A general approach to triphenylenes and azatriphenylenes: total synthesis of dehydrotylophorine and tylophorine†

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A convergent and flexible synthesis of substituted triphenylenes, azatriphenylenes, and the cytotoxic alkaloids dehydrotylophorine and tylophorine has been developed.

Triphenylenes are tetracyclic structures which represent the smallest examples of all-benzenoid polycyclic aromatic hydrocarbons (see the parent molecule **1** in Fig. 1).[1] Within the past decades interest in the synthesis and application of triphenylenes has continuously increased. This interest is based on the planar rigidity of these compounds and their ability to act as molecular scaffolds for the presentation of a wide range of functionalities that can be embedded in connected side chains. Triphenylenes have found widespread application in supramolecular and materials chemistry. For example, alkoxy-substituted triphenylenes bearing a variety of different side chains undergo self-assembly to form discotic liquid crystals.[2] This represents a highly desirable property for the construction of photoconductive polymers, optical data storage devices, solar cells, and light-emitting diodes.[2] Several synthetic routes to triphenylenes have been developed, including the metal-catalyzed cyclotrimerization of three benzyne molecules.[3]

It is noteworthy that the heterocyclic 2-azatriphenylene core structure **2** has rarely been investigated. Only one 2-azatriphenylene derivative is known,[4] and the parent compound **2** has only been synthesized twice (in 4 steps).[5] We speculate that the absence of azatriphenylene structures in the literature compared to the hundreds of synthesized triphenylenes is due to the lack of a facile synthetic access of these compounds, since their physical properties and electronic nature could be of interest in materials and other applications. The development of an efficient synthetic route would not only provide access to derivatives of **2**, but also to natural products containing the 2-azaanthracene motif, especially the phenanthroindolizidine alkaloid class. Examples of these natural products include dehydrotylophorine (**3**) and tylophorine (**4**),[6] both of which have the central tetracyclic motif of an azatriphenylene. Phenanthroindolizidine alkaloids exhibit important biological effects, including anti-inflammatory, antitumor, antifungal, and antibacterial activities.[7,8] Due to its biological properties, total syntheses of racemic[8–10] and enantiomerically enriched[11] tylophorine (**4**) have been reported. Dehydrotylophorine (**3**) has only been synthesized once.[8] Here, we describe a facile and high-yielding microwave-mediated [2 + 2 + 2] cyclotrimerization approach to azatriphenylenes and its application to the total synthesis of the natural products **3** and **4**. In contrast to our route, most previous syntheses of **4** employ an initial formation of the pyrrolidine ring followed by installation of the aromatic moiety. Our cyclotrimerization approach was inspired by a single example of a constrained 2,2′-diethynylbiphenyl reacting with ethylene.[12]

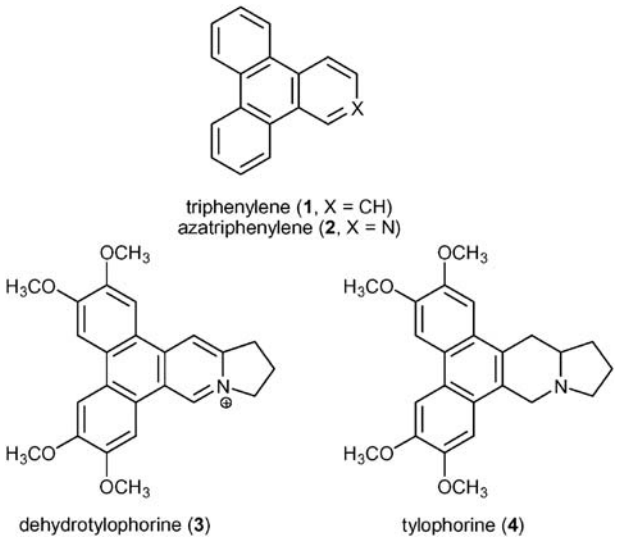
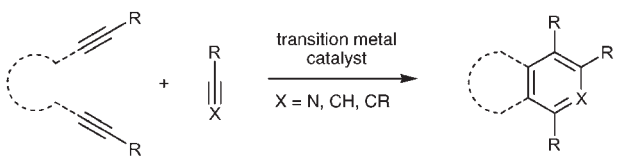


Fig. 1 Structures of the parent triphenylene **1** and 2-azatriphenylene **2**. Structures of the 2-azatriphenylene-related natural products dehydrotylophorine (**3**) and tylophorine (**4**).

