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The synthesis of a verdazyl radical-derived biphenylophane

Jeremy D. Dang *, Gordon K. Hamer, Michael K. Georges

Department of Chemical and Physical Sciences, University of Toronto at Mississauga, 3359 Mississauga Road, Mississauga, Ontario, Canada L5L 1C6

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ABSTRACT

Biphenylophanes with two stacked biphenyl units are synthetically challenging and consequently are rare. Herein, we report on the synthesis of a [3.3](3,4′,3,4′)biphenylophane, formed from bifunctional verdazyl radicals. Its formation is surmised to originate from two intermediate verdazyl radical-derived azomethine imines and their subsequent tandem inter-intramolecular 1,3-dipolar cycloaddition reaction with each other.

Verdazyl radicals have been shown to be useful as spin probes,[1] polymerization inhibitors,[2–4] substrates for molecular magnets,[5–7] and mediators for living-radical polymerizations.[8] They have also been demonstrated to be excellent substrates for organic synthesis and have provided a variety of distinctive nitrogen-containing heterocyclic compounds as a result of a disproportionation reaction that produces azomethine imine intermediates that can subsequently undergo 1,3-dipolar cycloaddition (1,3-DC) reactions with various dipolarophiles.[9] The emergence of verdazyl radicals as starting materials for organic synthesis marks a cornerstone in their history, opening up a whole new area of research for them. In a continuing effort to explore the chemistry of verdazyl radicals as novel organic substrates, our laboratory initiated a study to scope out the different types of verdazyl-derived molecular scaffolds that could be constructed from them.

Bridged aromatic compounds, known as phanes, have attracted considerable interest in the last few decades due to their synthetic challenges, conformational behaviors, structural properties, and their role as molecular receptors in host–guest binding chemistry.[10–14] Phanes that incorporate a single bridged biphenyl unit in their molecular structure are called biphenylophanes and only a small number of these structures have been synthesized.[15–17] Even rarer are biphenylophanes with two bridging biphenyl moieties arranged in a π-stacked orientation—face-to-face, edge-to-face, or slip-stacked. One of the few examples is 1,8-bis[(4-(tributylstannyl)phenyl]naphthalene, obtained from 1,8-[1,8-naphthalenediylbis(4′,4-biphenyldiyl)]naphthalene via a copper-catalyzed coupling reaction reported by Iyoda et al.[18] This scarcity of biphenyl-stacked biphenylophanes prompted us to see if verdazyl radicals could be used as an entry into their synthesis and in the process augment the collection of [12]-, [13]-, and [21]-paracyclophanes we recently reported.[19] Within this present investigation, we describe two synthetic routes to 1,5-dimethyl-3-(4′vinylbiphenyl-3-yl)-6-oxoverdazyl radical **4**, and its subsequent conversion into [3.3](3,4′,3,4′) biphenylophane **5**.

The blueprint for the synthesis of **5** required the intermediacy of the 6-oxoverdazyl radical **4**. Verdazyl radical **4** was specifically designed to incorporate a styrene dipolarophile functionality as part of its structure in order to grant the molecule the bifunctional role of a 1,3-dipole, via an intermediate azomethine imine, and a dipolarophile, via the styrene functionality.

Verdazyl radical **4** was initially synthesized in a three-step process that started with a Suzuki coupling reaction of 3-bromobenzaldehyde with 4-vinylphenylboronic acid in the presence of tetrakis(triphenylphosphine)palladium(0) and potassium carbonate at 110 °C that afforded 4′-vinylbiphenyl-3-carbaldehyde (**1**) in 85 % yield (Scheme 1). A condensation reaction of **1** with *N*,*N*′-dimethylcarbonohydrazide (**2**) at 85 °C gave 1,5-dimethyl-3-(4′-vinylbiphenyl-3-yl)-1,2,4,5-tetrazinan-6-one (**3**) in 45 % yield. Tetrazinanone **3** was treated with $NaIO_4$ in a biphasic system to afford verdazyl radical **4** in 85 % crude yield. The purification of **4,** using standard silica gel column chromatography, gave a low yield of the product. We suspect some decomposition of the verdazyl radical occurred on the column, which is not unusual for verdazyl radicals in general. Numerous attempts at crystallizing **4** from the crude reaction mixture failed. It was decided based on these results to use **4** as recovered from the oxidation reaction.

