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Pyridone photoelectrocyclizations to pyridophenanthrenes

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ABSTRACT

This article describes the synthesis of pyridophenanthrenes from the stereoselective electrocyclization and [1,5]-hydride shift sequences of biphenyl pyridones. The regioselectivity of the reaction of *meta*-substituted biphenyl substrates depended on the electronic environment of the substituents. That is, substrates having electron-withdrawing substituents underwent a regioselective sequence while electron-donating substituents gave mixtures of products.

As part of our program targeting the synthesis of quaternary substituted carbolines, we recently described the use of a four-step Suzuki coupling, oxidative cyclization, free-radical coupling sequence that converts bromodihydropyridone **1** into quaternary substituted carbolines like **6** (Scheme 1).[1]

In addition to its use in the sequence outlined above, we became interested in employing **1** to synthesize phenanthrene analogs, i.e. **8**, from vinyl biphenyl electrocyclization/[1,5]-hydride shift sequences from the corresponding dihydropyridones **7** (Scheme 2). We envisioned numerous applications for phenanthrene analogs including their use as precursors to structurally and biologically interesting targets like ergoline and ergoline analogs and their use as ligands/reagents/catalysts for organic synthesis.[2–4]

While dihydropyridones had not been used previously in vinyl biphenyl electrocyclization reactions, a wealth of information on related transformations exists.[5] In particular, Lewis and Zuo examined the photoinduced electrocyclization of vinyl biphenyl derivatives to give dihydrophenanthrene **10** from a tandem electrocyclization, [1,5]-hydride shift sequence.[6,7] Interestingly, Lewis and co-workers subsequently calculated an essentially barrierless transition for the reaction after excitation (see Scheme 3).[8]

In addition to determining whether dihydropyridones would participate in reactions related to Lewis' we planned to examine the effect of substituents on the regio- and stereoselectivity of the reaction. In this regard, the precedent for regioselective electrocyclization reactions is mixed. Schultz and co-workers reported that the photocyclization of *meta*-methoxy aryloxyenone **11a** was regioselective giving benzofuran **12a** as the only isolated product (Scheme 4).[9] In contrast to this result, *meta*-methyl enone **11b** and *meta*-methylester enone **11c** gave 3:1 and 2:1 mixtures of **12b** and **12c** and **13b** and **13c**, respectively. Schultz applied this reaction to the synthesis of the morphine skeleton.[10]

The effect of substitution on the electrocyclization of stilbene derivatives has also been examined. The studies that are most relevant to ours came from Mallory and Mallory where they reported that essentially 1:1 mixtures of phenanthrene isomers **15** and **16** were formed from the photocyclization/oxidation sequence of meta-CF_3, Cl, and CH_3 substituted stilbenes **14** (Scheme 5).[11]

Also worthy of mention are studies from Lewis and co-workers that demonstrated that amino pyridine **17** undergoes a regioselective tandem electrocyclization, [1,7]-hydride shift sequence that gives a mixture of **18** and **19** (Scheme 6).[12] Lewis reported that the amount of **18** was greatest when the reaction was run in the absence of oxygen and attributed this phenomenon to a reversible 6π electrocyclization reaction. That is, under anaerobic conditions the intermediate leading to **18** undergoes a relatively rapid [1,7]-hydride shift and aromatization while the intermediate leading to **19** preferentially reverts back to starting material. When the reaction was run in the presence of oxygen the equilibration was suppressed by the rapid oxidation of the regioisomeric electrocyclization products.

With the aforementioned studies in mind, we set out to examine the cyclization chemistry of dihydropyridones. A series of

