz, 6H), 3.89–3.64 (m, 60H), 1.69-1.40 (m, 6H), 1.41-1.10 (m, 6H), 0.89 (t, *J* = 7.2 Hz, 9H). ^{13}C NMR (75 MHz, DMSO-d_6, δ, ppm): 170.4, 168.6, 164.8, 144.5, 135.1, 130.5, 127.2, 58.6, 56.9, 50.8, 29.5, 19.7, 13.5. MS (MALDI-TOF, *m/z*): 1378.5 [M + H^+] (100), 1379.5 (70), 1380.5 (27). Anal. calcd. for $C_{66}H_{99}N_{21}O_{12}$: C, 57.50; H, 7.24; N, 21.34. Found: C, 57.37; H, 6.99; N, 21.28%.

N^2,N^2',N^2''-((1,3,5-triazine-2,4,6-triyl)tris(benzene-4,1-diyl)) tris(N^2-butyl-N^4,N^4,N^6,N^6-tetrakis(pyridin-2-ylmethyl)-1,3,5-triazine-2,4,6-triamine) (**4b**): Yield: 0.85 g, 87%. M.p.: 267-269 °C. IR (KBr, ν, cm^{-1}): 1568, 1476, 1359, 1215. ^1H NMR (300 MHz, $CDCl_3$, δ, ppm): 8.53 (d, *J* = 3.7 Hz, 12H), 8.41 (d, *J* = 8.3 Hz, 6H), 7.51 - 7.38 (m, 12H), 7.20 (dd, *J* = 11.5, 4.8 Hz, 12H), 7.13 (d, *J* = 8.5 Hz, 12H), 7.01 (d, *J* = 8.3 Hz, 6H), 5.07 (s, 24H), 3.79 (t, *J* = 6 Hz, 6H), 1.53 - 1.34 (m, 6H), 1.21 - 1.02 (m, 6H), 0.74 (t, *J* = 7.3 Hz, 9H). ^{13}C NMR (75 MHz, $CDCl_3$, δ, ppm): 171.2, 169.3, 164.6, 158.2, 156.9, 152.4, 149.5, 144.3, 138.2, 134.9, 130.8, 126.9, 50.6, 29.3, 19.1, 12.9. MS (MALDI-TOF, *m/z*): 1942.8 [M + H^+] (80), 1943.8 (100), 1944.8 (65). Anal. calcd. for $C_{114}H_{111}N_{33}$: C, 70.46; H, 5.76; N, 23.79. Found: C, 70.58; H, 5.66; N, 23.55%.

3. Results and discussion

We initiated our study with the synthesis of 2,4,6-*tris*(4-aminophenyl)triazine following a literature method [29,30]. The treatment of 4-nitrobenzonitrile with sodium methoxide in methanol followed by treatment with acetic acid gave 2,4,6-*tris*(4-nitrophenyl)triazine. Reduction of 2,4,6-*tris*(4-nitro phenyl)triazine led to the formation of 2,4,6-*tris*(4-amino phenyl)triazine in a reasonable yield. To avoid potential solubility problems associated with the final target compounds, *n*-butyl groups on the nitrogen atoms of 2,4,6-*tris*(4-amino phenyl)triazine were introduced [31,32]. Three-directional sulfonation followed by alkylation using *n*-butyl bromide under basic conditions of 2,4,6-*tris*(4-aminophenyl)triazine led to the desired intermediate. Deprotection of sulfonyl groups from this intermediate in warm concentrated sulfuric acid afforded 2,4,6-*tris*(4-*n*-butylaminophenyl)triazine (**1**) in excellent yield (Scheme 1) [31]. The solubility properties of compound **1** in common organic solvents such as THF, $CHCl_3$, ethyl acetate, acetone etc were improved greatly as compared to 2,4,6-*tris*(4-aminophenyl)triazine after the introduction of *n*-butyl chains [31]. Compound **1** was then reacted with cyanuric chloride in the presence of diisopropylethylamine (DIPEA) at 0 °C in THF solvent to provide desired star-shaped arylated product (**2**) in 62% isolated yield (Scheme 2) [31].

