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Substituted α -alkylidene cyclopentenones via the intramolecular reaction of vinyl cations with alkenes

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Abstract

Substituted α -alkylidene cyclopentenones are formed in up to 93% yield by the intramolecular capture of vinyl cations with pendent alkenes. An increased level of substitution at the β -position of the β -hydroxy- α -diazoketone starting material changed the course of the reaction to instead give a lactone product. A reaction path that involves bond reorganization via an acylium ion intermediate is proposed to explain these results. Substrate scope studies showed that more stable vinyl cations gave higher α -alkylidene cyclopentenone yields. This study provides a mild and efficient method to form α -alkylidene cyclopentenones that complements C-H insertion and Nazarov cyclization strategies.

Graphical Abstract

Cyclopentenones are versatile synthetic intermediates that are commonly used to make more-highly functionalized cyclopentanes, which are one of the most common ring systems found in biologically active organic structures (Figure 1).¹ Cyclopentenones are often prepared by the Nazarov cyclization^{2–4} or the Pauson-Khand reaction,^{5–9} but reactivity and selectivity issues and the need for stoichiometric quantities of reagents can limit the generality of these reactions. To circumvent these limitations, we and others have taken advantage of the carbene-like reactivity of vinyl cations to effect C-H insertion reactions that give cyclopentenone products.^{10–16}

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ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website.

General experimental details, experimental procedures, compound characterization data, and copies of ¹H and ¹³C NMR spectra (PDF)

The authors declare no competing financial interests.

Interest in vinyl cations as intermediates in synthesis has reemerged over the past few years with the advent of mild and selective ways to form these reactive species.¹⁷ In addition to their carbene-like reactivity, vinyl cations also act as more traditional electrophiles.^{18–23} We recently took advantage of this fact to develop an intramolecular vinylation of aromatic rings as a way to prepare 1-indenones.²⁴ This reaction, which uses a β -hydroxy- α -diazoketone as a vinyl cation precursor, presumably occurs by the pathway shown in Scheme 1. The Lewis acid facilitates elimination of the β -hydroxyl to generate vinyl diazonium **2**, which gives vinyl cation **3** upon loss of molecular nitrogen. This destabilized cation rearranges to the ring expanded cyclic vinyl cation **4**, which reacts via intramolecular electrophilic aromatic substitution to give indenone **6**.

In a similar vein, Karpf showed that cyclopentenone products were formed when acetylenes were acylated with unsaturated acid chlorides.^{25,26} Although adding electrophiles to alkynes is a viable method to prepare vinyl cations, inherent regioselectivity issues can lead to mixtures of regioisomers. In view of the importance of the cyclopentenone framework, we hypothesized that β -hydroxy- α -diazoketones bearing a pendent alkene would provide this scaffold in a regiochemically controlled manner via a reaction similar to that shown in Scheme 1.

We began these studies by preparing β -hydroxy- α -diazoketone **7a** by the aldol type addition of 1-diazo-3,3-dimethylpent-4-en-2-one to benzaldehyde. In optimizing the conversion of diazo ketones to cyclopentenones¹³ and 1-indenones²⁴, we determined that treating the diazo ketone with 1 equiv of tris(pentafluorophenyl)borane (BCF; (C₆F₅)₃B) in CH₂Cl₂ gave consistently good results. Under these conditions, diazo ketone **7a** returned cyclopentanone **8a** in 63% yield. During optimization studies (Table 1), we noted that purification by silica gel chromatography led to the formation of varying quantities of alkene regioisomer **9a**. The isomerization from **8a** to cross conjugated **9a** was quantitative when the reaction mixture was purified using silica gel that was pre-treated with 0.5% Et₃N, and this became standard protocol to avoid the formation of product mixtures. Although changing the concentration of the reaction had negligible effect on the yield (entry 1 vs 2 and 3 vs 4), increasing the temperature from –20 °C to room temperature increased the yield of **9a** to 69% (entry 3). Increasing the temperature further led to lower product recovery (entry 5), as did changing the Lewis acid to Sc(OTf)₃ or BF₃•Et₂O (entry 6 and 7).

With optimized conditions in hand, we assessed the scope of the reaction with respect to the identity of the starting aldehyde (Table 2). Adding a methyl group at the para position of the aryl ring did little to change the reaction outcome; the 4-methyl phenyl derivative returned cyclopentenone **9b** in 64% yield. We were surprised to observe that increasing the steric encumbrance of the aryl ring by incorporating methyl groups at the 2 and 6 positions led to a significant increase in yield; cyclopentenones **9c** and **9d** were formed in 89% and 93% respectively. It is not clear to us why this is the case, but the steric hindrance may promote rearrangement of the initial vinyl cation, or may act to protect the rearranged vinyl cation from intermolecular attack. The 2-naphthyl derivative returned cyclopentenone **9e** in 54% yield, whereas the 9-anthracenyl derivative **9f**, which also has increased bulk at the 2 and 6 position of the central ring, gave the expected product in 77% yield. Replacing the aryl ring with aliphatic groups was not productive and cyclopentenones **9g** and **9h** were each formed

in low yield in a complex mixture of products. α -Styrenyl cations are more stable than their aliphatic counterparts, and the alkyl derivatives may suffer from increased side reactions. Similarly, systems containing electron rich or neutral aryl rings gave significantly higher yields than systems with electron poor aryl rings. These results again correlate the stability of the styrenyl cation intermediate to the reaction outcome, with more stable cations giving higher yields.

