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INTRAMOLECULAR CYCLOADDITIONS OF ARYLKETENES WITH ALKENES. REACTIONS OF 5-ARYLBICYCLO[3.2.0]HEPTAN-6-ONES.

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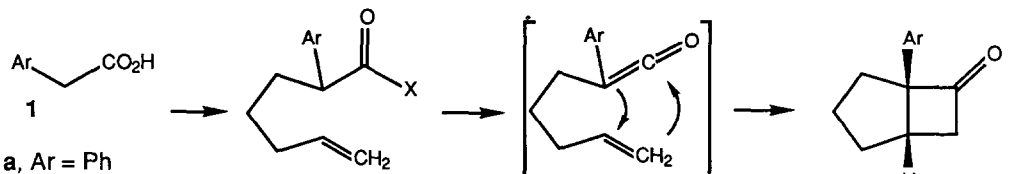
Summary: Intramolecular cycloadditions of arylketenes **4** proceed in excellent yield to give 5-arylbicyclo[3.2.0]heptan-6-ones **5**. Reaction of **5a** with KOH in THF gives a 95:5 mixture of **7** and **10**. Reaction of **5a** with KOEt in ETOH give a 1:3 mixture of **7** and **10**. Reaction of **5a** with vinyllithium and treatment of the resulting alcohol **23** with KH gives the 1,3-sigmatropic rearrangement product **25**.

We and others have recently begun a systematic exploration and exploitation of the intramolecular cycloaddition reaction of ketenes and alkenes.[1] Intramolecular cycloadditions of unsaturated arylketenes have not been examined, although the intermolecular cycloadditions of arylketenes and alkenes have been extensively explored,[2] and the reactivity of 2-arylcyclobutanones has been examined.[3] We report here the preparation and intramolecular cycloaddition of unsaturated arylketenes and the reactivity of the resulting 5-arylbicyclo[3.2.0]heptan-6-ones.

Phenylacetic acid (**1a**) was converted to the dianion with 2 equiv. of LDA in THF containing 1 equiv. of HMPA at -78 °C.[4] Treatment of the dianion with 5-bromo-1-pentene for 3 h at -78 °C followed by warming to 25 °C gave acid **2a** in 95% yield. Acid **2a** was converted to the acid chloride **3a** (NaH, oxalyl chloride, benzene, reflux 30 min). Acid chloride **3a** was added to a solution of 3 equiv of NEt_3 in toluene (0.03 M final concentration) at reflux to generate ketene **4a** which underwent cycloaddition to give cycloadduct **5a** in 74% overall yield from acid **2a**. In a similar manner, acid **2b**, prepared from 2-naphthylacetic acid (**1b**) in 88% yield, was converted to cycloadduct **5b** in 88% yield. Acid **2c**, prepared from 2-furylacetic acid (**1c**)[5] in 71% yield, was converted to cycloadduct **5c** in 91% yield.

The conversion of ketene **4** to cycloadduct **5** in excellent yield indicates the value of aryl groups in facilitating the cycloaddition since the corresponding aldoketene lacking an aryl group undergoes cycloaddition in only 3% yield.[1b] It should not be construed from this observation that the aryl group accelerates the cycloaddition. Its role in facilitating the reaction may be simply to slow down non-productive competing dimerization and polymerization.

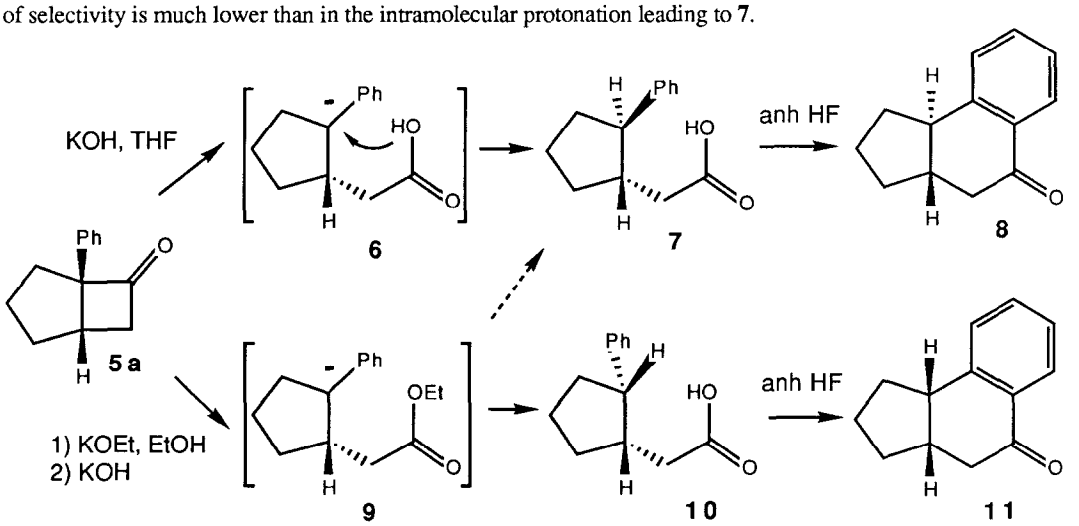


Having established that the intramolecular cycloaddition reaction of arylketenes produces cycloadducts in excellent yield, we turned our attention to exploring the synthetic utility of the 2-arylcyclobutanones. Base catalyzed ring opening of cyclobutanones containing a substituent on the α-carbon capable of stabilizing an anion, such as an aryl group, are well known.[3a,6] Treatment of **5a** with KOH in ethanol-ether[3a] proceeded normally to give a 1:1 mixture of *trans*- and *cis*-2-phenylcyclopentaneacetic acid (**7** and **10**) in quantitative yield. The produc-