The classical [2 + 2 + 2] cyclotrimerization reaction involves the reaction of three alkynes or two alkynes and a nitrile to form benzenes and pyridines (Scheme 1). Such reactions are typically conducted under cobalt,[13] nickel,[14] ruthenium,[15,16] and rhodium[16,17] catalysis, although other transition metals have been used as well.[18] In order to avoid chemoselectivity issues in the cyclotrimerization step, one of the alkynes can be immobilized on a solid-support,[19] or two alkynes can be



Scheme 1 General [2 + 2 + 2] cyclotrimerization reaction to benzenes and pyridines.

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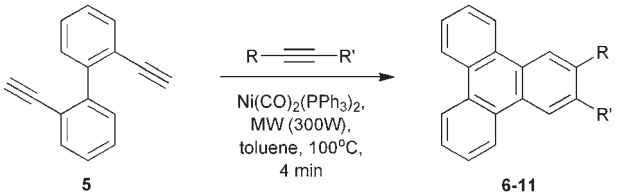
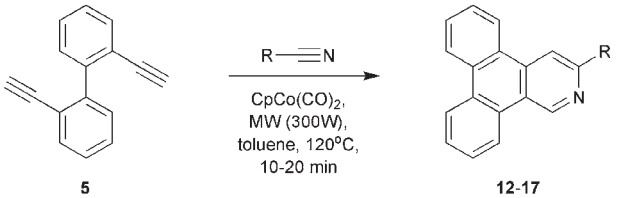


entry	R	R'	Cmpd	Yield
1	Bu	H	**6**	94%
2		H	**7**	63%
3	CH_2NBoc	H	**8**	91%
4	CH_2OH	H	**9**	89%
5	$(CH_2)_3CN$	H	**10**	88%
6	CH_2OCH_3	CH_2OCH_3	**11**	83%

Scheme 2 Synthesis of triphenylenes **6–11** *via* a [2 + 2 + 2] cyclotrimerization reaction.



entry	R	Cmpd	Yield
1	CH_3	**12**	100%
2	CH_2CH_3	**13**	72%
3	$CH{=}CH_2$	**14**	71%
4	C_6H_5	**15**	69%
5	$(CH_2)_3OH$	**16**	100%
6	CH_2CO_2Et	**17**	73%

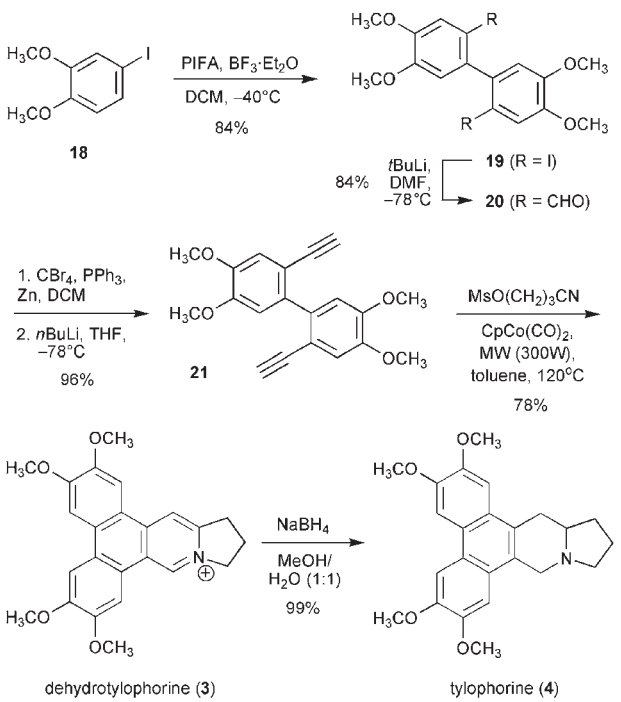
Scheme 3 Synthesis of azatriphenylenes **12–17** *via* a [2 + 2 + 2] cyclotrimerization reaction.

tethered together.[18] The latter leads to the synthesis of fused benzene and pyridine rings and has been applied in the assembly of a wide range of aromatic structures.[18] Recently, it was discovered by us[20] and others[21] that microwave irradiation[22] greatly facilitates [2 + 2 + 2] cyclotrimerization reactions by increasing reaction rates and yields.

