Design, Synthesis, and Diversification of 5,5-Dimethyl Cyclohexen-1,4-dione Library

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Quinones play important roles in a wide variety of different biological systems and as such they should be interesting molecules to include in small molecule libraries. However, when they have been included in libraries, quinones have often been found to be nonselective in their activity. The similarity of a cyclohexen-1,4-dione scaffold to the quinone structure suggests that it could be a potential source for interesting biological activity. Such molecules present the possibility of synthesizing libraries of molecules that have structures similar to quinones without having the relatively promiscuous redox activity that can lead to nonspecific activity. As an effort to explore methods to generate cyclohexen-1,4-diones for high-throughput screening a collection of molecules has been designed and synthesized.

The reaction of vinyl Fischer carbene complexes such as **1**, with alkynes[1−7] has been shown to form either hydroquinone or cyclohexadienone type products depending on whether R is H or an alkyl group (Scheme 1). Even though the mechanism of this reaction has not been fully established,[5,8,9] the chemical and regioselective outcomes are well understood.[1,5,9] Given the variety of commercially available alkynes, different molecules are accessible from the combination of these alkynes with a single Fischer carbene complex. Compound **1** (where R = H), reacts with alkynes to give substituted phenols (**2**), which can be further oxidized to the corresponding quinones (**3**) (Scheme 1). Terminal alkynes generally form a single product in which the substitution is *ortho* to the phenol (**2**). When R is an alkyl group (**1**), aromatization is blocked, resulting in cyclohexa-2,4-dienones (**4**), which can be used as synthetic intermediates or hydrolyzed to give cyclohexen-1,4-diones (**5**). This second manifold, the formation of cyclohexen-1,4-dione (**5**), is the reaction that has been exploited in the work reported here.

The synthesis was designed with vinyl carbene complex **6** (Scheme 1) as the key intermediate. This complex is easily accessed from chromium(0) hexacarbonyl and the commercially available 1-bromo-2-methyl-1-propene, under mild conditions, and is stable for months in the refrigerator. Reactions of this complex with alkynes proceed in high purity and under mild conditions. Using a protocol adapted from the Wulff group,[5] gram quantities of **6** were prepared in moderate yield. The initial set of compounds, with the general formula **7** (Scheme 1) was prepared using a variety of terminal and highly unsymmetric internal alkynes. Yields ranging between 60 to 95%, after purification, were obtained for compounds **14**−**45**.

While this protocol was successful with a variety of alkynes, examples with N-heterocyclic and other amino alkynes failed to yield the desired products. To counter this problem, as well as enhance the diversity of the library, stannane **10** was synthesized in moderate yield by reacting **6** with ethynyltributylstannane (**8**). Stannane **10** is an unknown compound and offers the opportunity to synthesize derivatives of this system by the Stille cross-coupling protocol.[10−13] However rather than use the Stille reaction, stannane **10** was quantitatively converted to the corresponding unknown vinyl iodide (**12**). This was done to eliminate any potential problems with carryover of tin into the library members synthesized with this substrate. Iodide **12** was also prepared by reacting **6** with the less expensive ethynylytrimethylsilane (**9**) to obtain the corresponding trimethylsilyl cyclohexa-2,4-dienone (**11**), followed by treatment with iodine monochloride[14] and hydrolysis. Vinyl iodide **12** was subjected to a Suzuki cross-coupling protocol[11] employing a variety of boronic acids to obtain products such as **13** (Scheme 2). Figure 1 contains the first set of compounds synthesized, either using different alkynes (**14**−**45**) or by the Suzuki reaction on iodide **12** (**46**−**48**) (Figure 2). These examples illustrate that while alkyne containing heterocycles can be problematic in the Fischer carbene annulation this problem can be circumvented thru the use of iodides such as **12**.

Running the reaction on bromophenyl alkynes provided products (**49**) that can then be modified further by palladium catalyzed reactions (Scheme 3). The bromides on compounds **36** and **38** were utilized in a series of Suzuki reactions to provide compounds (**54**−**74**). The 21 compounds that were synthesized consisted of *meta* and *para* biphenyls as well as a few examples where aromatic heterocycles were attached. The Suzuki reactions were run under microwave conditions and proceeded in 60 to 95% yield in 15 to 20 min.

The annulation reaction tolerates free hydroxyl and phenolic groups to provide products that can be further modified (**21**, **35**, **42**, and **45**). Endiones **21** and **35** were esterified with a variety of acyl chlorides (Scheme 3) to form a series of compounds (**75**−**92**) (Figure 3).

