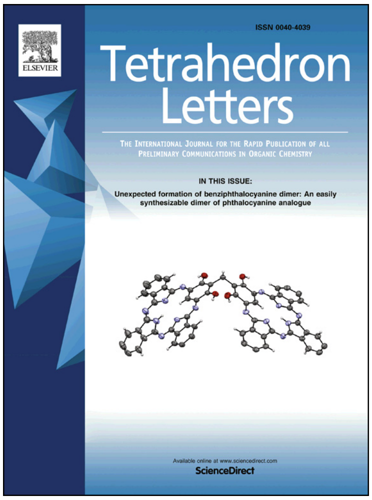

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Synthesis and Structural Characterization of a Highly Substituted Triazine Ring Comprising a Sterically Flexible Methylene Linker and Coordinating Substituents

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Abstract

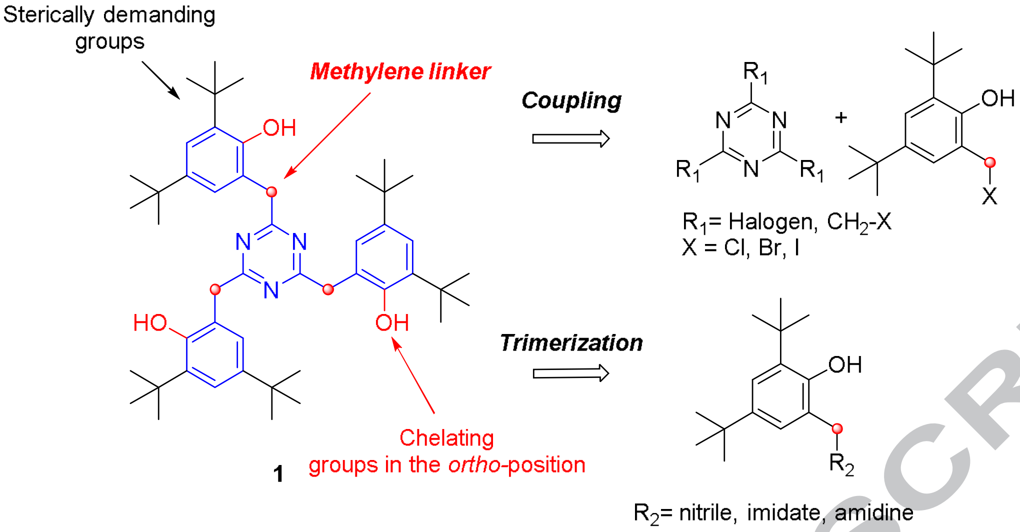
The efficient multi-step, large-scale synthesis, spectroscopic characterization and solid-state molecular structure of a new type of three-fold functionalized, sterically demanding triazine is reported. The aromatic heterocycle 6,6',6''-((1,3,5-triazine-2,4,6-triyl)tris(methylene))tris(2,4-di-*tert*-butylphenol) 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.

Keywords

Triazine; Heterocycles; Cyclotrimerization; Imidates

Introduction

Among the broad family of heterocycles,[1] *N*-containing congeners,[2] such as 1,3,5-triazines (*s*-triazine), 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,[3] materials,[4] supramolecular building blocks,[5] and ligands[6] to reagents for chemical transformations.[7] 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.[8] 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,[9] *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^3-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 π^* orbitals, ought to provide an efficient platform for δ-backbonding with the symmetry-equivalent metal *f*-orbitals.[9d, 10] 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_2, CO, CO_2, O_2, and H_2O.[11]