We envisioned the application of this strategy to the synthesis of triphenylenes and azatriphenylenes, and thus assembled the known diyne **5** in three steps from commercially available (2′-hydroxymethylbiphenyl-2-yl)methanol with an overall yield of 74%.[23] The diyne **5** was cyclotrimerized with a set of alkynes featuring a range of functional groups, including alkyl chains, a nitrile, alkoxy groups, a pyridine ring, a carbamate, and a hydroxy group. Gratifyingly, the desired triphenylenes **6–11** were obtained in good to excellent yield (Scheme 2). In the reaction towards **11**, dimerization of the diyne starting material **5** was observed due to the lower reactivity of internal alkynes. The cyclotrimerization reactions were conducted with 10 mol% $Ni(CO)_2(PPh_3)_2$ catalyst in toluene under microwave irradiation (300 W) in a CEM Discover microwave synthesizer for 4 min.[24] A final reaction temperature of 100 °C was measured by an IR pyrometer.

The developed [2 + 2 + 2] cyclotrimerization approach to triphenylenes was then readily adapted towards the preparation of the 2-azatriphenylene core by simply switching to nitrile reaction partners instead of alkynes and using a cobalt instead of a nickel catalyst. A set of nitriles containing methyl, ethyl, vinyl, phenyl, hydroxyl, and carboxy groups was employed. The reactions of the diyne **5** with these nitriles proceeded in moderate to quantitative yields when conducted with 10 mol% $CpCo(CO)_2$ catalyst in toluene under microwave irradiation (300 W) for 10–20 min with a final temperature of 120 °C, delivering the desired azatriphenylenes **12–17** (Scheme 3). This methodology provides a rapid entry into otherwise difficult to access 2-azatriphenylene structures.

Subsequently, this approach was applied to the facile and flexible synthesis of the phenanthroindolizidine alkaloids dehydrotylophorine (**3**) and tylophorine (**4**). The synthesis commences with the commercially available iodobenzene **18** which is selectively dimerized through treatment with phenyliodine bis(trifluoroacetate)[25] to give **19** in 84% yield (Scheme 4). Suprisingly, all attempts to install the required alkynes by a double Sonogashira coupling of **19** failed. Thus, a three-step conversion *via* a Corey–Fuchs reaction[23] was employed for the transformation of **19** into **21**. A halogen–lithium exchange followed by formylation with DMF delivered the bisaldehyde **20** in 84% yield. The two-step conversion of **20** into **21** *via* the corresponding bis(vinyldibromide) was achieved in 96% yield. This set the stage for the microwave-mediated [2 + 2 + 2] cyclotrimerization reaction, which was conducted with a cyano mesylate[26] under cobalt catalysis in 20 min. In the course of this reaction, the non-nucleophic *N*-center of the nitrile is converted into a nucleophilic pyridine moiety which subsequently undergoes an intramolecular nucleophilic substitution



Scheme 4 Total synthesis of dehydrotylophorine (**3**) and tylophorine (**4**).

reaction with the tethered sulfonate leaving group. This tandem process directly delivered dehydrotylophorine (**3**) in 78% yield, and represents the shortest total synthesis of this alkaloid. Due to the symmetry of the diyne **21**, no regioisomeric cyclotrimerization products were obtained. Treatment of the natural product **3** with $NaBH_4$[27] completed this facile synthesis of tylophorine (**4**) in quantitative yield.

In summary, we have developed a rapid and high-yielding approach to triphenylenes using a microwave-mediated [2 + 2 + 2] cyclotrimerization reaction. This has enabled the facile synthesis of several members of this important compound class. Moreover, the developed approach was adapted to the synthesis of azatriphenylenes, molecules which have been largely unexplored. This new azatriphenylene synthesis enabled the efficient assembly of the penta-cyclic phenanthroindolizidine alkaloids dehydrotylophorine (**3**) and tylophorine (**4**) in 5 and 6 steps from commercially available material. This compares favorably with the previously shortest syntheses of **3** and **4**, delivering these natural products in 8 and 6 steps, respectively.[8,10]

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