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Electrocyclic Ring Closure of the Enols of Vinyl Quinones. A *2H*-Chromene Synthesis

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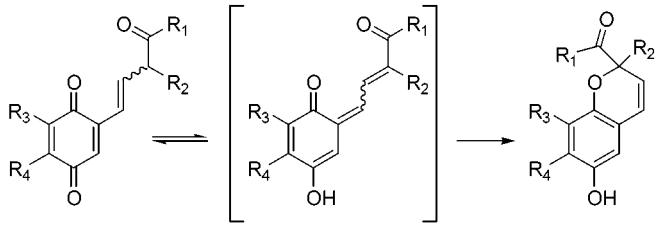
ABSTRACT

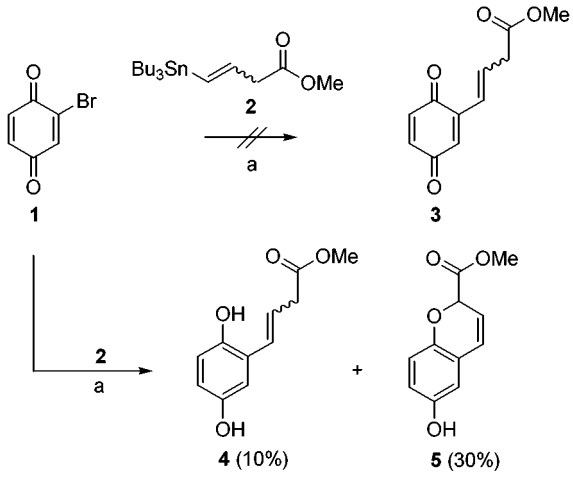


Thermolysis of enolizable vinyl quinones in polar, aprotic media provides *2H*-chromenes. Experimental evidence supports a two-step mechanism in which enolization is followed by a thermal 6π-electrocyclic reaction of an intermediate quinone methide. Application of this method led to the total synthesis of the reputed structure of an *Ageratum* juvenile hormone. When enolizable vinyl quinones are the products of Stille coupling, the chromene annulation product is obtained directly.

Although the science of organic synthesis offers countless predictable methods for functional group conversions, practitioners continue to be surprised by the appearance of unexpected transformations. These fortuitous discoveries enrich and expand the collection of design principles available for the planning of synthetic schemes. In this Letter, we report a new, efficient, and serendipitously discovered *2H*-chromene preparation and its subsequent application in a rationally designed synthesis.

In the context of the total synthesis of quinonoid natural products,[1] we attempted the preparation of quinone **3** by Stille coupling of bromobenzoquinone (**1**)[2] with stannane **2**.[3] Instead of affording the expected product, this reaction yielded a mixture of hydroquinone **4** and a compound to which we assigned the *2H*-chromene structure **5** (Scheme 1). This assignment was later confirmed by X-ray crystallography (Figure 1).

Scheme 1. Fortuitous Discovery of the Formation of 2*H*-Chromene **5** from a Stille Coupling Procedure[a]



[a] (a) 5 mol % of $(Ph_3P)_4Pd$, toluene, reflux.

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(1) Parker, K. A.; Georges, A. T. *Org. Lett.* **2000**, *2* (4), 497−499 and references therein.

(2) From the $KBrO_3$ oxidation of commercially available bromo hydroquinone according to McElvain, S. M.; Engelhardt, E. L. *J. Am. Chem. Soc.* **1944**, *66*, 1077−1080.

(3) Collins, P. W.; Kramer, S. W.; Gasiecki, A. F.; Weier, R. M.; Jones, P. H.; Gullikson, G. W.; Bianchi, R. G. *J. Med. Chem.* **1987**, *30*, 193−197.