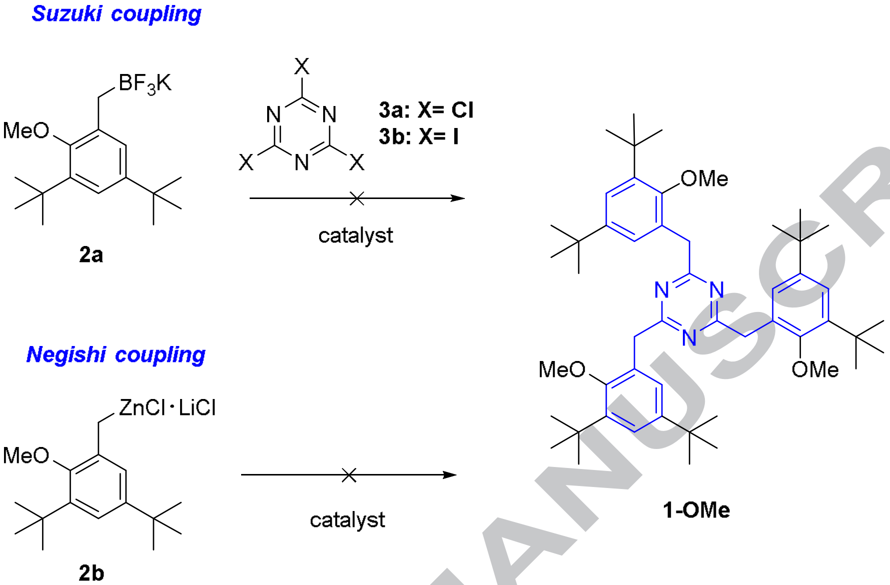


Scheme 1. Structure of triazine **1** and two attempted synthetic approaches.

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.[12] 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 phenol group capable of coordinating metal ions.[13] 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.

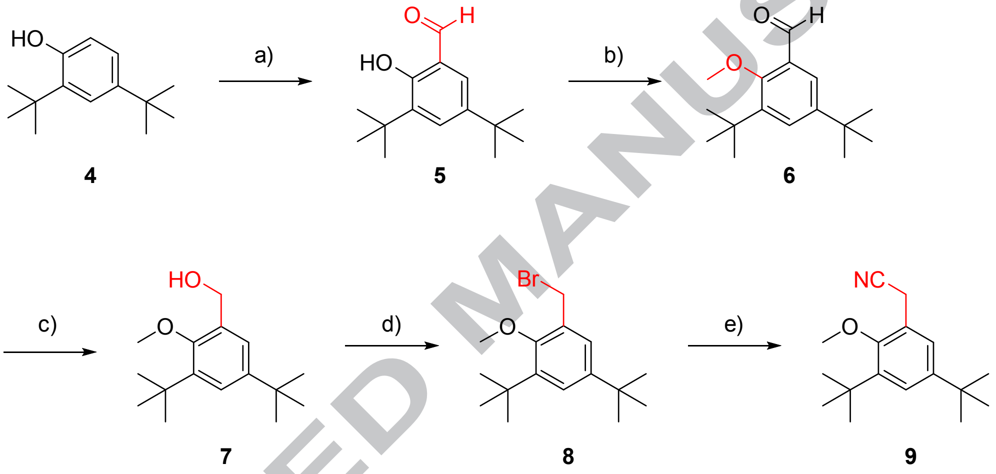
Results and Discussion

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 reaction[12g, 14] of aryltrifluoroborate **2a** with triazine **3** in the presence of $PdCl_2(dppf)\cdot CH_2Cl_2$ (with dppf = 1,1'-bis(diphenylphosphino)ferrocene), and triethylamine in a mixture of *i*PrOH-H_2O at reflux or, alternatively, the Negishi coupling reaction[12j, 15] of **3** with zinc reagent **2b** using Pd(OAc)$_2$ and *S*-Phos (with *S*-Phos = 2-dicyclohexylphosphino-2',6'-dimethoxybiphenyl) in THF at reflux (Scheme 2).



