



# Synthesis and structural characterization of a highly substituted triazine ring comprising a sterically flexible methylene linker and coordinating substituents



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## ARTICLE INFO

### Article history:

Received 25 April 2017

Revised 19 May 2017

Accepted 23 May 2017

Available online 25 May 2017

### Keywords:

Triazine

Heterocycles

Cyclotrimerization

Imidates

## ABSTRACT

The efficient multi-step, large-scale synthesis, spectroscopic characterization and solid-state molecular structure of a new type of three-fold functionalized, sterically demanding triazine is reported. The aromatic heterocycle 6,6',6''-((1,3,5-triazine-2,4,6-triyl)tris(methylene))tris(2,4-di-*tert*-butylphenol) possesses three 2,4-di-*tert*-butylphenol synthons bound to the 1,3,5-triazine ring via synthetically challenging methylene linkages in the 2,4,6 positions. The key to success was found in the generation of a highly reactive imidate hydrochloride salt, namely ethyl 2-(3,5-di-*tert*-butyl-2-methoxyphenyl)acetimidate hydrochloride, that readily undergoes cyclotrimerization. The reported preparation opens new perspectives in the design and synthesis of novel triazine molecules bearing flexible and sterically demanding functionalized groups for various applications.

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## Introduction

Among the broad family of heterocycles,<sup>1</sup> *N*-containing congeners,<sup>2</sup> such as 1,3,5-triazines (*s*-triazines), have gained importance in several different fields. The applications are certainly too numerous to be listed here, but cover a very broad area ranging from pharmaceuticals,<sup>3</sup> materials,<sup>4</sup> supramolecular building blocks,<sup>5</sup> and ligands<sup>6</sup> to reagents for chemical transformations.<sup>7</sup> Intrinsic to this growing interest are the development of new synthetic methodologies for the efficient preparation of more elaborate and sophisticated polyfunctional 1,3,5-triazines.<sup>8</sup> In the course of our ligand design program towards potential new ligands capable of coordinating large, oxophilic metal centers, such as *f*-block metal ions,<sup>9</sup> *s*-triazine derivatives such as **1** (Scheme 1) were found to be of particular interest. This functionalized molecular platform constitutes a very interesting architecture incorporating a methylene linkage connecting the heteroaromatic ring and the phenol groups at alternating carbon atoms. Incorporation of an *sp*<sup>3</sup>-hybridized carbon linker is thought to provide sufficient structural flexibility to properly accommodate the coordination of a metal ion through the sterically shielding and chelating phenol arms. Most importantly, the anchoring triazine unit, specifically the doubly degenerate set of triazine  $\pi^*$  orbitals, ought to provide

an efficient platform for  $\delta$ -backbonding with the symmetry-equivalent metal *f*-orbitals.<sup>9d,10</sup> This allows the synthesis of electron-rich, low-valent coordination complexes for the reductive activation of small molecules of biological and industrial importance, for example H<sub>2</sub>, CO, CO<sub>2</sub>, O<sub>2</sub>, and H<sub>2</sub>O.<sup>11</sup>

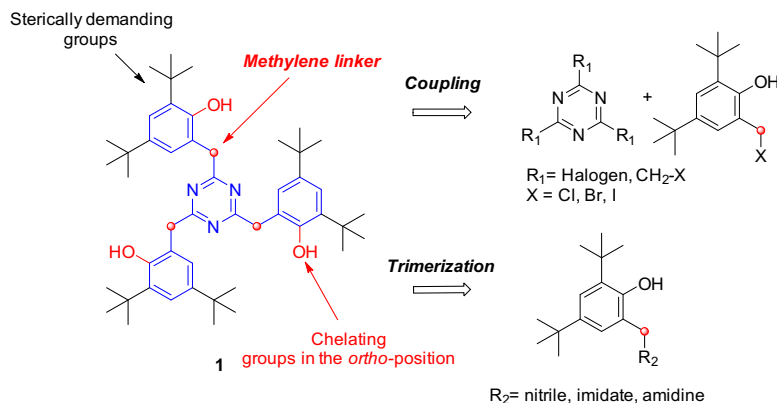
To our surprise, literature procedures for the envisioned methylene linker on such heterocycles are extremely scarce. This undoubtedly transpires from an inherent difficulty in constructing this very specific linkage on triazine molecules. Recent developments in synthetic methodologies, particularly in cross-coupling reactions involving various transition metal catalysts, *e.g.* Suzuki, Kumada, or Negishi coupling, have allowed for the construction of arylmethylheteroaromatic molecules.<sup>12</sup> Nevertheless, only a handful of triazine molecules displaying this interesting skeleton are reported, but with rather simple motifs and without functional groups in the *ortho*-position of the linked aryl group capable of coordinating metal ions.<sup>13</sup> For our purposes, it was therefore necessary to establish a facile and efficient entry into this elusive class of molecules, sufficiently robust and flexible to enable further derivatization.