Biphenylophane **5** was obtained in 14% yield by heating verdazyl radical **4** in THF at 55 °C for 5 days under an atmosphere of oxygen gas. The yield was determined with respect to the crude verdazyl radical mixture and is in line with the yields reported

* Corresponding author. Tel.: +1 905 828 5528.
E-mail address: jdpenny.dang@mail.utoronto.ca (J.D. Dang).

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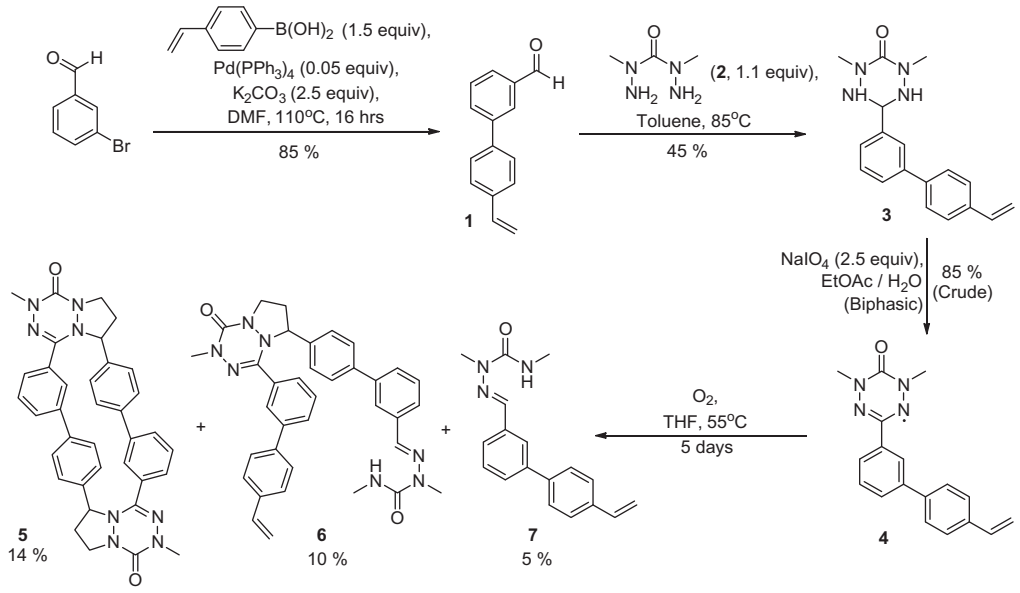
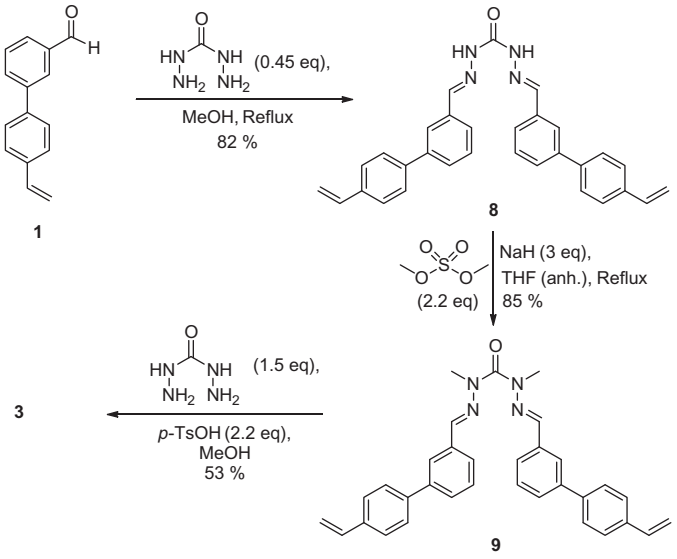


Scheme 1. Synthetic route to biphenylophane **5**.

by other groups for the synthesis of their biphenyl-stacked biphenylophanes.[20–22] ^{1}H and ^{13}C NMR spectra were consistent with the structure of **5** and were further confirmed via a single crystal X-ray diffraction analysis (See Supplementary data, CCDC deposition number: 880927).

