Rearrangement

DOI: 10.1002/anie.200603538

Thermally Induced Cyclobutenone Rearrangements and Domino Reactions**

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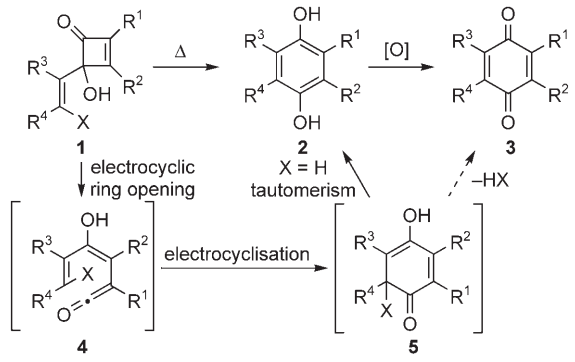
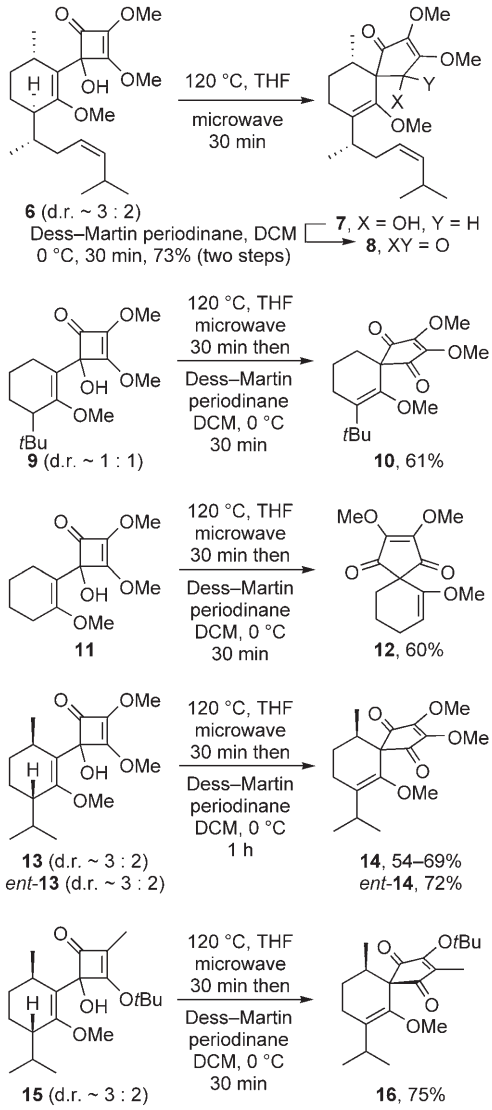
The thermal rearrangement of vinylcyclobutenones has become established as a reliable method of preparing hydroquinones owing, in large part, to the pioneering work of the research groups of Moore and Liebeskind.[1–3] The basic reaction, **1**→**2**, extends to various aryl- and heteroaryl cyclobutenones,[3–5] and has been incorporated into a number of more-elaborate domino sequences.[1,6] From a synthetic perspective, the rearrangement has been used primarily to access quinones by the oxidation of **2** into **3** and in that capacity has featured in several natural-products total syntheses.[1,5] Mindful of this, we conceived a simple extension to facilitate the direct conversion of vinylcyclobutenones into quinones. Our plan was to incorporate a leaving group on the vinyl appendage in the hope that thermolysis would induce a domino reaction comprising electrocyclic ring opening to **4**, electrocyclization to **5**, and elimination of HX to quinone **3** (Scheme 1). Herein we describe our realization of that objective and the discovery of four new thermal rearrangements of cyclobutenones.



Scheme 1. The Moore rearrangement and our planned approach to quinones.