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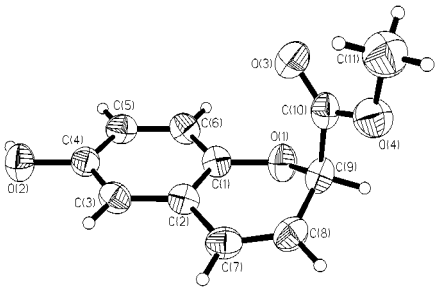
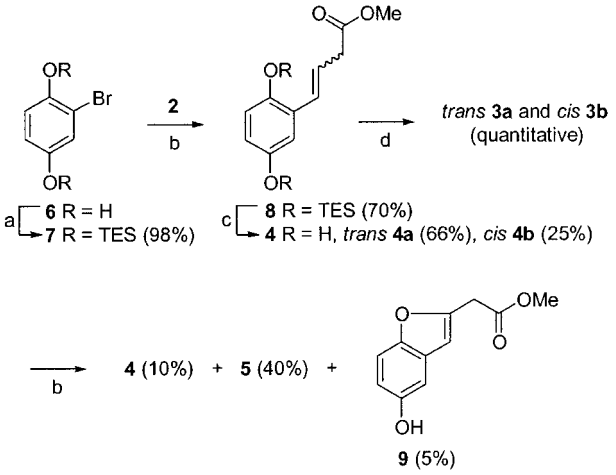


Figure 1. ORTEP plot of 2*H*-chromene **5**.

The chromane or benzopyran substructure is frequently found in naturally occurring heterocycles, many of which exhibit biological activity.[4] The key bicyclic ring system has inspired a number of different synthetic approaches.[5] However, that represented by Scheme 1 is novel and its possible utility prompted us to investigate the mechanism of the formation of chromene **5** and the generality of the conversion.

To determine whether the expected coupling product **3** was an intermediate on the path to the chromene product, we decided to prepare this compound by an independent synthesis (Scheme 2) and to study its chemistry. Thus, bromo

Scheme 2. Synthesis of Proposed Intermediate **3** and Its Conversion to 2*H*-Chromene **5** under Stille Coupling Conditions[a]



[a] (a) TESOTf, imidazole, DMF; (b) 5 mol % of $(Ph_3P)_4Pd$, toluene, reflux; (c) AcOH, H_2O, THF; (d) Ag_2O, O_2, THF.

hydroquinone **6** was protected as its di-TES derivative **7**. Coupling with stannane **2** (presumably a cis/trans mixture)[6] provided intermediate **8**. Deprotection gave hydroquinone **4** as a cis/trans (1:3) mixture. The trans isomer **4a** crystallized cleanly from ethyl acetate/hexane, and the cis isomer **4b** was recovered from the mother liquor as an oil. Oxidation completed the synthesis of the desired quinones trans **3a** and cis **3b**.

Exposure of either isomer of quinone **3** to the conditions of the Stille coupling resulted in the formation of products **4** and **5** in yields similar to those in the original experiment. A trace of a new side product, benzofuran **9**, was also recovered in each case. This result is consistent with a mechanistic picture in which both products **4** and **5** arise from subsequent transformations of coupling products **3a** and **3b**.

We therefore focused on discovery of the requirements for the conversion of quinones **3** to benzopyran **5** and on its optimization. We soon learned that neither the palladium reagent nor the phosphine ligand was needed. Experiments with a Stille catalyst in which there was no phosphine ligand[7] left the substrate **3a** or **3b** unchanged. However, experiments with a variety of phosphorus reagents (phosphine oxides as well as phosphines)[8] in the absence of palladium catalysts effected conversion to product mixtures. Because the rate enhancement of the conversion appeared to be independent of the functional group of the phosphorus reagent, we concluded that these additives do not participate in the reaction but facilitate it by altering the polarity of the reaction medium. Examination of a variety of media revealed that no reaction occurred in the absence of a polar additive and that the polar additive need not be a phosphorus compound (for example, nontoxic DMPU[9] proved to be an effective additive). However, the additive must be aprotic; for example, the presence of water led to decomposition products at the elevated temperatures required for the cyclization. Of those procedures tested, the most effective involved heating of a dilute solution of substrate, in the dark, in dry toluene that contains traces of HMPA (0.5%). We also found that the addition of mild Lewis acids, most conveniently $FeCl_3$, improved the conversion of the less reactive trans **3a** but that it had no effect on the conversion of cis **3b**. These optimized conditions precluded the formation of side products and provided chromene **5** in yields up to 86% from cis **3b** and 76% from trans **3a** (Scheme 3).

Consideration of the possible mechanism by which product chromene **5** might arise led to the postulate that *o*-quinone methide intermediate **10** might undergo a 6π-electrocyclic reaction (Scheme 3). The formation of a long-lived intermediate was suggested by the impressive, transient red color[10]

(4) (a) Bowers, R. S.; Ohta, T.; Cleere, J. S.; Marsella, P. A. *Science* **1976**, *193*, 542−547. (b) Ellis, G. P. Chromenes, Chromanones and Chromones. In *Chemistry of Heterocyclic Compounds*; John Wiley& Sons: New York, 1977; Vol. 31, pp 11−141.