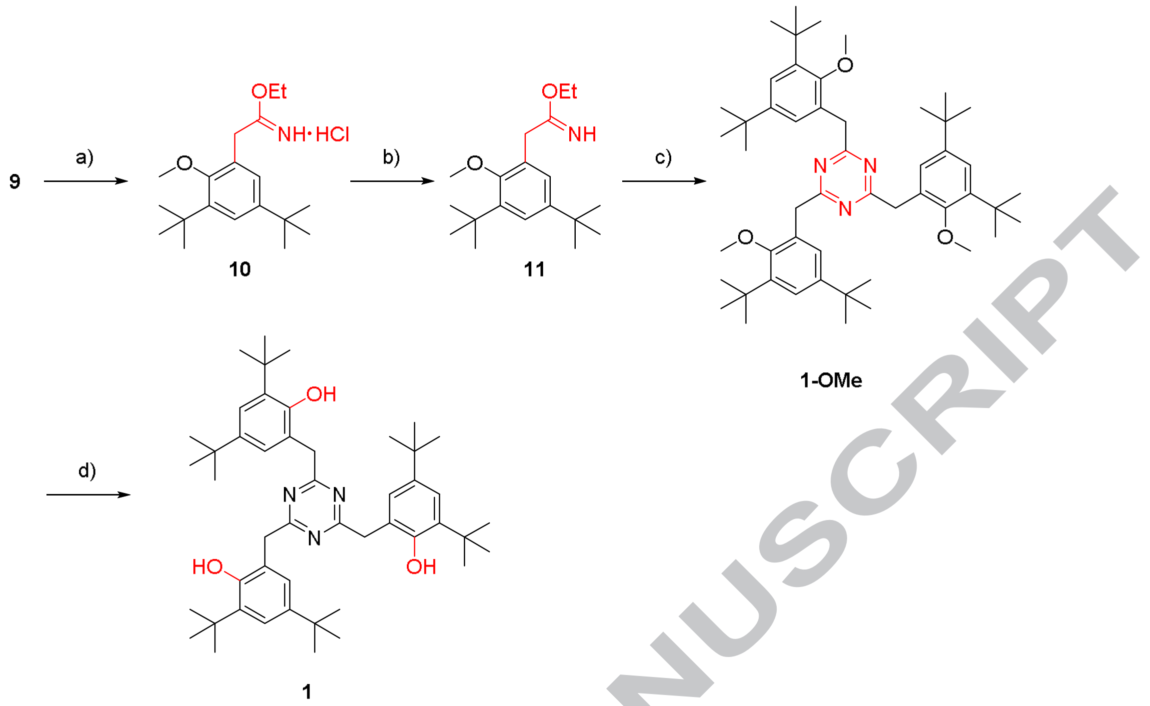
Scheme 2. Coupling routes investigated for the synthesis of triazine **1-OMe**.

Unfortunately, these reaction pathways to the desired triazine **1-OMe** 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.[16] However, depending on the nature of the substrate, the catalyst (*i.e.* Lewis acids, basic compounds or lanthanides),[16f, 16i-k, 17] or the reaction conditions (*i.e.* temperature, pressure, solvent),[18] 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.[19] 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 **5** which was then reduced with $NaBH_4$ to afford the corresponding benzyl alcohol **7**. The succeeding reaction with phosphorus tribromide in CH_2Cl_2 afforded the desired benzyl bromide (**8**).[9e] Bromide **8**, without further purification, was treated with NaCN in an ethanol/water mixture to yield the targeted nitrile derivative **9** on gram-scale with an overall yield of 68%. The solid-state molecular structure of key compound **9** was unambiguously established by single-crystal X-ray diffraction analysis of colorless needles (see ESI).



Scheme 3. Reagents and conditions: a) $SnCl_4$, PFA, NEt_3, toluene, 80 °C, 12 h, 88%; b) MeI, NaOH, THF/DMSO (10:1), RT, 12 h, 98%; c) $NaBH_4$, ethanol, RT, 2 h, 95%; d) PBr_3, 0 °C → RT, 1 h, 89%, e) NaCN, ethanol/H_2O (10:1), 90%.