Our study began with the thermolysis of enol ether **6**. Unexpectedly, heating a THF solution of **6** at 120°C for 30 min by microwave irradiation failed to yield the anticipated quinone and gave instead a complex product mixture from which two diastereoisomers of spirocycle **7** and dione **8** were isolated in yields ranging from 20 to 27%. Further experimentation showed dione **8** to be an artifact derived by aerial oxidation of **7**, and that it could be produced in 73% yield by oxidation of the crude product mixture with the Dess–Martin periodinane reagent (Scheme 2).[7]

Our discovery of a new vinylcyclobutenone rearrangement raised questions as to the mechanistic course of the reaction and the factors responsible for promoting this pathway over the classical sequence depicted in Scheme 1.



Scheme 2. Thermal rearrangements of (alkoxyvinyl)cyclobutenones that lead to spirocycles. DCM = dichloromethane.

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[**] The authors thank EPSRC for their support of this programme.

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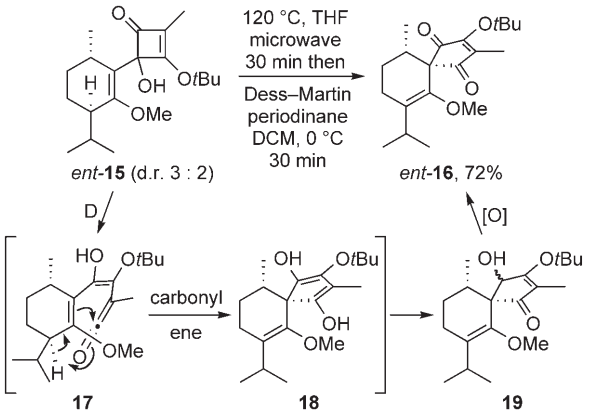
To gain a better understanding of the rearrangement, we first prepared a series of related enol ethers (**9**, **11**, **13**, *ent*-**13**, **15**, and *ent*-**15**) and subjected them to thermolysis. In each case a spiro[4.5]deca-2,6-dien-1,4-dione (**10**, **12**, **14**, *ent*-**14**, **16**, and *ent*-**16**, respectively) was given as the major product after oxidation of the crude product mixture with the Dess–Martin periodinane reagent (Scheme 2 and 3). Of particular note was the formation of a single diastereoisomer of spirocycle *ent*-**16** from *ent*-**15**, as it implies that rearrangement occurs by an initial electrocyclic ring opening to ketene **17**, which in turn induces a carbonyl-ene reaction to spirocycle **18** and tautomerism to **19** (Scheme 3).[8] Though a nonconcerted addition of the nucleophilic enol ether to the ketene carbonyl in **17** is also plausible, it is hard to rationalize the stereochemical course of the reaction in that case.

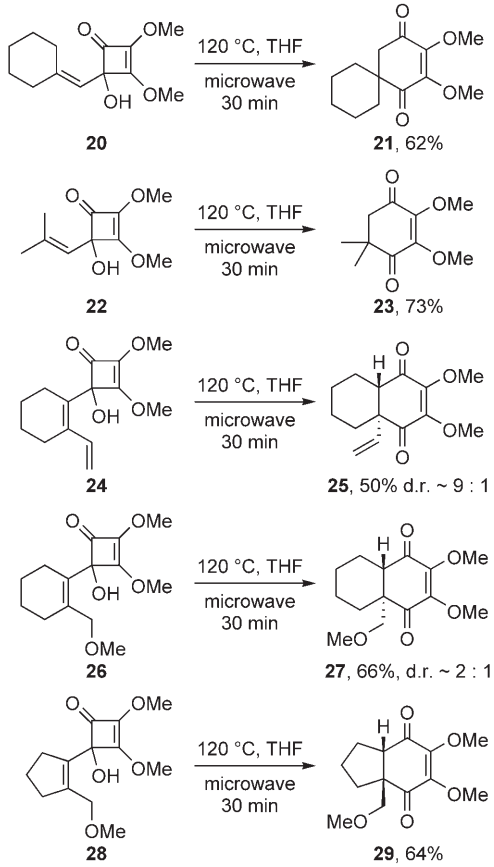


Scheme 3. Thermal rearrangement of cyclobutenone *ent*-**15** to *ent*-**16** and proposed mechanistic course of the reaction.