(5) (a) Chauder, B. A.; Lopes, C. C.; Lopes, R. S. C.; daSilva, A. J. M.; Snieckus, V. *Synthesis* **1998**, 279−282 and references therein. (b) Schweizer, E. E.; Minami, T.; Crouse, D. M. *J. Org. Chem.* **1971**, *36* (26), 4028−4032. (c) Zsindely, J.; Schmid, H. *Helv. Chim. Acta* **1968**, *51* (7), 1510−1514.

(6) The NMR spectra of this product are complex because of Sn coupling.

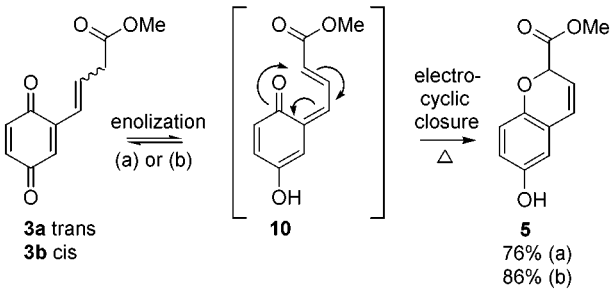
(7) Tris(dibenzylideneacetone)dipalladium(0) = $Pd_2(dba)_3$.

(8) The following additives were tested in amounts of 0.5−5 equiv of Ph_3P, $(MeO)_3P$, $(Me_2N)_3P$, $(MeO)_2P(OH)$, Ph_3PO, $(MeO)_3PO$, $MeP(O)(OMe)_2$, and $(Me_2N)_3PO$.

(9) DMPU = 1,3-dimethyl-3,4,5,6-tetrahydro-2(1*H*)-pyrimidinone.

(10) The intermediate was characterized by the absorbance spectrum of the reaction mixture which underwent a bathochromic shift from 333 nm (yellow) to 485 nm (dark red).

Scheme 3. Optimized Reaction Conditions and Mechanism of the Transformation of Quinone **3** to 2*H*-Chromene **5**[a]

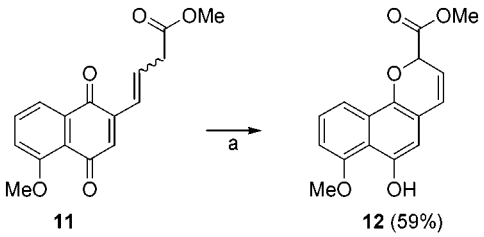


[a] (a) 5mM **3a** in toluene, 0.5% HMPA, $FeCl_3$, reflux, dark, 45 min; (b) 5 mM **3b** in toluene, 0.5% HMPA, reflux, dark, 2 h.

that appeared when HMPA was added to a toluene solution of substrate. The intermediate could not be trapped or isolated. However, it is sufficiently stable at 10 °C to allow characterization by NMR experiments.[11] Although quinone methides have been postulated as intermediates in the formation of chromene products,[12] these structures have not previously been directly observed in these transformations.

The potential of the benzopyran annulation methodology in total synthesis led us to examine its generality.[13] First we tested the conversion of the naphthoquinone **11**[14] to the tricyclic product **12**. This reaction provided cleanly the anticipated naphthopyran (Scheme 4).

Scheme 4. Synthesis of Tricyclic Naphthopyran **12** by Means of the Novel Annulation Methodology[a]



[a] (a) 5 mM in toluene, 0.5% HMPA, reflux, dark, 8 h.

Next, because we were interested in the eventual application of our methodology to the synthesis of 2*H*-chromene **13**, reported to be the structure of a juvenile hormone (JH)

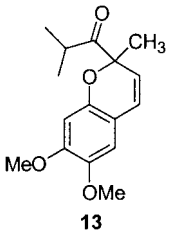
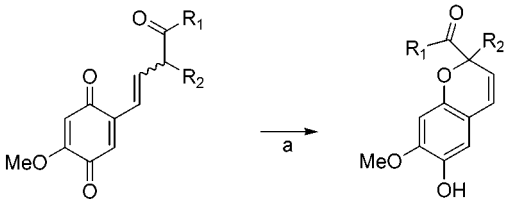


Figure 2. Reported structure of the juvenile hormone from *Ageratum conyzoides*.

from *Ageratum conyzoides* (Figure 2),[15] we turned our attention to studies in which the quinonoid moiety was the 2-substituted 5-methoxybenzoquinone.