The synthetic route outlined above for **3** involved the use of two hazardous chemicals, triphosgene, and methyl hydrazine. A safer, and more reproducible, alternative route to **3** involved the reaction of carbohydrazide with **1** to form the bishydrazone **8** in 82% yield (Scheme 2).[23] A sodium hydride-induced dimethylation reaction of **8** gave **9** in 85% yield. A subsequent ring closure in the presence of *p*-toluenesulfonic acid and carbohydrazide produced tetrazinanone **3** in 53% yield.

In a previous paper, we reported on the synthesis of pyrazolotetrazinanone heterocyclic compounds from their respective verdazyl radicals and proposed that their formation occurred via the intermediacy of an azomethine imine, which subsequently underwent a 1,3-DC reaction with various dipolarophiles.[5] In the present investigation, where the styrene dipolarophile functionality is appended

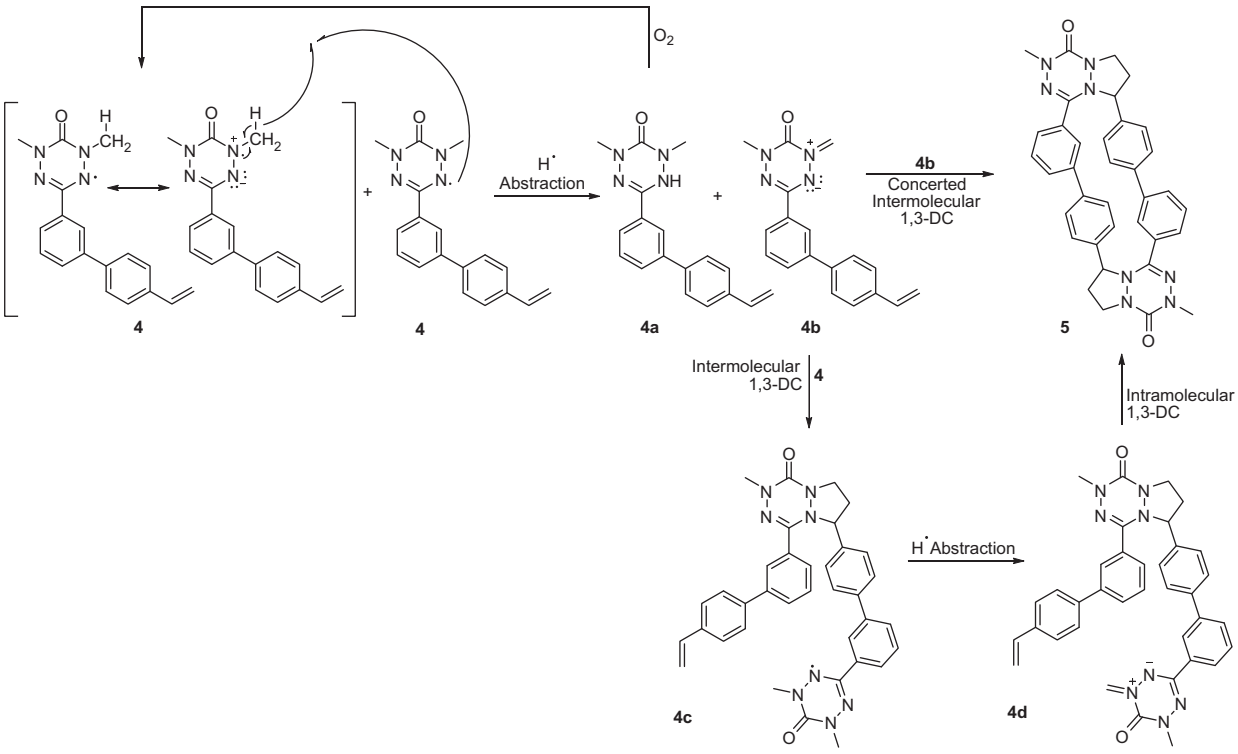


Scheme 2. Alternative synthetic route to tetrazinanone **3**.