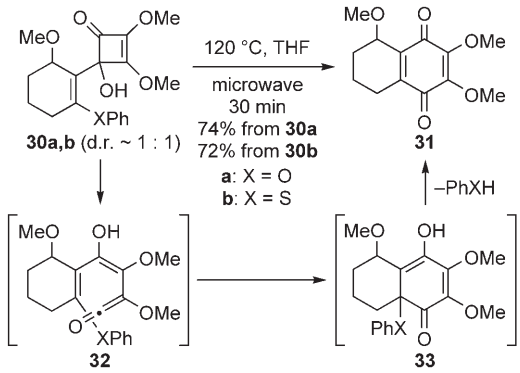
To ascertain whether the mode of collapse of the ketene intermediate was determined by electronic or steric factors, we prepared a series of vinylcyclobutenones bearing two organyl substituents on the distal carbon atom of the vinyl appendage. In each case thermolysis led to a cyclohex-2-en-1,4-dione (Scheme 4), thereby demonstrating that the electrocyclization pathway outpaces the carbonyl-ene reaction in such cases.

Further evidence that the course of thermal vinylcyclobutenone rearrangements is dictated by electronic rather than steric factors came with the thermolysis of phenyl vinyl ether **30a** and vinyl sulfide **30b**. In stark contrast to the analogous methyl vinyl ethers (Schemes 2 and 3), both substrates were smoothly transformed into quinone **31**. Thus, by the simple expedient of attenuating electron density in the vinyl ether, we had been able to promote the electrocyclic ring-opening–electrocyclization–elimination sequence (Scheme 5) over the spirocyclization pathway.

At this juncture our attention switched to other systems for which an alternative pericyclic process might compete with the classical electrocyclization pathway. 4-(*o*-Styryl)cyclobutenones provide a noteworthy case as these molecules smoothly rearrange to form benzobicyclo[3.2.1]octenones on heating (Scheme 6). The products can be viewed as arising from an electrocyclic opening of the cyclobutenone and a

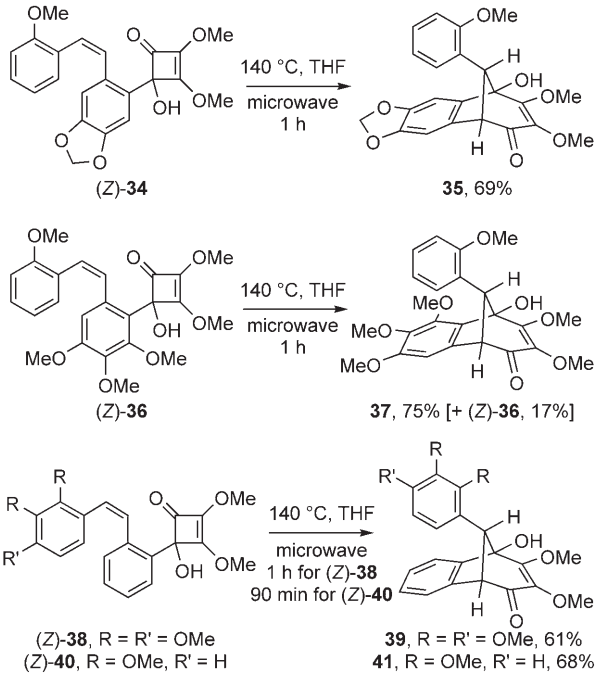


Scheme 4. Thermal rearrangements that lead to cyclohex-2-en-1,4-diones.