## Results and discussion

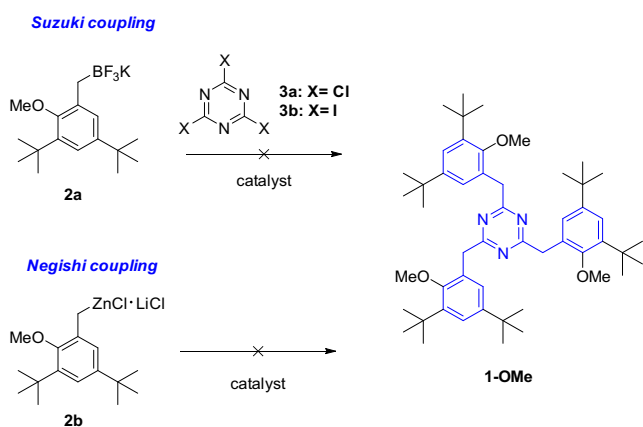
Our initial synthetic approach for introduction of the methylene linkage focused on coupling reactions following the above-mentioned recent developments. For example, the Suzuki coupling

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**Scheme 1.** Structure of triazine **1** and two attempted synthetic approaches.



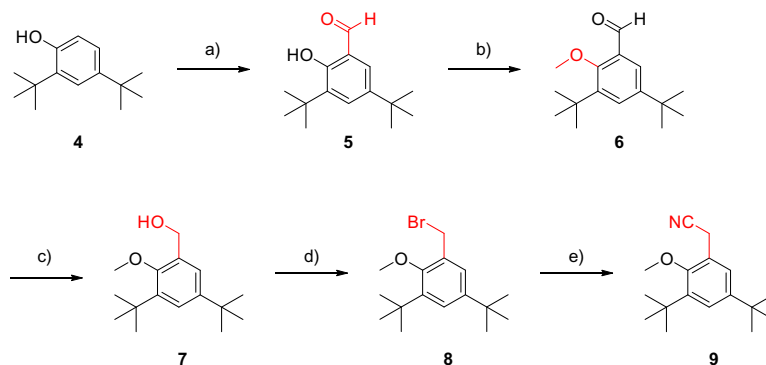
**Scheme 2.** Coupling routes investigated for the synthesis of triazine **1-O-Me**.

reaction<sup>12g,14</sup> of aryltrifluoroborate **2a** with triazine **3** in the presence of  $\text{PdCl}_2(\text{dppf})\cdot\text{CH}_2\text{Cl}_2$  (with  $\text{dppf} = 1,1'$ -bis(diphenylphosphino)ferrocene), and triethylamine in a mixture of  $i\text{PrOH-H}_2\text{O}$  at reflux or, alternatively, the Negishi coupling reaction<sup>12j,15</sup> of **3** with zinc reagent **2b** using  $\text{Pd}(\text{OAc})_2$  and *S*-Phos (with *S*-Phos = 2-dicyclohexylphosphino-2',6'-dimethoxybiphenyl) in THF at reflux (Scheme 2).

Unfortunately, these reaction pathways to the desired triazine **1-O-Me** were unsuccessful in our hands as evidenced by mostly slow decomposition of the starting materials. In our attempts

toward the heterocycle synthesis, we therefore considered the cyclotrimerization of nitrile derivatives (Scheme 1). The cyclization of three identical (or different) RCN groups constitutes a well-established method that has previously allowed for the isolation of a number of 1,3,5-triazines.<sup>16</sup> However, depending on the nature of the substrate, the catalyst (*i.e.* Lewis acids, basic compounds or lanthanides),<sup>16f,16i-k,17</sup> or the reaction conditions (*i.e.* temperature, pressure, solvent),<sup>18</sup> fluctuating yields have been reported. In order to investigate the viability of this route, 2-(3,5-di-*tert*-butyl-2-methoxyphenyl)acetonitrile **9** was readily synthesized following a five-step procedure, starting from commercially available 2,4-di-*tert*-butylphenol **4** (Scheme 3). The first step involved the formylation of phenol **4** using tin(IV) chloride, paraformaldehyde (PFA), and triethylamine.<sup>19</sup> The resulting aldehyde was then *O*-methylated *via* deprotonation of the alcohol with sodium hydroxide and subsequent quench with methyl iodide leading to 3,5-di-*tert*-butyl-2-methoxybenzaldehyde **6** which was then reduced with  $\text{NaBH}_4$  to afford the corresponding benzyl alcohol **7**. The succeeding reaction with phosphorus tribromide in  $\text{CH}_2\text{Cl}_2$  afforded the desired benzyl bromide **8**, without further purification, was treated with  $\text{NaCN}$  in an ethanol/water mixture to yield the targeted nitrile derivative **9** on gram-scale with an overall yield of 75%. The solid-state molecular structure of key compound **9** was unambiguously established by single-crystal X-ray diffraction analysis of colorless needles (see ESI).

Our first cyclotrimerization attempts of nitrile **9** were guided by reported procedures for the synthesis of other analogues.<sup>16</sup> Thus, several catalysts such as triflic acid ( $\text{TfOH}$ ), triflic anhydride ( $\text{Tf}_2\text{O}$ ), trifluoroacetic acid (TFA), or samarium(II) iodide were investigated. Reaction times spanning from 30 min to 24 h, at



**Scheme 3.** Reagents and conditions: a)  $\text{SnCl}_4$ , PFA,  $\text{NEt}_3$ , toluene, 80 °C, 12 h, 88%; b) MeI, NaOH, THF/DMSO (10:1), RT, 12 h, 98%; c)  $\text{NaBH}_4$ , ethanol, RT, 2 h, 99%; d)  $\text{PBr}_3$ , 0 °C → RT, 1 h, 98%; e) NaCN, ethanol/ $\text{H}_2\text{O}$  (10:1), 90%.

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