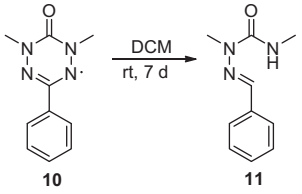
to the verdazyl radical structure, we surmise that the mechanism for the transformation of **4** to **5** proceeds by a tandem inter-intramolecular double 1,3-DC process (Scheme 3). Two molecules of verdazyl radicals **4** react with each other in a disproportionation-type hydrogen abstraction reaction to form the leucoverdazyl **4a** and the azomethine imine **4b,** a 1,3-dipole. To improve the yield of **5**, the reaction is carried out under an atmosphere of oxygen to oxidize **4a** back to **4**. The azomethine imine **4b** reacts in an intermolecular 1,3-DC reaction with a molecule of **4** via the styrene functionality to give the verdazyl cycloadduct **4c**. A second disproportionation reaction converts **4c** into the azomethine imine cycloadduct **4d**, which cyclizes through an intramolecular 1,3-DC reaction to afford biphenylophane **5**. An alternative mechanism, where two intermolecular 1,3-DC reactions take place simultaneously between two azomethine imines **4b**, is unlikely. The formation of **4b** is suggested to be the rate-determining step and once it is formed in situ, it reacts immediately with a nearby dipolarophile, in this case the styryl unit on another verdazyl radical. Due to their high reactivity it is highly improbable that two azomethine imines would remain around long enough that they would approach each other at the same time, with the right orientation, and undergo two intermolecular 1,3-DC reactions simultaneously to form **5**.

The yield of **5** is reduced, in part, due to the formation of two semicarbazone compounds, **6** and **7**, formed in 10 % and 5 % yields, respectively. These semicarbazone structures, with a nitrogen atom missing from the tetrazinanone backbone, were unexpected. To determine if this is a general reaction of verdazyl radicals, a solution of 1,5-dimethyl-3-phenyl-6-oxoverdazyl radical (**10**) in DCM was allowed to stir at room temperature for 7 days (Scheme 4). From the reaction mixture, **11** was isolated in 11 % yield. This signifies that verdazyl radicals do decompose over time to form semicarbazones, a finding previously unreported.

The versatility of verdazyl radicals as organic substrates in heterocyclic syntheses was examined by employing one of these stable radicals in the synthesis of a biphenyl-stacked biphenylophane, rare compounds found in the family of phanes. Within this Letter, we have described the synthetic approach to both the [3.3](3,4′,3,4′)biphenylophane (**5**) and its precursor, 1,5-dimethyl-3-(4′-vinylbiphenyl-3-yl)-6-oxoverdazyl radical (**4**). The four-step synthesis to forming **5** was initiated with the Suzuki coupling reaction between 4-vinylphenylboronic acid and 3-bromobenzaldehyde to give 4′-vinylbiphenyl-3-carbaldehyde (**1**), which was subsequently



Scheme 3. Proposed mechanism for the transformation of verdazyl radical **4** to biphenylophane **5**.



Scheme 4. Decomposition of verdazyl radical **10** to a semicarbazone **11**.

reacted with *N*,*N*′-dimethylcarbonohydrazide (**2**) in a condensation reaction to produce 1,5-dimethyl-3-(4′-vinylbiphenyl-3-yl)-1,2,4,5-tetrazinan-6-one (**3**). An alternative method was also reported for the synthesis of **5**, which does not involve the use of either triphosgene or methyl hydrazine. Following an oxidation reaction with sodium (meta)periodate, **3** was converted into the 1,5-dimethyl-3-(4′-vinylbiphenyl-3-yl)-6-oxoverdazyl radical (**4**), which was further reacted in a double 1,3-DC reaction to afford the target biphenylophane **5**. It was surmised that the formation of biphenylophane **5** originated from two intermediate azomethine imines derived from **4**, and their subsequent tandem inter-intramolecular 1,3-DC reaction with each other.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2012.06.141.

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