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Formation and isomerization of polycyclic 1,5-enynes^{†1}

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ABSTRACT

A 1,5-enyne with the alkyne flanked by a cyclopropane and a cyclobutane, formed by intramolecular [2+2] photocycloaddition of a pyridone with an enyne, undergoes gold catalyzed ring closure to give a cyclopentene, without isomerization of either small ring. The ring closure can also be effected by thiol radical conditions. The chemistry of the resulting tetracycle with its five stereogenic centers, has been studied.

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Assembly of polycyclic molecules with useful complexity from simple reagents is a gold standard in organic synthesis.² During our investigations of 2-pyridone photochemistry we have studied its cycloaddition with 1,3-enynes and discovered two different pathways based on the presentation of the enyne.^{3,4} When the enyne is attached through the alkyne (**1**), only [4+4] cyclization results and the highly strained allene product **2** is, in most cases, unstable and undergoes further reaction. In contrast, when the enyne is linked to the pyridone through the alkene (**3**), only [2+2] products are observed. The stereochemically rich cyclobutane **4** presented opportunities to study the reactivity of this strained and densely functionalized structure, particularly its cis-1,5-enyne. We report herein our investigation of the formation and reactivity of **4** and related structures.

Scheme 1. Tether-dependent pyridone-enyne photocycloaddition.⁴

The formation of [2+2] adduct **4** is notable for several reasons. In addition to creating two adjacent quaternary carbons, the cycloaddition occurs with retention of the alkene stereochemistry, whereas [2+2] cycloaddition of enones with alkenes is typically accompanied by scrambling of the alkene stereochemistry.⁵ Enone photochemistry is largely triplet-derived and bond formation in enone [2+2] cycloadditions are often stepwise and reversible, leading to the stereochemical isomerization. In contrast, pyridone photochemistry is mostly singlet-derived.⁶ A singlet process for the photocycloaddition of **3** would be consistent with the retention of (*E*) alkene geometry observed for this reaction as well as for the corresponding (*Z*) alkene **5**, Scheme 2.

Scheme 2. Stereochemistry of the alkene is preserved in pyridone [2+2] photocycloadditions.

In four additional examples, with hydrogen, trimethylsilyl and cyclopropyl (**7a–d**) terminating the alkyne, with and without

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[†] Dedicated to Harry H. Wasserman.

bromine at C-5 of the pyridone, a clean [2+2] cycloaddition is observed, yielding the [2+2] adducts **8a-d** as single isomers, Scheme 3. These reactions were typically run in NMR spectrometer tubes (3.5 mm diameter) using a 400W medium-pressure mercury lamp in a water-cooled jacket and a Pyrex® filter, standardized as 0.025 M solutions of **3** or **7** in C₆D₆ or toluene. As noted in Scheme 3 for the reaction of **7b**, increasing the size of the reaction tube from 3.5 mm to 15 mm diameter led to a near tripling of the time required for completion of the reaction (TLC) and a drop in the isolated yield by 8%. Use of a flow apparatus led to a much improved process.⁷ Using 3.2 mm diameter PTFE tubing allowed the reaction volume to be dramatically increased and the reaction time substantially decreased. Moreover, under these conditions the yield of product **8b** increased by 9%.⁷

Scheme 3. Pyridone-enyne [2+2] photocycloadditions.

One exception to the stereochemical fidelity found for substrates **7** was substrate **7e**, that gave a diastereomeric mixture of products **8e** and **9e**, Scheme 3. The loss of stereocontrol for substrate **7e** is a consequence of the conjugated phenyl group. It should be noted that isomerization of the alkene in **7e** is not observed during the photoreaction, suggesting that if the photoreaction of **7e** involves triplet intermediates the photocycloaddition with the pyridone is faster than isomerization, and that the resulting **8e** may isomerize to **9e** in a subsequent photochemical transformation. Indeed, subjecting a purified sample of **9e** to identical photochemical conditions resulted in a mixture of **8e** and **9e**, in a ratio that changed over time, Scheme 4. After six hours the 2:1 mixture observed for the initial cycloaddition was achieved. This is consistent with either photocleavage of the product cyclobutane to reform starting **9e** followed by rapid re-photocycloaddition, or reversible cleavage of the cyclobutane bond that is both propargylic and allylic. Photocleavage reactions have been described for related structures.⁸

Scheme 4. Equilibration of the phenylalkyne product.