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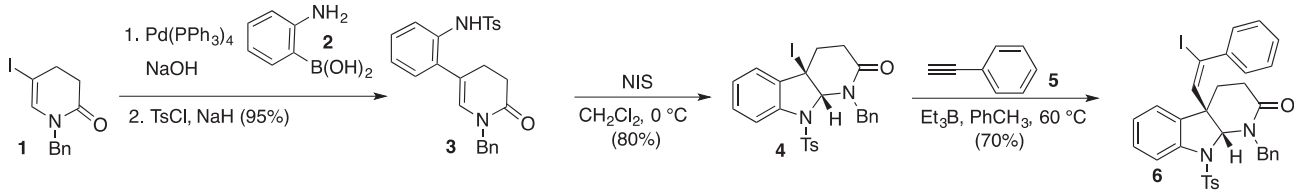
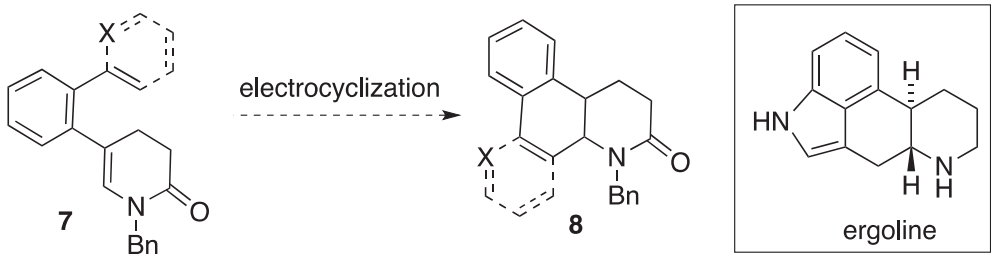
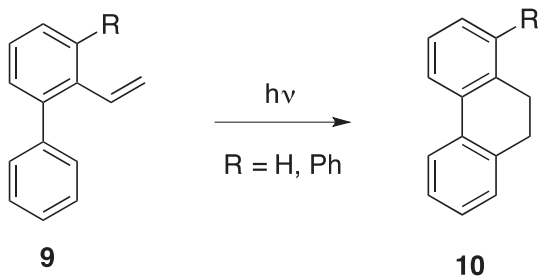


Scheme 1. Suzuki Coupling-Oxidative Cyclization Sequence to Carbolines.



Scheme 2. Proposed Electrocyclization Sequence to Dihydrophenanthrenes.

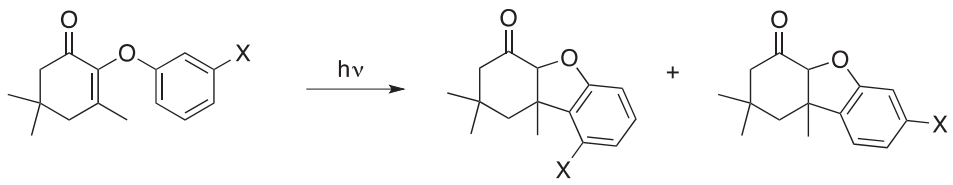


Scheme 3. Lewis and Zuo's Generation of Dihydrophenanthrenes.

substituted cyclization precursors that differed in their substitution pattern on the aromatic ring distal to the dihydropyridone were obtained from a sequential Suzuki-Miyaura coupling sequence as is outlined in Table 1.[13] We initially investigated the electrocyclization reaction of unsubstituted substrate **24** (entry 1) that came from the coupling of bromoarene **22** with boronic acid **23** (R, R" = H). Based on work from other laboratories it was not surprising that our attempts to carry out the thermal electrocyclization of **24** were unsuccessful. In contrast, piperidonephenanthrene **35** was isolated in 90% yield when **24** was subjected to 350 nm UV light. Shorter wavelength light (300 nm) gave lower yields presumably as a result of significant decomposition of starting material and/or product. As has been proposed for related reactions, we believe that the conversion to **35** is the result of a photochemically allowed conrotatory 6π electrocyclization and a subsequent thermally allowed suprafacial [1,5]-hydrogen shift from the cyclohexadiene intermediate (See Scheme 8). Substituted variants of **24** also underwent photochemical electrocyclization. The cyclization of *ortho*-methoxy biphenyl dihydropyridone **25** (entry 2) gave dihydrophenanthrene **36** in 88% yield.

In contrast to Mallory's precedent, when *meta*-substituted biphenyldihydropyridones were subjected to 350 nm UV light the regioselectivity of the cyclization was dependent on the electronic nature of the substituents. When meta-electron-withdrawing substituents (R' = $C(O)CH_3$, CF_3, NO_2) were present, ^{1}H NMR of the crude reaction mixture showed dihydrophenanthrene **A** to be the only product after photocyclization (entries 3–5). In contrast, the presence of electron-donating substituents (R' = OCH_3, F, Cl, CH_3) led to a nearly equal mixture of dihydrophenathrenes **A** and **B** (entries 6–9). The exception to this was dimethyl amino substrate **33** (entry 10) which gave a 20:1 ratio of **A:B** in 95% yield. Because the corresponding isopropyl substrate **34** gave a 4:3 ratio of **A** and **B** (entry 10) we do not believe that the selectivity of **33** was a consequence of steric interactions during the reaction.