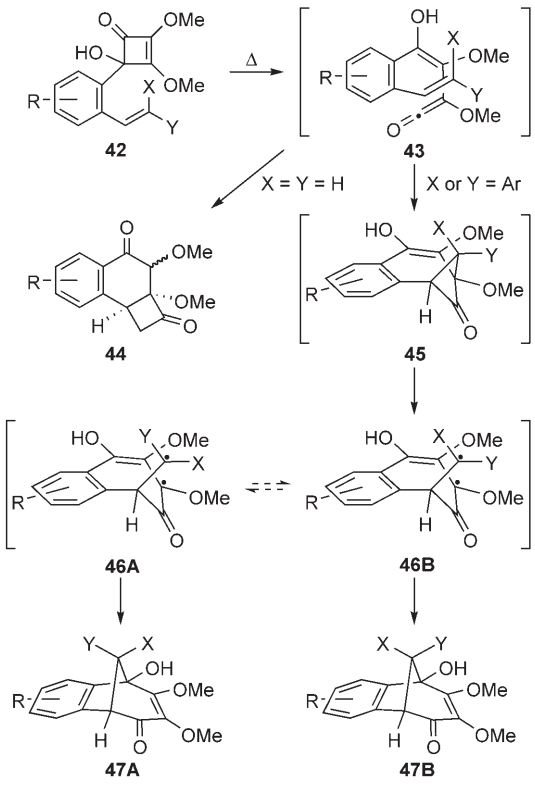
Scheme 5. Thermally induced domino reactions for the synthesis of quinones from vinylcyclobutenones.

subsequent intramolecular Diels–Alder cycloaddition, namely **42**→[**43**]→**47B**. Several factors weigh against that explanation, however. In particular, the transition state for an intramolecular [4+2] cycloaddition in **43** is highly strained, whereas that for the more-usual [2+2] cycloaddition to **44** or **45** is readily adopted.[9] Indeed, we observed formation of a [2+2] cycloadduct in the related rearrangement of styrylcyclobutenone **48** into benzobicyclo[4.2.0]octenone **49** (Scheme 8), albeit with a different regiochemistry. Additionally, while thermolysis of (*Z*)-4-(*o*-styryl)cyclobutenones gave

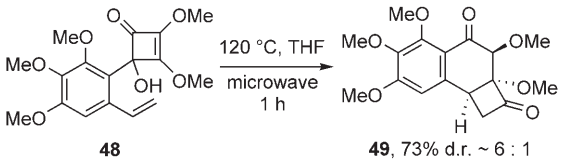


Scheme 6. Rearrangements of (*Z*)-4-(*o*-styryl)-cyclobutenones to benzobicyclo[3.2.1]octenones.

benzobicyclo[3.2.1]octenones as single diastereoisomers (Scheme 6), the isomeric (*E*)-4-(*o*-styryl)cyclobutenones led to diastereomeric mixtures (See Supporting Information).



Scheme 7. Proposed mechanism for the thermal rearrangement of 4-(*o*-styryl)-cyclobutenones.



Scheme 8. Rearrangement of 4-(*o*-styryl)-cyclobutenone **48** to benzobicyclo[4.2.0]octenone **49**.

The results are thus consistent with rearrangement occurring by an initial electrocyclic ring opening of the cyclobutenone, **42**, to an unsaturated ketene, **43**, which in turn undergoes a [2+2] cycloaddition to benzobicyclo[4.1.1]octenone **45**. A vinylcyclobutane rearrangement via biradical **46** completes the sequence with the dynamics of rotation between **46B** and **46A** dictating the stereochemical outcome (Scheme 7).[10]

In conclusion, we have shown that a host of carbocyclic ring systems can be prepared by the thermal rearrangement of cyclobutenones. Of particular note is our finding that the course of vinylcyclobutenone rearrangements is dictated by the nature of substituents on the vinyl appendage. When the distal carbon atom carries a powerful electron-donating group, electrocyclic ring opening of the cyclobutenone is followed by a carbonyl-ene reaction, which leads to a cyclopentendione after oxidation (Scheme 2 and 3). In other cases the unsaturated ketene intermediate undergoes an electrocyclization reaction, which leads to a cyclohexadienone, for example, **5**. The nature of the saturated carbon atom within that cyclohexadienone then dictates whether it collapses with elimination to a quinone (Scheme 5), or tautomerizes to a hydroquinone (Scheme 1) or a cyclohexenedione (Scheme 4). From a synthetic perspective, the high yields and lack of reagents add to the appeal of the transformations described herein.

Received: August 30, 2006
Published online: December 5, 2006

Keywords: cyclization · domino reactions · rearrangement · spiro compounds · thermochemistry

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