With cyclobutane products **8** in hand, we turned to investigations of the reactivity of this 1,5-enyne. Nonconjugated enynes can cyclize when treated with a variety of reagents such as gold and radicals. For substrates **4** and **8**, the cyclobutane adjacent to the alkyne could participate in these reactions, based on precedent of substrate **10**, for example, Scheme 5.⁹ For substrates **8b** and **8d** in particular, with the alkyne flanked by both cyclobutane and cyclopropane, the potential for new reaction pathways through participation of these strained rings was obvious. Alternatively, the electron-rich ene-amide group nearby might intercept the coordinated alkyne and its reaction intermediates, much like other nucleophiles can, e.g., **15**.¹⁰

Scheme 5. Gold-catalyzed cyclization of 1,5-enynes.^{9,10}

In the event, treatment of **8b** with a mixture of Au^I in wet acetonitrile gave tetracycle **14** in high yield, Scheme 6, with no change in the strained rings. This reaction presumably starts with coordination of the gold with the alkyne, with the resulting intermediate **15** possibly electronically biased by the cyclopropane. Fensterbank and Malacria found that platinum-catalyzed reactions of non-conjugated enynes were compatible with terminal cyclopropane substitution similar to **8b**.¹¹ Trapping of this electrophile by the electron-rich enamide then yields iminium **16** that is intercepted by water, yielding **14**. The structure of **14** was confirmed by X-ray crystallography (see Supporting Information).

Scheme 6. Gold-catalyzed cyclization of 1,5-enynes.

Not surprisingly, cyclization is possible only when the ene and yne are cis to each other. Subjecting the mixture of **8e** and **9e** to the gold catalyzed cyclization conditions led to quantitative recovery of the trans enyne **9e** and formation of cyclization product **17** in good yield.

Scheme 7. Only cis enynes cyclize.

Without the cyclopropane of **8b** terminating the alkyne, substrate **4**, lower yields for the gold-catalyzed cyclization were observed, Scheme 8. Treatment of **4** under the standard conditions gave **18** in 23% yield. With a terminal alkyne and a bromine on the enamide (**8c**), gold catalysis gave cyclization but with a twist: the bromine was lost and the hemiaminal functionality was replaced with a carbonyl, imide **19**. It is likely that **19** results from initial trapping of the iminium by water, viz., **15**, followed by dehydrohalogenation. The latter presumably is an E2-like process, with solvolysis of the allylic bromide initiating the dehydrohalogenation.

Scheme 8. Additional gold-catalyzed cyclizations. Dehydrohalogenation leads to an imide product

While the gold-catalyzed cyclization was promoted by substitution of the alkyne by phenyl and cyclopropane, attempts to elicit cyclization of trimethylsilyl substrate **8a** led only to recovered starting material. Low reactivity for platinum-catalyzed reactions of an alkyne terminated by a trimethylsilyl group has been noted.¹¹ Nevertheless, treatment of **8a** with thiophenol in the presence of AIBN led to clean cyclization and formation of product **21**, Scheme 9.¹²

Scheme 9. Thiol radical cyclization.

Several reactions of the tetracyclic aminal **14** have been explored, Scheme 10. Reduction of the aminal hydroxyl was readily accomplished by treatment with sodium cyanoborohydride under acidic conditions to give **21**.¹³ Alternatively, the alcohol was replaced by methoxy by dissolving in acidic methanol. This methoxy group was efficiently replaced with an allyl group with a combination of borontrifluoride and

allyl silane, yielding **23**.^{14,15} In all cases, the nucleophiles were found to add only from the convex face of the system.

Scheme 10. Elaboration of the aminal.

Photochemical reactions of enynes with 2-pyridones can take the form of [4+4] cycloaddition or [2+2] cycloadditions, depending on the presentation of the enyne, readily controlled by performing the reactions intramolecularly.⁴ The [2+2] pathway is notable for the retention of alkene geometry, suggesting a singlet photochemical pathway. Moreover, this intramolecular cycloaddition creates two quaternary carbons. When the alkyne in the cycloaddition product is cis to the alkene of the enamide derived from the pyridone, cyclization to give a cyclopentene can be effected using gold (I) catalysis or by thiol radical addition. For the former pathway, the resulting hemi-aminal can be readily elaborated. Overall, the 2-4 step sequence creates a tetracyclic product with up to six stereogenic centers from an achiral starting material with single aromatic ring. Further studies are in progress.

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References and notes

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