Although more extensive studies are needed, the facial selectivity in the electrocyclization reaction can be influenced by substituents on the pyridone amine. When phenethyl and naphthethyl amide biphenyl substrates **46** and **47** were subjected to photochemical conditions we isolated dihydrophenanthrenes **48** and **49** as 3.3:1 and 6:1 mixtures of diastereomers, respectively (see Scheme 7).



11a (X = OCH_3)
11b (X = CH_3)
11c (X = CO_2CH_3)

12a (X = OCH_3): 90%[a] **13a** (X = OCH_3): ---
12b (X = CH_3): 75%[b] **13b** (X = CH_3): 25%[b]
12c (X = CO_2CH_3): 65%[b] **13c** (X = CO_2CH_3): 35%[b]
[a]isolated yield
[b]yield from ^{1}H NMR

Scheme 4. Schultz and co-workers aryloxyenone photocyclization.

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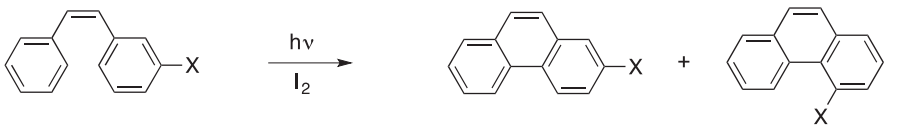
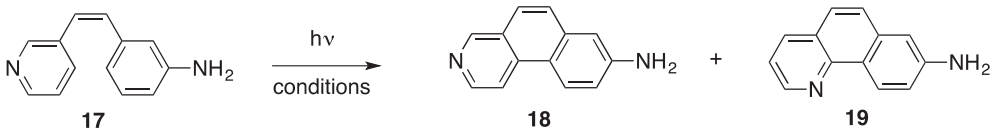


14a: R = CH_3
14b: R = CN
14c: R = Cl

15a: R = CH_3 (51%)
15b: R = CF_3 (52%)
15c: R = Cl (52%)

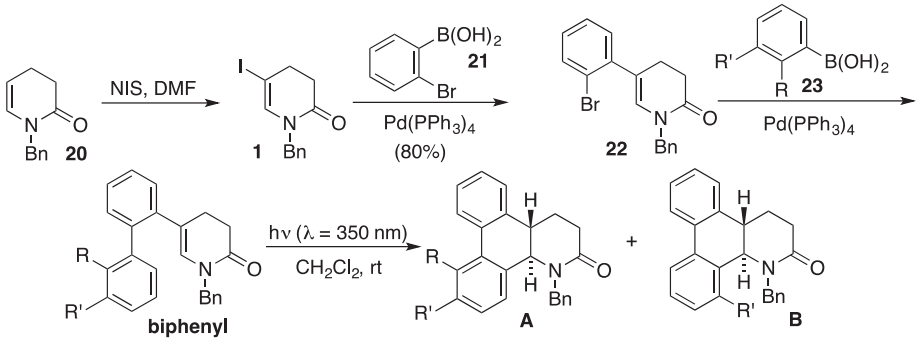
16a: R = CH_3 (49%)
16b: R = CF_3 (48%)
16c: R = Cl (48%)

Scheme 5. Mallory and Mallory's Stilbene Electrocyclization Reactions.

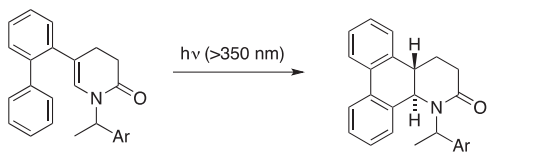


Scheme 6. Lewis and Co-Workers Regioselective Stilbene Cyclizations.