tion of **7** and **10** as a mixture of isomers limits the utility of the reaction. We therefore turned our attention to procedures which would permit the selective synthesis of either **7** or **10**.

Treatment of **5a** with an insoluble source of hydroxide in an aprotic solvent will give intermediate **6**. Under aprotic conditions the only source of protons to protonate the carbanion of **6** is the carboxylic acid. Intramolecular protonation by a 1,5-proton transfer should occur readily leading selectively to the *trans*-isomer **7**. In fact, treatment of **5a** as a 0.2 M solution in THF with 2 equiv. of anhydrous KOH at reflux for 12 h gave a 94% yield of a 20:1 mixture of **7** and **10**.

Treatment of **5a** with alkoxide in alcohol should give intermediate **9**. The anion of **9** must be protonated by the solvent since there is no carboxylic acid proton. Protonation should occur selectively from the less hindered face to give predominantly the *cis*-isomer **10**. In fact, treatment of **5a** with 5 equiv. of KOEt in EtOH (0.1 M) at reflux for 3 h, followed by addition of water and continued heating to hydrolyze the ester, gave a 96% yield of a 3:1 mixture of **10** and **7**. Although intermolecular protonation is selective for the *cis*-isomer **10**, the degree of selectivity is much lower than in the intramolecular protonation leading to **7**.



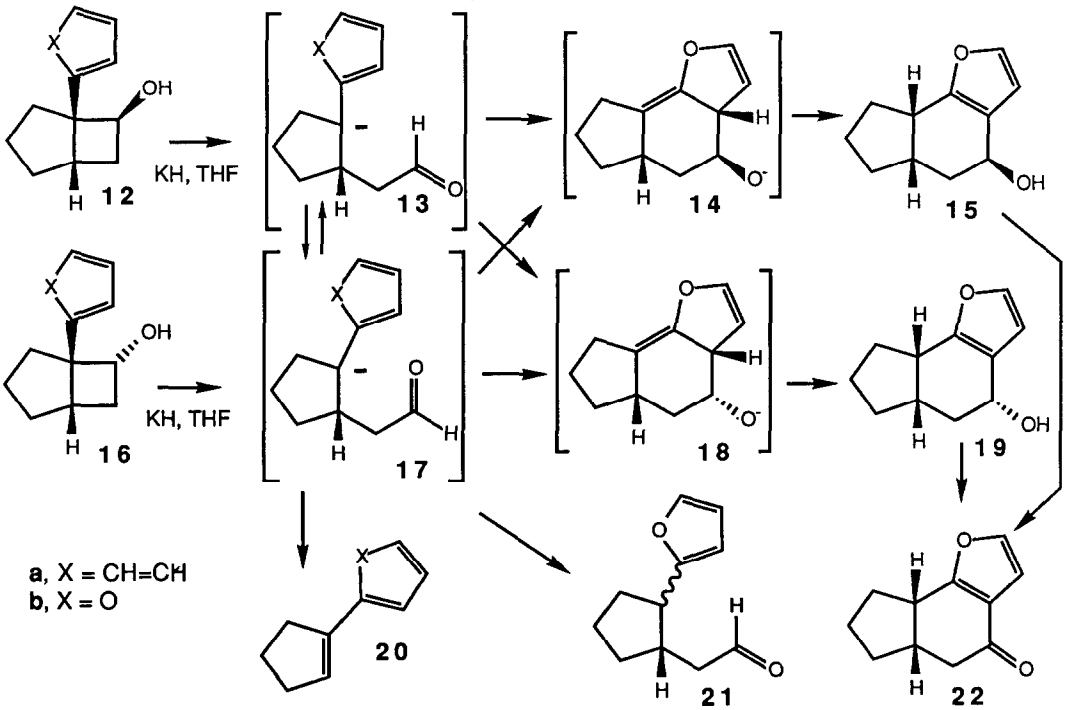
2-Phenylcyclopentaneacetic acids **7** and **10** are versatile intermediates. As previously described,[3a,7] dissolution in anhydrous hydrogen fluoride leads to a Friedel-Crafts reaction to give ketones **8** and **11** in 89% and 93% yield, respectively. This two step sequence, stereoselective ring opening followed by Friedel Crafts acylation, provides an efficient method for ring expansion of these cyclobutanones to cyclohexanones which should prove useful in steroid synthesis.