In addition to performing the Suzuki reaction on endiones, two examples of a microwave-assisted Sonogashira coupling[15] (Scheme 4) were performed. Reaction of bromide **38** with *p*-methylphenylacetylene and *p*-methoxyphenylacetylene provided unique compounds **93** and **94**.

Seventy-seven compounds have been synthesized either by using unique alkynes, the Suzuki reaction, esterfication or in two cases Sonogashira coupling. It has been shown that through the reaction of a vinyl Fischer carbene

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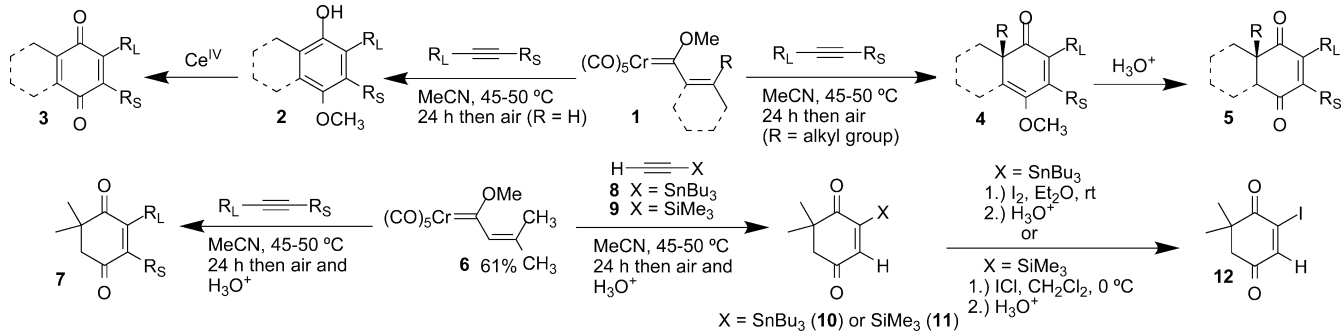
Scheme 1. Synthesis of Endiones by Fischer Carbene Annulations



Scheme 2. Suzuki Reaction of Endione Iodides

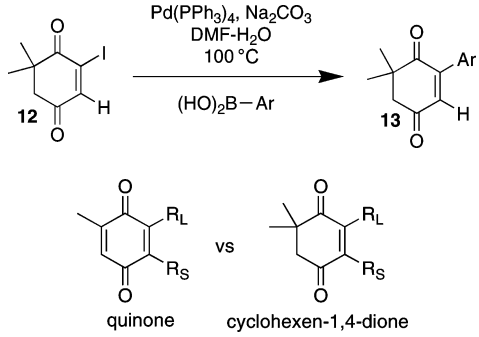
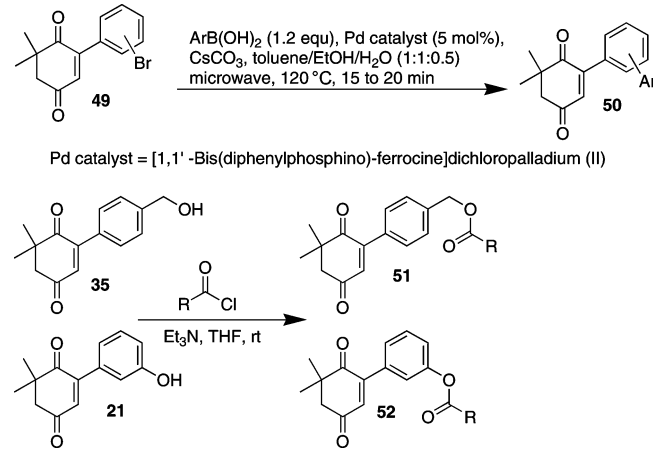


Figure 1. Structures of quinones versus cyclohexen-1,4-diones.

complex with different acetylenes a variety of endiones can be synthesized that possess interesting functionality. The reaction with trimethyl silyl and tributyl stannyl alkynes provides endiones that can be converted to iodides that were shown are viable substrates for the Suzuki reation. When alkynes are selected that possess reactive

Scheme 3. Suzuki and Ester Formation for the Synthesis of Second-Generation Compounds



functionality, such as halides or alcohols, the annulation products can be used to synthesize second generation products.