Quinone **14a** proved to be a good substrate for the thermal isomerization, giving **15a** in good yield (Scheme 5). There-

Scheme 5. Annulation of a Variety of Benzoquinone Substrates[a]



a R_1 = OMe, R_2 = H; 8h, 70%
b R_1 = OMe, R_2 = CH_3; 15h, 63%
c R_1 = *i*-Pr, R_2 = H; 2h, 75%
d R_1 = *i*-Pr, R_2 = CH_3; 5h, 73%

[a] (a) 5 mM in toluene, 0.5% HMPA, reflux, dark.

fore, our next experiments in which we varied the enolizable functional group and the substitution on the side chain were carried out with this system. Yields for cyclization of α-substituted ester **14b**, ketone **14c**, and α-substituted ketone **14d**[14] were uniformly good.

Although methylation of phenol **15d** (methyl iodide, potassium carbonate, 18-crown-6, DMF) provided the target structure **13** in 79% yield, comparison of the spectroscopic data for this product with those reported in the literature revealed that our synthetic material does not correspond to the *Ageratum* juvenile hormone. Close examination of the NMR data listed for the natural product indicates that it is

(11) The ^1H and ^{13}C NMR spectra of this solution are contained in the Supporting Information. These spectra support the conclusion that >80% of the quinone **3** had isomerized to enol **10**.

(12) (a) Kopanski, L.; Karbach, D.; Selbitschka, G.; Steglich, W. *Liebigs Ann. Chem.* **1987**, 793−796. (b) Iyer, M. R.; Baskaran, S.; Trivedi, G. K. *J. Indian Chem. Soc.* **1994**, *71*, 341−343. (c) Bissada, S.; Lau, C. K.; Bernstein, M. A.; Dufresne, C. *Can. J. Chem.* **1994**, *72*, 1866−1869. (d) See also refs 4b and 5.

(13) Similar electrocyclic closures of dienones give mixtures of products; these do not benefit from the restoration of aromaticity obtained when the product is a benzopyran. See, for example: (a) Büchi, G.; Yang, N. C. *J. Am. Chem. Soc.* **1957**, *79*, 2318−2323. (b) Ishii, K.; Mathies, P.; Nishio, T.; Wolf, H. R.; Frei, B.; Jeger, O. *Helv. Chim. Acta* **1984**, *67*, 1175−1183.

(14) The preparation of these substrates is described in the Supporting Information. Quinones were prepared immediately before use, and all except substrates **3a** and **3b** were used as cis/trans mixtures. All new compounds were fully characterized. NMR spectra of quinones **11** and **14** show impurities which may be the corresponding enols. Quinones and benzopyran products bearing a hydrogen at the C-2 position were notably less stable than the C-2 (α to carbonyl) alkylated analogues.

(15) Pari, K.; Rao, P. J.; Subrahmanyam, B.; Rasthogi, J. N.; Devakumar, C. *Phytochemistry* **1998**, *49* (5), 1385−1388.

not a *2H*-chromene.[16] We have not been able to obtain a sample of the natural material for comparison or for the collection of additional structural data.

A scheme in which a halo hydroquinone is elaborated to a benzopyran by protection, Stille coupling, deprotection, oxidation, and thermolysis in better than 50% yield overall (Scheme 2, steps a−d followed by Scheme 3) may be considered relatively efficient by today's standards. However, the one-pot Stille coupling (of a haloquinone), enolization, and cyclization method (Scheme 1) provides 30% of the chromene product directly. The efficiency of this approach to *2H*-chromenes (which does require a chromatographic separation of the chromene from the byproducts) may be competitive in some situations. The extension of the enolization/electrocyclization strategy to the preparation of other ring systems is currently under investigation.

(16) For a tabular comparison of the ^{1}H NMR data for compounds **5**, **13**, and the reputed *Ageratum* juvenile hormone, see the Supporting Information.

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Supporting Information Available: Detailed description of the experimental procedures and complete analytical data of all new compounds. X-ray crystallographic data of *2H*-chromene **5** in CIF format. This material is available free of charge via the Internet at http://pubs.acs.org.

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