Keeping in view the rigid nature and reactivity of six chloro groups present in compound (**2**), it was then reacted with functionalized nucleophiles (**3**) to produce our targeted molecular synthons (**4**) (Scheme 3). A variety of reaction conditions including different bases and solvents were tried (Table 1). Use of THF as solvent with Na_2CO_3 as base produced 40% of polyhydroxylated compound (**4a**) and 45% of multi-N-donor compound (**4b**) in 14 hours time (Entry 1, Table 1). Other inorganic (K_2CO_3, Cs_2CO_3) and organic (DIPEA, Et_3N) bases in THF solvent under reflux conditions gave moderate to good yield of both **4a** and **4b** (Entry 2-5, Table 1). As K_2CO_3 was proved to be the best base in THF solvent providing maximum yield of both **4a** and **4b**, we thought it valuable to monitor the effect of other more polar solvents for further improvement in the yield. Unfortunately, all other solvents such as 1,4-dioxane, 1,2-dimethoxyethane (DME), Acetone, $CHCl_3$, CH_3CN were found to be less effective as compared to THF with the production of both **4a** and **4b** in lower yields (Entry 6-9, Table

1). It is interesting to note here that increase in the base concentration from 3 to 4 equivalents resulted in the increase in the yield of both **4a** and **4b** (Entry, 10, Table 1). However, further increase in the base concentration from four to five equivalents had the detrimental effect on the reaction yields (Entry 11, Table 1).

The structures of compounds (**4**) were established on the basis of spectroscopic data and microanalysis. In the ^{1}H and ^{13}C NMR spectras, both the compounds (**4**) showed a single set of proton and carbon signals, respectively showing highly symmetric structure in solution. In ^{1}H NMR spectras, the AB quartet proton signals were observed for all *para*-substituted benzene rings. It is important to address here that altered physiochemical properties of resultant compounds due to the presence of twelve hydroxy groups or twelve chelating pyridyl groups would make these molecular subunits a unique carriers or delivery systems in aqueous phase or in living systems in addition to their applications in supramolecular self-assembly.

4. Conclusion

In conclusion, we have demonstrated the synthesis of new triazine-core polyhydroxylated and multi-*N*-donor synthons in high yields. The reaction of star-shaped intermediate having six reactive chloro-substituents with *bis*(2-hydroxyethyl) amine and *bis*(2-pyridylmethyl)amine provided versatile polyhydroxy lated and multi-*N*-donor molecular subunits. These compounds with twelve hydroxyl groups or twelve 2-pyridyl ligands are excellent future candidates for hydrogen bond and metal driven assemblies for desired properties and functions in supramolecular and material chemistry. In addition, modified physiochemical properties such as hydrophilicity and metal chelating capacity of these synthons may provide a route towards developing unique carriers or delivery systems in aqueous phase or in living systems.

