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Studies Toward the Synthesis of the Epoxykinamycin FL-120B': Discovery of a Decarbonylative Photocyclization

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Abstract

Photo-Friedel-Crafts acylation of a naphthoquinone was attempted in an effort to access a diazobenzofluorenone en route to the epoxykinamycin natural product FL-120B'. Photoirradiation of the naphthoquinone substrate which resulted in the unexpected formation of a tetracyclic naphthofuran *via* a decarbonylative photocyclization process is described.

Kinamycin C (**1**)¹ and the epoxykinamycin FL-120B' (**2**)² belong to the family of diazobenzofluorene natural products which possess broad antibacterial and antitumor activities (Figure 1). The unique diazo functionality and its involvement in the diazobenzofluorenes' ability to damage DNA have made this class of molecules attractive targets for synthetic organic chemists.³ In 2006 and 2011, our laboratory reported the total syntheses of kinamycin C and FL-120B', respectively.⁴ Our approach to **1** and **2** involved elaboration of a benzofluorenone intermediate **3** which was accessed from a trifluoroacetic anhydride (TFAA)-mediated intramolecular Friedel-Crafts cyclization of carboxylic acid precursor **4**. During our studies toward the synthesis of FL-120B', an alternative cyclization involving intramolecular photoacylation of an aldehyde substrate containing a naphthoquinone chromophore was also explored. In the present study, we describe our efforts to implement the intramolecular photo-Friedel-Crafts acylation which resulted in the serendipitous discovery⁵ of a novel decarbonylative photocyclization to form naphthofurans.⁶

Historically, intermolecular photo-Friedel-Crafts acylations of quinones and aldehydes have been demonstrated to yield acylated hydroquinones.⁷ For example, photoirradiation of 1,4-naphthoquinone **5** in the presence of propionaldehyde **6** provided the acylated hydroquinone **7** (Scheme 1).⁷ⁱ This reaction serves as an environmentally friendly alternative to the classical Friedel-Crafts acylation. In this regard, Mattay and coworkers performed this photoacylation on a 500 gram scale using a solar-chemical reactor.^{7f–g} One mechanism accounting for formation of **7** involves abstraction of the acyl hydrogen by photoexcited naphthoquinone **8** to give semiquinone **9** and acyl radical **10**. Subsequent carbon-carbon bond formation *via* an in-cage coupling⁸ of **9** and **10** provides the observed acyl hydroquinone **7**.⁹ On this mechanistic basis, we hypothesized that photoirradiation of naphthoquinone **11** may provide benzofluorenone **12** as a useful intermediate for our synthesis of FL-120B' (Scheme 2). This

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Supporting Information Available Experimental procedures, compound characterization data, and X-ray crystallographic information files. This material is free of charge *via* the Internet at <http://pubs.acs.org>.

photo-Friedel-Crafts cyclization would require diradical **13** to undergo intramolecular hydrogen abstraction through a seven-membered¹⁰ cyclic transition state, in which the resulting biradical species **14** would further cyclize to **12**.

Naphthoquinone **11** was obtained in six steps from epoxyketone **15**,^{4a} an intermediate in our synthesis of kinamycin C (Scheme 3). Acetylation of **15** followed by reduction (LiEt₃BH) provided *syn*-epoxyalcohol **16** (5:1 dr)¹¹ which was protected as Boc-carbonate **17**. Desilylation and oxidation with Dess-Martin periodinane (DMP)¹² afforded aldehyde **18**. Oxidative dealkylation with ceric ammonium nitrate (CAN) provided **11** as our desired substrate for intramolecular photo-Friedel-Crafts acylation studies.

Photoirradiation of **11** in a Rayonet reactor (315–400 nm) gave full conversion to a product that could not be identified as the expected benzofluorenone **12** (Scheme 4). In addition, lactone **19** was not observed. Photochemical studies on a substrate closely resembling **11** by Echavarren and coworkers led to observation of a lactone byproduct in their synthetic efforts toward prekinamycin.¹³ Analysis of ¹³C NMR and mass spectra suggested formation of a decarbonylated product which was tentatively assigned as naphthofuran **20**. However, a supporting correlation between the C(4)-proton and C(16)-carbon was not revealed in the HMBC spectrum given that they are four bonds removed and connected through a heteroatom.

