Tetrahedron Letters 50 (2009) 1851–1854

Contents lists available at ScienceDirect

Tetrahedron Letters

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

Synthesis of a halo-methylphenylene periphery-functionalized triazine-based dendritic molecule with a 3,3′-dimethyl-biphenyl linker using tris(halo-methylphenylene)triazines as building blocks

Ioannis D. Kostas [a,*], Fotini J. Andreadaki [a], Elaine A. Medlycott [b], Garry S. Hanan [b], Eric Monflier [c]

[a] National Hellenic Research Foundation, Institute of Organic and Pharmaceutical Chemistry, Vas. Constantinou 48, 116 35 Athens, Greece
[b] Département de Chimie, Université de Montréal, 2900 Edouard-Montpetit, Pavillon Roger-Gaudry, Montréal, Que., Canada H3T-1J4
[c] Unité de Catalyse et de Chimie du Solide-UMR 8181, Université d'Artois, rue Jean Souvraz, Lens Cédex, France

ARTICLE INFO

Article history:
Received 15 December 2008
Revised 26 January 2009
Accepted 4 February 2009
Available online 8 February 2009

Keywords:
Dendrimer
Triazine
Cyclotrimerization
Suzuki coupling
Phosphine oxide
Hydroformylation

ABSTRACT

A tris(bromo-methylphenylene)triazine and its corresponding phosphine oxide derivative have been synthesized; the latter compound was found to be a potent ligand for the hydroformylation reaction. Suzuki coupling of the mono-pinacolboronate derivative of the former compound with a tris(iodo-methylphenylene)triazine was possible at two of the three iodine atoms, yielding a bromo- and iodo-methylphenylene periphery-functionalized triazine-based dendritic molecule with a 3,3′-dimethyl-biphenyl linker.

Dendrimers and dendritic molecules are the subject of significant academic and industrial interest.[1,2] Compounds containing *s*-triazine units and dendrimers based on triazine have received a remarkable amount of attention owing to their potential applications[3] and have shown molecular recognition and self-assembly properties.[4] They are of interest for their electroluminescent and electrochemical properties due to the role of the electron-deficient triazine unit as an electron transport component[5] and also for their liquid-crystalline and nonlinear optical properties.[5b,6] Triazine dendritic structures, and in particular those based on melamine, have shown very promising results for drug delivery and can sequester a range of hydrophobic guests effectively, including candidate anticancer drugs, and with the absence of toxicity.[7]

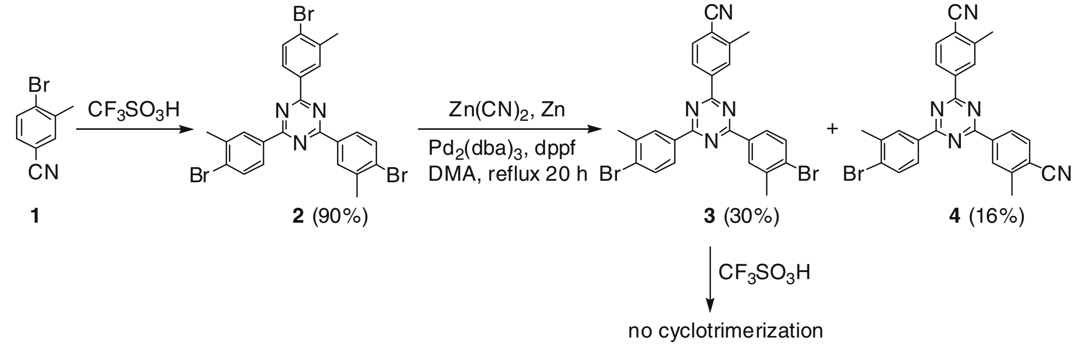
Triazine dendrimers can be synthesized by various routes based on divergent and convergent methods. The most common methods are cycloaddition reactions to form the triazine ring, cyclotrimerization of organic cyanates and nucleophilic aromatic substitution of cyanuric chloride.[1–8] In the great majority of triazine dendritic molecules, the triazine rings are linked by nitrogen-containing spacers such as amino groups. In this Letter, we report the synthesis of a halo-methylphenylene periphery-functionalized triazine-based dendritic molecule with a 3,3′-dimethyl-biphenyl linker, by the use of tris(halo-methylphenylene)triazines as building blocks. We used compound **2** with a methyl substituent instead of the analogue without the methyl group due to its higher solubility in organic solvents. Indeed, we found that in boiling toluene, the solubility of **2** was 2.8 g/100 mL compared to 0.8 g/100 mL for the analogue without methyl substituents.