Our first cyclotrimerization attempts of nitrile **9** were guided by reported procedures for the synthesis of other analogues.[16] Thus, several catalysts such as triflic acid (TfOH), triflic anhydride (Tf_2O), trifluoroacetic acid (TFA), or samarium(II) iodide were investigated. Reaction times spanning from 30 min to 24 h, at temperatures ranging from 40 °C to 120 °C, in commonly used solvents (*ie.* toluene, *n*-hexane, dichloromethane) were considered. Unfortunately, none of these procedures were successful; In most attempts starting material **9** was recovered unreacted. When catalysts, such as Tf_2O or TfOH were used, a complex mixture of products with no traces of triazine **1-OMe** was obtained, as evidenced by GC-MS and ^{1}H NMR analysis. Clearly, the persistence of starting material **9** in the resulting reaction mixtures points to a lack of reactivity of the involved nitrile toward cyclotrimerization. Therefore, an alternative pathway with drastically increased reactivity for **9** had to be found. This difficulty was circumvented by generating the corresponding imidate hydrochloride salt following a modified Pinner type reaction.[20] This highly reactive imidate salt **10** exhibits the increased reactivity required to overcome the electronic and steric constraints and undergo cyclotrimerization.[13e, 13g, 21] Imidate salt **10** was readily obtained by passing anhydrous hydrogen chloride gas through a solution of nitrile **9** in a diethyl ether-ethanol mixture, leading to precipitation of the salt in almost quantitative yield (Scheme 4). The isolated imidate **10** is moisture sensitive[22] but can be stored in the freezer under an inert gas atmosphere. Following our synthetic route (Scheme 4), imidate salt **10** was then converted to the conjugated ethyl imino ester **11** under basic conditions. The reaction of **10** with **11** in a 1:5 ratio at 80 ºC smoothly furnished the expected triazine **1-OMe** in relatively good yield (66%) after 20 h. Finally, removal of the protecting groups using boron tribromide in dichloromethane led to the targeted triazine **1** with an overall yield of 36% over 9 steps. The purity of **9** was confirmed by CHN elemental combustion analysis and its molecular structure was determined by single-crystal X-ray diffraction analysis.



Scheme 4. Reagents and conditions: a) HCl(g), Et_2O/EtOH (10:1), 0 °C to RT, 12 h, 97%; b) NEt_3, Et_2O/CH_2Cl_2 (1:1), 2 h, 87%; c) **10**, neat, 80 °C, 20 h, 66%; d) BBr_3, CH_2Cl_2, 0 °C to RT, 12 h, 98%.

Spectroscopic characterizations and structural analysis

The molecular structure of triazine **1** in solution was confirmed by ^1H NMR and ^{13}C NMR spectral analyses. The ^1H NMR spectrum of **1** in $CDCl_3$ displayed the expected characteristic peaks of the molecule (see ESI). Since the triazine core does not possess any hydrogen atoms, the hydrogen peaks of the phenyl groups were investigated instead and their number was confirmed by peak integration. Furthermore, ^1H NMR spectroscopy showed a single set of sharp signals for the different protons of the molecule; thus, suggesting freely rotating phenyl groups in solution. The ^{13}C NMR displayed the characteristic carbon atoms of the triazine core at high chemical shifts (*i.e.* 178.5 ppm), which likely is caused by the proximity of two strongly electronegative N atoms. This chemical shift was also in accordance with other reported literature examples.[4a, 8f, 23] The highly shifted signals of the other characteristic groups in the molecule, such as the C atom of the methylene linker (43 ppm) or the aromatic C atoms (152 ppm) directly attached to the OH group, can be explained based on the same rationale.

Compound **1** was analysed by IR vibrational spectroscopy; all signals were in line with the vibrational spectra of reported 1,3,5-triazines.[24] The most notable and characteristic feature was the strong signal at 1533 cm^{-1} ascribed to the C=N stretching vibrations of the *s*-triazine ring. Several other bands in the range of 2900-3000 cm^{-1} were assigned to the characteristic absorptions of the C–H bending and stretching vibration modes of the aromatic hydrogen atoms. The characteristic O–H group vibrations are known to be more sensitive to the environment and the absorption band positions dependent on the strength of the hydrogen bond. In case of **1**, intramolecular hydrogen bonding occurs (see Fig. 1) and the resulting hydroxyl group stretching band appears at 3250 cm^{-1}.