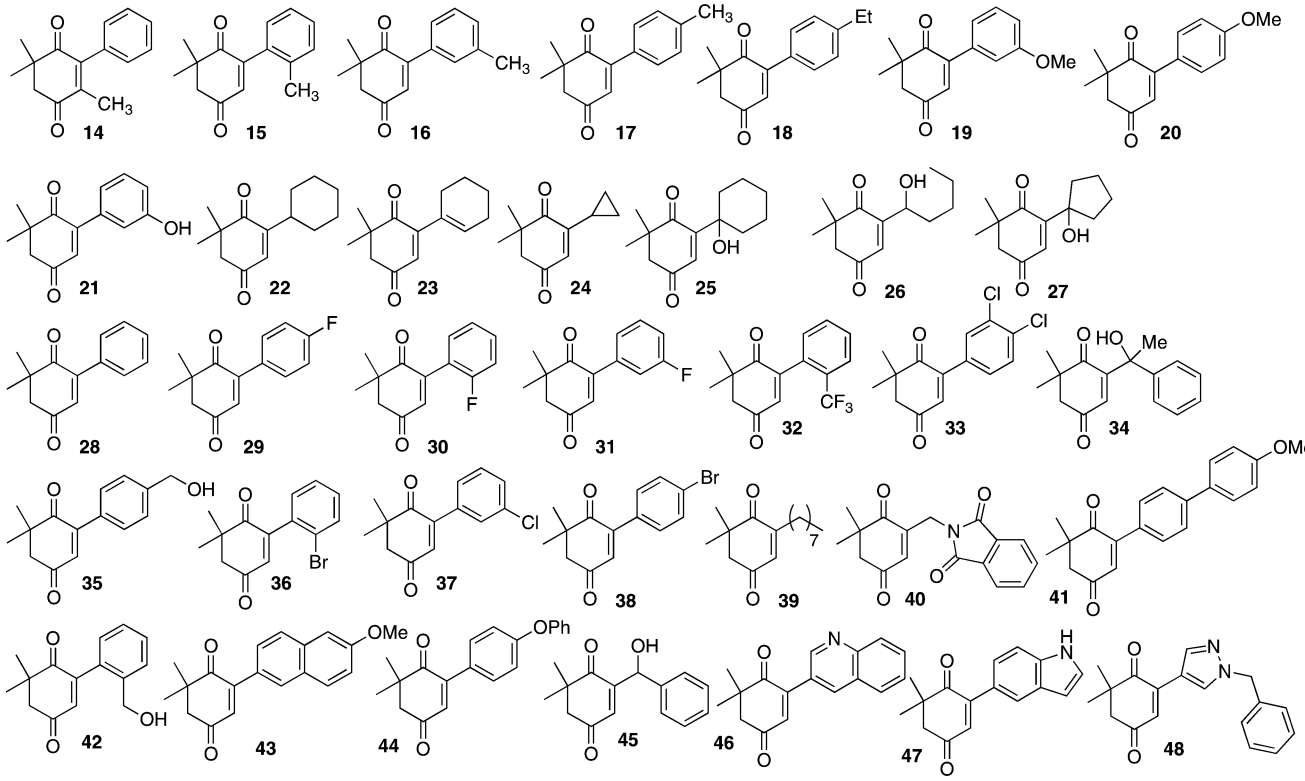


Figure 2. First generation cyclohexen-1,4-dione library members.