The synthesis of the title dendritic molecule was first attempted by cyclotrimerization of the corresponding nitrile as shown in Scheme 1. The tris(bromoaryl)triazine **2** was prepared in high yield by cyclotrimerization of 4-bromo-3-methylbenzonitrile **(1)** with neat trifluoromethanesulfonic acid. The procedure was analogous to that previously described for the cyclotrimerization of 4-bromobenzonitrile.[9] The CH_3 resonance in **2** was observed as one signal in the ^1H and ^{13}C NMR spectra at δ 2.57 and 23.17, respectively, indicating the equivalence of the three CH_3 groups. Compound **2** could be regarded as the 0th generation of a symmetric halo-methylphenylene periphery-functionalized triazine dendrimer. In the next step, cyanation of **2** was achieved by the use of $Pd_2(dba)_3$, dppf and Zn as the catalyst and $Zn(CN)_2$ as the cyanide source, in accordance with a known protocol for the cyanation of aryl chlorides.[10] Although the ratio of Br/CN was kept at 2.5:1, cyanation was not selective, leading to unreacted **2** (32%) and a mixture of mono- and dicyanated derivatives **3** and **4**, in yields of 30% and

---

* Corresponding author. Tel.: +30 210 7273878; fax: +30 210 7273831.
E-mail address: ikostas@eie.gr (I.D. Kostas).

0040-4039/$ - see front matter
doi:10.1016/j.tetlet.2009.02.011

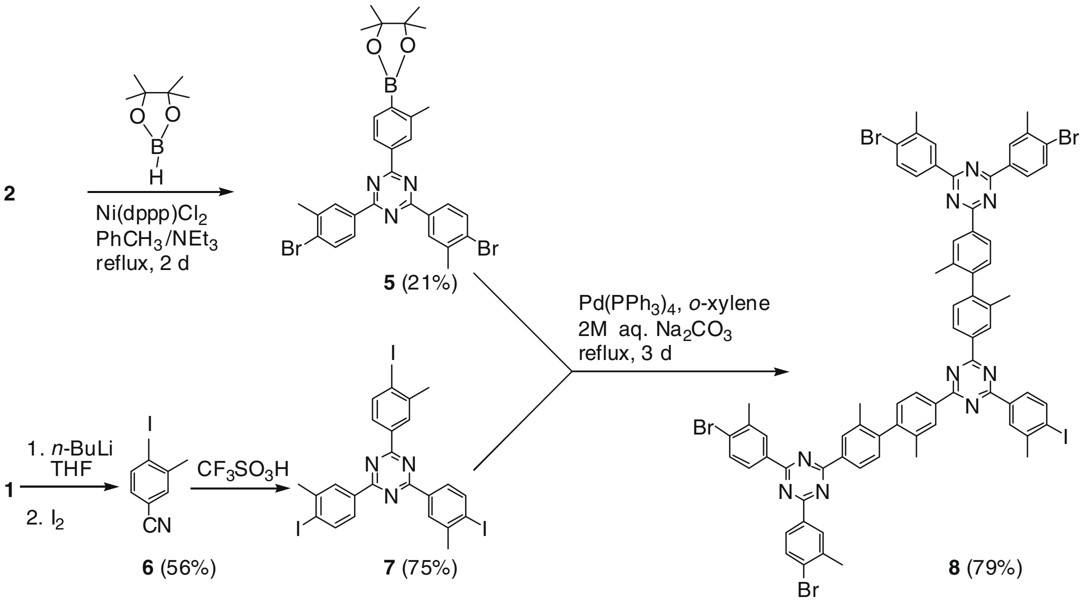


Scheme 1.