We next sought to expand this methodology to more substituted systems, and prepared diazo alcohol **10a** from cyclohexanone. Treating **10a** with BCF in CH_2Cl_2 gave small quantities of three products (Scheme 2). The expected cyclopentenone **11a** and cyclopentenone **12a**, which is presumably formed via C-H insertion at methyl, were each formed in trace amounts. We were surprised to find that the major product was carboxylic acid **13a**. We reasoned that the low mass recovery of this reaction might be due to loss of acid **13a** during workup. Removing the extractive workup step from the procedure and purifying the crude reaction mixture after solvent removal gave lactone **14a** in 49% yield in place of the carboxylic acid. Under these latter conditions, heptanone based substrate **10b** returned lactone **14b** in 38% yield. SnCl_4 , $\text{Sc}(\text{OTf})_3$, $\text{BF}_3 \cdot \text{Et}_2\text{O}$, and $\text{In}(\text{OTf})_3$ were examined as alternatives to BCF in this reaction, but none gave superior results.

We propose that **14a** forms by the path shown in Scheme 3. Diazo ketone **10a** would react with BCF as expected to give vinyl cation **15**. Addition of the pendent alkene to the cation would result in either concerted or stepwise rupture of the adjacent σ -bond to give acylium **17**. A concerted process seems more likely since the stepwise process would generate a secondary cation in a 5-membered ring, which would have poor stereoelectronic alignment with the bond that ruptures. Acylium **17** would ultimately react with water to give carboxylic acid **18**, which would cyclize to lactone **14** when concentrated in the presence of acid.

With these results in mind, we propose that aldehyde based substrates react as shown in Scheme 4. Diazo **19** would react with the Lewis acid to give destabilized vinyl cation **20**. In this case migration of hydrogen to give the more energetically favorable cation **21** outcompetes alkene capture. The newly formed vinyl cation could then react with the pendent alkene to give acylium **23**. Cyclization of the pendent alkene onto the acylium ion would provide tertiary cation **24**, and loss of a proton would give the α -alkylidene cyclopentenone product.

In summary, we have described a method to form β -substituted α -alkylidene cyclopentenones from β -hydroxy- α -diazo ketones. This method takes advantage of the intramolecular capture of a vinyl cation intermediate by a pendant alkene. The electronic and steric properties of an aryl ring substituent at the β -position of the diazo starting material affects the outcome of the reaction. Sterically hindered and electron rich aryl rings provided higher yields of α -alkylidene cyclopentenones than small or electron poor aryl rings, and an alkyl substituent at this position provided little desired product. These effects can be rationalized by considering how the substituent influences the rearrangement of a destabilized vinyl cation intermediate to a more stable vinyl cation by 1,2-migration across the alkene. Systems that promote this rearrangement through steric or electronic bias gave higher yields of α -alkylidene cyclopentenones. Changing the system to include an additional

substituent at the β -position (e.g. cyclohexanol **10a**) gave lactone products. In this case, slower migration of the aliphatic group across the alkene of the vinyl cation seems to allow the pendent alkene to capture the vinyl cation before rearrangement, leading to the different product. These reactions provide a unique way to synthesize β -substituted α -alkylidene cyclopentenones that complements existing C-H insertion and cyclization methods.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1.
Representative examples of biologically active cyclopentanes.

Scheme 1.
Indenone formation via aromatic vinylation of a vinyl cation.

Scheme 2.

More substituted diazo alcohol gives lactone product.

Scheme 3.
Lactone product from acylium intermediate.

Scheme 4.

α -Alkylidene cyclopentenones from less substituted β -hydroxy- α -diazo ketones.

Table 1.

Optimization of the alkene addition conditions.

	Lewis Acid (1 equiv.)	Conc. (M)	Temp (°C)	Yield 8a	Yield 9a
1 ^a	(C ₆ F ₅) ₃ B	.2	−15	60%	-
2 ^a	(C ₆ F ₅) ₃ B	.4	−20	59% (2.4:1 8a : 9a)	
3 ^b	(C ₆ F ₅) ₃ B	.4	rt	-	69%
4 ^b	(C ₆ F ₅) ₃ B	.2	rt	-	67%
5 ^b	(C ₆ F ₅) ₃ B	.4	35	-	59%
6 ^b	Sc(OTf) ₃	.2	rt	-	30%
7 ^b	BF ₃ •Et ₂ O	.2	−20	-	40%

^aPurified using untreated silica gel.^bPurified using silica gel washed with 0.5% Et₃N.

Table 2.

Substrate scope of alkene addition.

^aYield on 1 mmol scale.