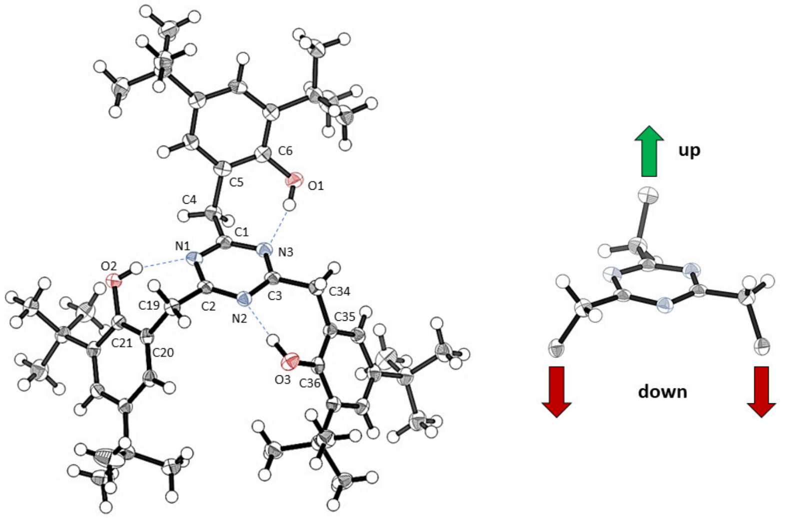


Figure 1. Molecular structure of triazine **1** in crystals of **1** • CH_3CN (left), and a schematic representation displaying the up/down orientation of the phenyl groups (right), thermal ellipsoids are drawn at 50 % probability.

The solid-state molecular structure of **1** in single-crystals of **1** • CH_3CN (Fig. 1) was unambiguously established by single crystal X-ray structural analysis of colorless crystals obtained by diffusion of a water/HCl mixture into an acetonitrile solution of the triazine. According to this XRD analyses, **1** crystallizes in the centrosymmetric, monoclinic space group $P2_1/c$. All non-hydrogen atoms were refined anisotropically. The compound crystallized with two independent molecules of the triazine derivative and two independent molecules of CH_3CN in its asymmetric unit. The crystal packing displayed a shifted orientation between the triazine cores with alternating electronegative N and electropositive C atoms (ESI; Fig. S3, S4). The angles and bond lengths are similar to those reported in the literature for structural analogues and thus the observed angles and bond lengths can be confirmed (ESI; Table S2, S3).[13b, 23-24, 25]

Conclusion

In the course of this project, we discovered that, although important synthetic methodologies have been developed in the past, the efficient synthesis of polyfunctional triazine rings still holds synthetic challenges to be tackled. Overall, the synthesis of triazine **1** described herein is robust, facile, and provides a platform for structural modifications. Although more steps are required than for the direct cyclotrimerization of nitriles, or by applying coupling methods, this synthetic strategy is considerably more flexible toward functionalization while incorporating the desired methylene linkage and a potentially coordinating group, such as a phenol. This synthesis illustrates the power of hydrochloride salts to undergo cyclotrimerization when elaborate and highly substituted target molecules are sought. The new molecule described here displays an interesting architecture for diverse applications; notably as a potential ligand in metal coordination for small molecule activation and functionalization chemistry as well as in electrocatalysis. Initial forays in these areas are currently being pursued.

Supporting Information

Spectroscopic data of **1**, **1-OMe**, **9-11**. CCDC-1543709 (**1**) and CCDC-1543710 (**9**) contain the supplementary crystallographic data for this paper.

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Highlights

- An efficient synthesis of a novel three-fold functionalized, sterically demanding triazine ring is presented.
- Three 2,4-di-*tert*-butylphenol synthons are bound to the 1,3,5-triazine ring *via* a challenging methylene linkage.
- Cyclotrimerization of imidate salts constitutes a powerful method for the generation of highly functionalized 1,3,5-triazine rings.

Graphical abstract