16%, respectively. Unfortunately, the formation of the 1st generation dendrimer by cyclotrimerization of **3**, as described for **1**, was not possible, probably due to steric hindrance.

The formation of the 1st generation dendrimer was then attempted via a Suzuki coupling of an aryl halide and a pinacolboronate in a mixture of an organic solvent and an aqueous solution of Na_2CO_3 using $Pd(PPh_3)_4$ as the catalyst (Scheme 2), in accordance with the synthesis of hyperbranched polyphenylene by the homocoupling of (3,5-dibromophenyl)boronic acid.[11] The pinacolboronate **5** was synthesized by the nickel-catalyzed reaction of **2** with pinacolborane using $Ni(dppp)Cl_2$ in refluxing $PhCH_3/NEt_3$, as previously described for the synthesis of pinacolboronates by reaction of di- or tribromobenzene with pinacolborane.[12] A ratio of Br/B of 2.3:1 afforded **5** in 21% yield after two days refluxing. Palladium-catalysis using $Pd_2(dba)_3$/2-dicyclohexylphosphino-2′-(*N*,*N*-dimethylamino)biphenyl was also attempted, however, without any improvement in the yield. In order to avoid homocoupling of **5** to give a mixture of hyperbranched polymers, the Suzuki coupling was performed between **5** and tris(iodoaryl)triazine **7** instead of the bromo-analogue **2**, since it is known that the reaction of arylboronic acid (or ester) proceeds at a higher rate with iodoarenes than with bromoarenes.[13] The tris(iodoaryl)triazine **7** was synthesized as described for **2**, by cyclotrimerization of 4-iodo-3-methylbenzonitrile **(6)**, prepared via bromine–lithium exchange in **1**, and further treatment with iodine. Suzuki coupling of the boronate **5** with the iodide **7** using $Pd(PPh_3)_4$ as the catalyst afforded the dendritic molecule **8** in 79% yield. Although the ratio of B/I was 1.3:1, coupling to only two of the three iodine atoms was achieved, presumably due to steric hindrance. This result is in contrast to the full coupling of arylboronic acid dendrimer arms to tribromobenzene[14] or the coupling of 4-(2,2′-dipyridylamino)phenylboronic acid to tris(4-bromophenyl)-1,3,5-triazine.[5d] The structure of **8** was determined by spectroscopic techniques. In the ^1H NMR spectrum, the ratio of the total number of aromatic protons to the total number of CH_3 protons was 1:1, and the ratio of the 5 × CH_3 protons closest to the halogens (δ 2.57) to the CH_3 protons attached to the other four aromatic rings (δ 2.30) was found to be 15:12, as expected for **8**. In the ^{13}C NMR spectrum, the CH_3 resonances were present as three signals at δ 29.70, 23.14 and 20.06, which were assigned to the CH_3 groups closest to iodine, bromine and the internal CH_3 groups, respectively.

The halogen atoms in compounds **2** and **8** can serve for further functionalization such as phosphorous-functionalized dendritic molecules, and thus, these reagents may be regarded as potent ligands for transition-metal homogeneous catalysis.[15] For example, we synthesized the phosphine oxide derivative **9** as shown in Scheme 3.[16] Replacement of the bromine atoms by the diphenylphosphine oxide group was achieved by reaction of **2** with potassium diphenylphosphide and subsequent oxidation of the resulting tris(triarylphosphine)triazine by hydrogen peroxide. The presence of only one singlet at δ 31.84 in the ^{31}P NMR spectrum of **9** clearly indicated the equivalence of the three phosphorous



Scheme 2.