To support the structural assignment for **20**, the decarbonylative photocyclization was performed on the simplified naphthoquinone **21** which provided naphthofuran **22** (Scheme 5). In addition to **22**, a non-decarbonylated byproduct arising from putative allylic hydrogen abstraction was formed.¹¹ Fortunately, an X-ray crystal structure of **22** was obtained, confirming the predicted carbon and oxygen connectivities which can be directly correlated to the more complex naphthofuran **20**. The yield for formation of **22** was calculated to be 61% using nitromethane (CH₃NO₂) as internal standard. However, purification by silica gel chromatography resulted in a lower isolated yield (37%) of **22** which was consistent with the isolated yield (34%) for **20**.

A mechanism for the decarbonylative photocyclization may involve a photochemical, concerted [1,5]-hydride shift of the acyl hydrogen to the vinylic carbon to afford ketene intermediate **23** (Scheme 6). Photoinduced hydride shift for *o*-vinylbenzaldehydes has been demonstrated in several studies^{14–15} and in some instances decarbonylation products have been reported.¹⁵ In this regard, decarbonylation of the derived vinyl ketene **23** may provide β-acyl alkenyl carbene intermediate **24**. Isomerization of **24** to carbene **25** would provide a suitable orientation for naphthofuran formation upon 6π-electrocyclization.¹⁶

To explore the reaction mechanism, deuterium-labelled aldehyde **26**¹¹ was prepared to study the photocyclization to naphthoquinone **27** and the possibility for deuterium incorporation at the C(8)-position (Scheme 7).¹⁷ However, photoirradiation of **26** in benzene-*d*₆ provided **22** in which **27** or deuterium-incorporation of the phenol was not observed. The half-life of **27** may be relatively short in the presence of small amounts of water through keto-enol tautomerization. The latter hypothesis was disproved upon failure to observe the reverse process - deuterium incorporation at the C(8)-position after exchange of **22** with D₂O. Furthermore, deuterium exchange was not observed when **22** was photoirradiated in a 10% solution of D₂O in anhydrous benzene.¹⁸

An alternative mechanism accounting for the deuterium-labelling studies may not involve direct transfer of deuterium to the C(8)-carbon. For example, photoexcited quinone **28** may cyclize to form biradical **29** (Scheme 8). Benzoquinones bearing an alkenyl moiety with a vinyl hydrogen have been demonstrated to undergo photocyclization to diradical

intermediates, in which a subsequent hydrogen shift yields benzofurans.¹⁹ Likewise, intramolecular abstraction of the deuterium in **29** would provide acyl radical **30** which upon decarbonylation²⁰ may afford furan intermediate **31**. Rearomatization with water would give naphthofuran **22** without deuterium incorporation.

The serendipitous discovery of the decarbonylative photocyclization represents a novel synthesis of a benzofuran-containing a highly-substituted, fused cyclohexene moiety.²¹ This motif is found in natural products (*e.g.* propolis-benzofuran B)²² in which application of this photochemical methodology may prove beneficial for total synthesis. Moreover, the methodology provides neutral conditions to synthesize the benzofuran unit without using harsh acidic or basic conditions that may compromise the integrity of functionalized cyclohexenes. Further mechanistic studies and applications of the decarbonylative photocyclization are currently in progress and will be reported in due course.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1.
Synthetic approaches to kinamycin C and FL-120B'

Scheme 1.
Intermolecular Photo-Friedel-Crafts Acylation⁷ⁱ

Scheme 2.
Proposed Intramolecular Photo-Friedel-Crafts Acylation

Scheme 3.
Synthesis of Naphthoquinone **11**

Scheme 4.
Unexpected Decarbonylative Photocyclization to **20**

X-ray crystal structure of **22****Scheme 5.**Synthesis and X-Ray Crystal Structure of **22**^aYield determined by ¹H NMR analysis using CH₃NO₂ as an internal standard.

Scheme 6.
Proposed Mechanism for Decarbonylative Photocyclization

Scheme 7.
Deuterium-Labelling Studies

Scheme 8.
Alternative Mechanism for Decarbonylative Photocyclization