Table 1
Synthesis and Photoelectrocyclization of Dihydropyridones.



entry	R	R'	biphenyl	yield	dihydophenanthrene(s)	yield	A:B
1	H	H	**24**	89%	**35**	90%	----
2	OCH_3	H	**25**	91%	**36**	88%	----
3	H	$C(O)CH_3$	**26**	88%	**37**	70%	>95:5
4	H	CF_3	**27**	85%	**38**	88%	>95:5
5	H	NO_2	**28**	72%	**39**	72%	>95:5
6	H	OCH_3	**29**	88%	**40**	83%	11:9
7	H	F	**30**	81%	**41**	83%	1:1
8	H	Cl	**31**	80%	**42**	80%	2.3:1
9	H	CH_3	**32**	73%	**43**	70%	3:2
10	H	$N(CH_3)_2$	**33**	65%	**44**	95%	20:1
11	H	$CH(CH_3)_2$	**34**	82%	**45**	86%	4:3



46: Ar = Ph
47: Ar = Naphthyl

48: Ar = Ph, d.r. = 3.3:1
49: Ar = Naphthyl, d.r. = 6:1

Scheme 7. Chiral Amide Cyclizations.

The presumed mechanism for dihydrophenanthrene formation is shown in Scheme 8. In an attempt to explain the reactivity trends for the meta-substituted substrates we proposed two possibilities for the selective cyclization reactions: (a) a reversible electrocyclization for **53** and a relatively rapid [1,5]-hydride shift for **52** (R' = electron-withdrawing group) or[14]; (b) a shorter excited state lifetime for **51** when compared to **50** (R' = electron-withdrawing group). To be accurate this argument requires that when R′ is an electron-donating groups that **52** and **53** were generated in nearly equal amounts and that they underwent [1,5]-hydride shifts at equivalent rates. It also requires that when R′ is an electron-donating groups that both **50** and **51** undergo photoinduced electrocyclization. These suppositions were testable; if correct the substrates having electron-withdrawing substituents should react

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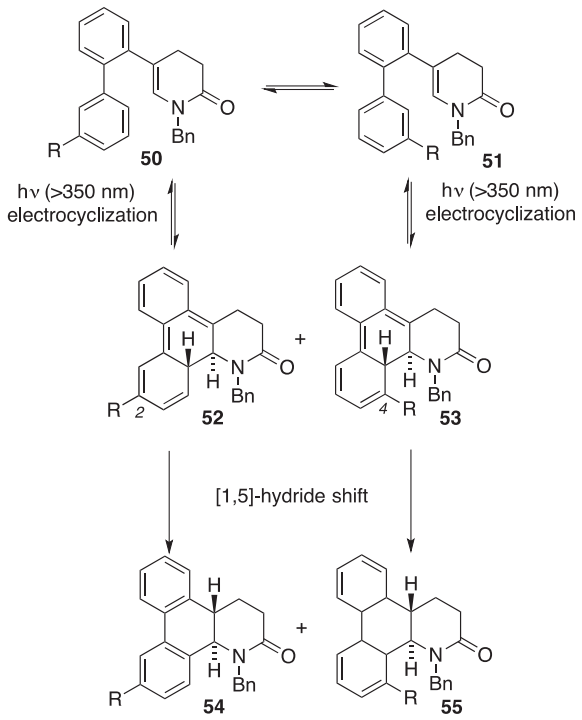

Scheme 8. Proposed Electrocyclization Mechanism.

more slowly and show a lower quantum yield than the substrates having electron-donating substituents. To test this we examined **27** (R' = CF_3) and **30** (R' = CH_3) and found that the quantum yields were exactly the opposite of our prediction: the quantum yield for **27** was 6.3% while that for **30** was 4.4%. Although we do not currently understand the nature of the selectivity for this reaction, our data suggests that it probably is not a result of a reversible electrocyclization or a longer lived excited state. While a number of other mechanistic possibilities exist, e.g. an increased barrier for the retro-electrocyclization for electron-withdrawing substrates from conformer **52** relative to **53**, thus far our attempts at calculating the relative energetics of the intermediates in this process using DFT have not been informative.

Conclusion

This manuscript has demonstrated that readily available biphenyl dihydropyridones are effective precursors to substituted dihydrophenanthrenes. Our investigations have shown a regioselective electrocyclization with biphenyl precursors having an electron-withdrawing substituent at the meta-position but a mixture of regioisomers with electron-donating groups. We will continue to study this reaction and to utilize the products in complex molecule synthesis.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.tet.2017.06.062.

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