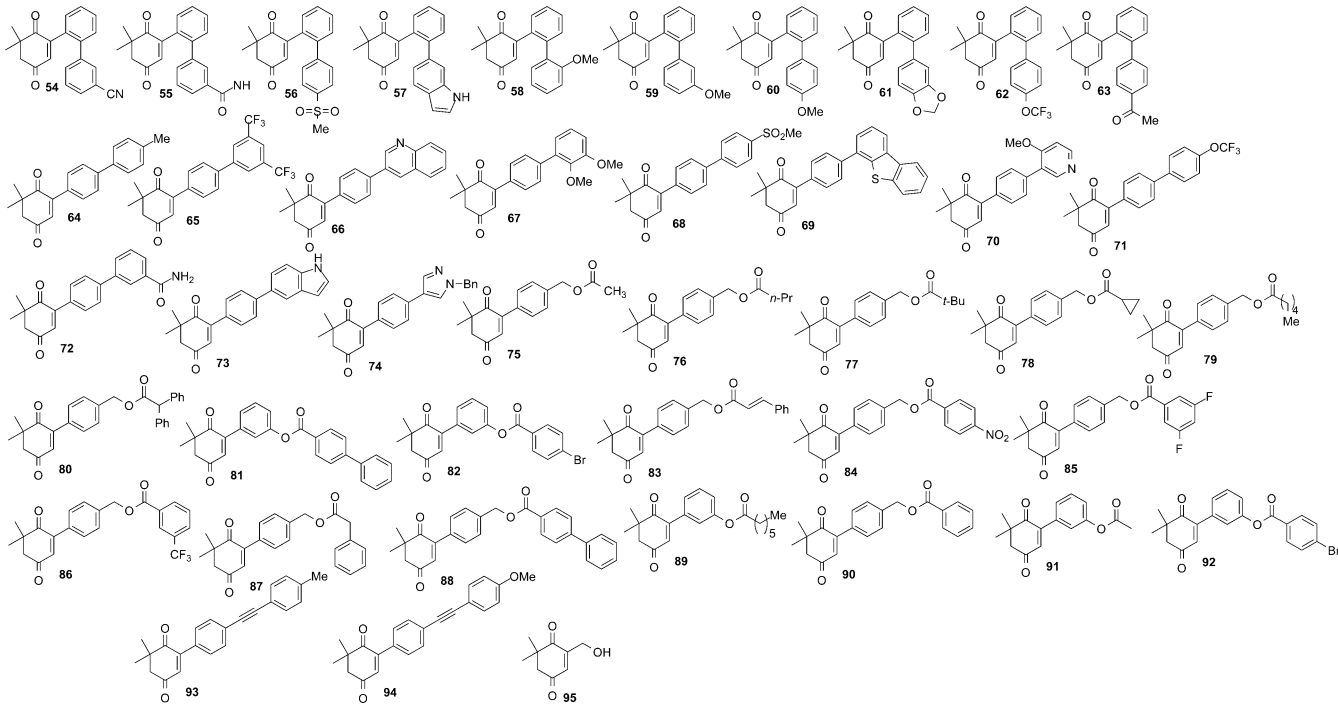
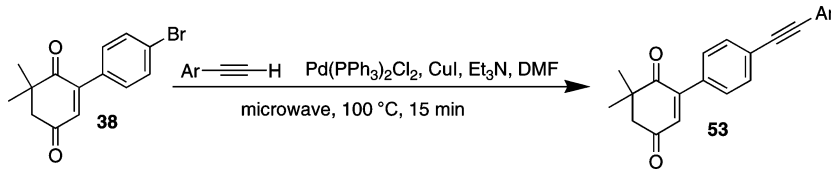


Figure 3. Cyclohexen-1,4-dione library members from Suzuki reaction, Sonogashira coupling, and esterification.

Scheme 4. Sonogashira Coupling Protocol to Obtain Alkynes



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Supporting Information Available. General procedures for library synthesis and ^{1}H NMR data for the compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

References and Notes

(1) Wulff, W. D.; Tang, D.-C.; McCallum, J. S. *J. Am. Chem. Soc.* **1981**, *103*, 7677–7678.
(2) Dotz, K. H. *Pure Appl. Chem.* **1983**, *55*, 1689–1706.
(3) Wulff, W. D.; Yang, D. C. *J. Am. Chem. Soc.* **1984**, *106*, 7565–7567.
(4) Tang, P.-C.; Wulff, W. D. *J. Am. Chem. Soc.* **1984**, *106*, 1132–1133.
(5) Wulff, W. D.; Tang, P.-C.; Chan, K.-S.; McCallum, J. S.; Yang, D. C.; Gilbertson, S. R. *Tetrahedron* **1985**, *41*, 5813–5832.
(6) Barluenga, J. *Pure Appl. Chem.* **2002**, *74*, 1317–1325.
(7) White, J. D.; Smits, H. *Org. Lett.* **2005**, *7*, 235–238.
(8) Torrent, M.; Duran, M.; Sola', M. *Chem. Commun.* **1998**, 999–1000.
(9) Barluenga, J.; Aznar, F.; Gutierrez, I.; Martin, A.; Garcia-Granda, S.; Llorca-Baragano, M. A. *J. Am. Chem. Soc.* **2000**, *133*, 1314–1324.
(10) Kurti, L.; Czako, B. *Strategic applications of named reactions in organic synthesis*; Elsevier Academic Press: Amsterdam; Boston, 2005; pp 438−439.
(11) Kurti, L.; Czako, B. *Strategic applications of named reactions in organic synthesis*; Elsevier Academic Press: Amsterdam; Boston, 2005; pp 448−449.
(12) Tunney, S. E.; Stille, J. K. *J. Org. Chem.* **1987**, *52*, 748–753.
(13) Scott, W. J.; Crisp, G. T.; Stille, J. K. *J. Am. Chem. Soc.* **1984**, *106*, 4630–4632.
(14) Alimardanov, A.; Negishi, E. *Tetrahedron Lett.* **1999**, *40*, 3839–3842.
(15) Petricci, E.; Radi, M.; Corelli, F.; Botta, M. *Tetrahedron Lett.* **2005**, *44*, 9181–9184.

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