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References

[1]. Naseer, M. M.; Hameed, S. *Cryst. Eng. Comm.* **2012**, *14*, 4247-4250.
[2]. Leininger, S.; Olenyuk, B.; Stang, P. J. *Chem. Rev.* **2000**, *100*, 853-907.
[3]. Northrop, B.; Zheng, Y. R.; Chi, K. W.; Stang, P. J. *Acc. Chem. Res.* **2009**, *42*, 1554-1563.
[4]. Li, S. S.; Northrop, B.; Yuan, Q. H.; Wan, L. J.; Stang, P. J. *Acc. Chem. Res.* **2009**, *42*, 249-259.
[5]. Pluth, M. D.; Bergman, R. G.; Raymond, K. N. *Science* **2007**, *316*, 85-88.
[6]. Rebek J. Jr. *Acc. Chem. Res.* **2009**, *42*, 1660-1668.
[7]. Tiefenbacher, K.; Rebek, J. Jr. *J. Am. Chem. Soc.* **2012**, *134*, 2914-2917.
[8]. Tiefenbacher, K.; Ajami, D.; Rebek, J. Jr. *Angew. Chem. Int. Ed.* **2011**, *50*, 12003-12007.
[9]. Desiraju. G. R. *Angew. Chem. Int. Ed.,* **1995**, *34*, 2311-2327.
[10]. Gondi, S. R.; Son, D. Y. *Synth. Commun.* **2004**, *34*, 3061-3072.
[11]. Black, C. T.; Ruiz, R.; Breyta, G.; Cheng, J. Y.; Colburn, M. E.; Guarini, K. W.; Kim, H. C.; Zhang, Y. *IBM J. Res. Dev*. **2007**, *51*, 605-633.
[12]. Fendler, J. H. *Chem. Mater.* **2001**, *13*, 3196-3210.
[13]. Zhang, S.; Marini, D. M.; Hwang, W.; Santoso, S. *Curr. Opin. Chem. Biol.* **2002**, *6*, 865-871.
[14]. Otsuka, H.; Nagasaki, Y.; Kataoka, K. *Curr. Opin. Colloid Interface Sci.* **2001**, *6*, 3-10.
[15]. Chen, W.-Y.; Ouyang, L.; Chen, R.-Y.; Li, X.-S. *Synth. Commun.* **2012**, *42*, 2585-2594.
[16]. Arai, T.; Yamada, Y.; Yamamoto, N.; Sasai, H.; Shibasaki, M. *Chem. Eur. J.* **1996**, *2*, 1368-1372.
[17]. Weis, M.; Waloch, C.; Seiche, W.; Breit, B. *J. Am. Chem. Soc.* **2006**, *128*, 4188-4189.
[18]. Stojanovic, M. N.; De Prada, P.; Landry, D. W. *J. Am. Chem. Soc.* **2000**, *122*, 11547-11548.
[19]. Yang, X.; Johnson, S.; Shi, J.; Holesinger, T.; Swanson, B. *Sens. Actuators B* **1997**, *45*, 79-84.
[20]. Yang, H.; Yu, C.; Song, Q.; Xia, Y.; Li, F.; Chen, Z.; Li, X.; Yi, T.; Huang, C. *Chem. Mater.* **2006**, *18*, 5173-5177.
[21]. Jiang, S. P.; Liu, Z.; Tian, Z. Q. *Adv. Mater.* **2006**, *18*, 1068-1072.
[22]. Yoshizawa, M.; Klosterman, J. K.; Fujita, M. *Angew. Chem., Int. Ed.* **2009**, *48*, 3418-3438.
[23]. Hof, F.; Craig, S. L.; Nuckolls, C.; Rebek, J. *Angew. Chem., Int. Ed.* **2002**, *41*, 1488-1508.
[24]. Lindoy, L. F.; Atkinson, I. M. Self-Assembly in Supramolecular Systems (Monographs in Supramolecular Chemistry), Volume 7, Royal Society of Chemistry, Cambridge, 2000.
[25]. Fujita, M. Molecular Self Assembly: Organic Versus Inorganic Approaches. Structure and Bonding, Volume 96, Springer, Berlin, 2000.
[26]. Megger, D. A.; Muller, J. *Synth. Commun.* **2011**, *41*, 2524-2529.
[27]. Fiedler, D.; Leung, D. H.; Bergman, R. G.; Raymond, K. N. *Acc. Chem. Res.* **2005**, *38*, 351-360.
[28]. Kusukawa, T.; Nakai, T.; Okano, T.; Fujita, M. *Chem. Lett.* **2003**, *32*, 284-285.
[29]. Schaefer, F. C.; Peters, G. A. *J. Org. Chem.* **1961**, *26*, 2778-2784.
[30]. Juarez, R.; Gomez, R.; Segura, J. L.; Seoane, C. *Tetrahedron Lett.* **2005**, *46*, 8861-8864.
[31]. Naseer, M. M.; Wang, D.-X.; Zhao, L.; Huang, Z.-T.; Wang, M.-X. *J. Org. Chem.* **2011**, *76*, 1804-1813.
[32]. Naseer, M. M.; Hameed, S. *Appl. Organometal. Chem.* **2012**, *26*, 330-334.