1,3-Sigmatropic rearrangement of 2-vinylcyclobutanols has been developed by Danheiser and Cohen as a general ring expansion procedure leading to 3-cyclohexenols.[8] Cohen has also reported the 1,3-sigmatropic rearrangement of 2-(2-furyl)-cyclobutanol.[8b] Reduction of ketone **5c** with LAH gave an 89% yield of a 2:1 mixture of **12b** and **16b**.[9] Treatment of **12b** with excess KH in THF at 25 °C for 12 h gave **20b** (47%), **21** (4%), **22** (5%), **19**[10](8%) and **15**[10] (12%)in order of elution from silica gel. Similar treatment of **16b** gave **20b** (47%), **21** (7%), **22** (5%), **19**[10] (4%) and **15**[10] (20%). Oxidation of both **19** and **15** with PDC in DMF gave 73% of ketone **22**. The stereochemistry of the ring fusion of **22** is assigned based on the absorption for the benzylic proton at δ 3.33 (ddd, J = 6.3, 6.3, 6.3) which is consistent only with the *cis*-isomer. The *trans*-isomer would

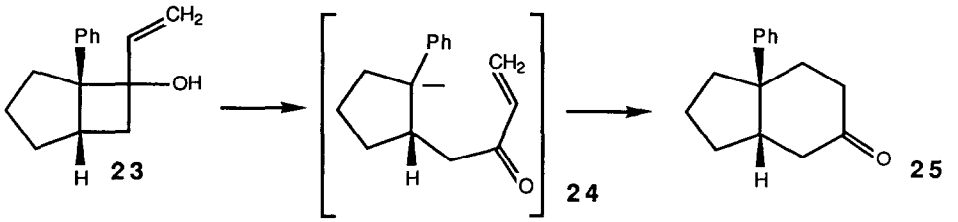
have two large couplings. This establishes that alcohols **19** and **15** both have a *cis*-ring fusion and differ in the alcohol stereochemistry.

Reduction of **5a** with LAH gave an 89% yield of a 1:1 mixture of **12a** and **16a**.[9] Treatment of either isomer with KH in THF for 12 h at 25 °C gave only fragmentation product **20a**[11] in 50-60% yield. As indicated by Cohen, *et al.*, the furan double bond participates marginally in the 1,3-sigmatropic rearrangement. A benzene double bond does not participate in the rearrangement; napthalene double bonds were not investigated.

Cleavage of the alkoxides derived from **12b** and **16b** gave the intermediate carbanion (**13b** and **17b** are different conformers of the same intermediate). The major process is further fragmentation to give **20b**. The major tricyclic alcohol, **15**, is derived from **14**, in which the alkoxide has adopted the less hindered configuration. Alcohol **16b** gives a greater percentage of **15** than does **12b**, indicating that ring closure to **14** and **18** is sufficiently fast to prevent complete conformational equilibration of **13b** and **17b**.



1,3-sigmatropic rearrangements of 1-vinylcyclobutanols have been observed with anion stabilizing substituents such as sulfur or phenyl on the 2-carbon.[12] Addition of vinyllithium to **5a** gave a 51% yield of **23** as a single diastereomer. The low yield and apparent stereospecificity may result from the selective destruction of one of the two diastereomers. Treatment of **23** with excess KH in THF at -40 °C for 4 h gave a 68% yield of **25** and a 15% yield of **20a** derived from fragmentation of the intermediate **24**. Addition of an alkenyllithium to **5** and base induced 1,3-sigmatropic rearrangement provides an alternative method for ring expansion of 2-arylcyclobutanones.



These results indicate that intramolecular cycloaddition of unsaturated arylketenes is an attractive route to synthetically useful polycyclic α-arylcyclobutanones. We are continuing to explore the scope of this reaction and the synthetic utility of the cycloadducts.

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9. The stereochemistry of **12** and **16** are tentatively assigned as indicated below. The quaternary aromatic carbons of the *exo*-isomers **12a** and **12b** are shielded by the *cis*-hydroxy group and absorb at δ 141.8 and 157.3, respectively. The protons α to the alcohol absorb at δ 4.03 (dd, J = 7.0, 7.0) and 4.00 (dd, J = 7.0, 7.0). The quaternary carbons of the *endo*-isomers **16a** and **16b** absorb at δ 150.1 and 160.6. The protons α to the alcohol absorb at δ 4.38 (dd, J = 8.9, 6.9) and 4.51 (dd, J = 10.0, 6.3). The larger coupling constants and lower chemical shift for the protons of **16** are expected for the less shielded pseudoaxial proton of a *cis*-1,2,2,3-tetrasubstituted cyclobutane.
10. The stereochemistry of **15** and **19** are tentatively assigned as indicated below. The *cis*-isomer **19** exists largely in the conformation with an equatorial hydroxy group to avoid 1,3-diaxial interactions between the hydroxy and alkyl groups. The proton α to the alcohol at δ 4.72 is axial (dd, J = 8.0, 5,9). The *trans*-isomer **15** exists as a mixture of conformers which results in smaller coupling constants for the proton at δ 4.70 (dd, J = 4.7, 4.7).
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