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An Intra/Intermolecular Suzuki Sequence to Benzopyridyloxepines Containing Geometrically Pure Exocyclic Tetrasubstituted Alkenes

Matthew W. Carson,* Matthew W. Giese, and Michael J. Coghlan

Discovery Chemistry Research and Technology, Lilly Research Laboratories, Eli Lilly and Company, Indianapolis, Indiana 46285

carsonma@lilly.com

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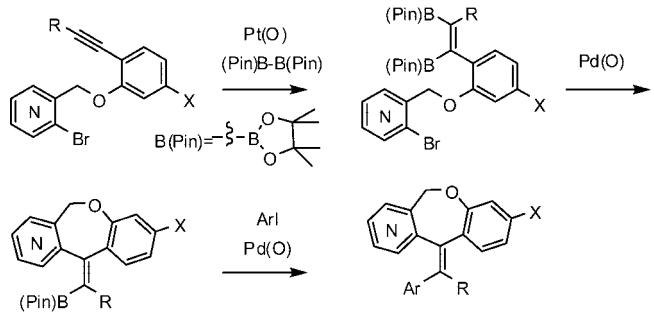
ABSTRACT



A route to enable the preparation of 5-benzylidenyl-benzopyridyloxepine analogues was developed to continue our research in the field of nuclear hormone receptor modulators. The key steps are1) a syn-stereoselective diboration of a tethered aryl alkyne; 2) an intramolecular Suzuki cross-coupling reaction, which forms in a stereo- and regiocontrolled fashion, the 5-exoalkylidenyl 7-membered ring imbedded within the core of the scaffold and; 3) an intermolecular Suzuki to furnish the final tetra-substituted olefinic benzopyridyloxepines.

The highly substituted olefin motif is found in a number of biologically active series including the triphenylethylenes, most notably represented by the SERM tamoxifen,[1] and Lilly's dibenzoxepine nuclear hormone receptor (NHR) modulators.[2] Recently there has been impressive progress on the regio- and stereoselective syntheses of tetra-substituted alkenes.[3] At Lilly, we developed a one-pot procedure to the dibenzoxepines, which contain a tri- or tetrasubstituted exobenzylidene moiety, utilizing an intramolecular carbometalation of an alkyne followed by cross-coupling with a boronic acid (Heck-Suzuki).[4,5] In this paper, we report on a complimentary route involving a stereospecific dimetalation of an alkyne followed by regioselective sequential intra/intermolecular cross couplings, which allowed us to synthesize a series of benzopyridyloxepines containing stereodefined tetra-substituted exocyclic alkenes.

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(5) (a) For previous examples of intramolecular addition of arylpalladium intermediates to tethered alkynes followed by cross coupling to give exocyclic tetrasubstituted alkenes, see Burns, B.; Grigg, R.; Sridharan, V.; Stevenson, P.; Sukirthalingam, S.; Worakum, T *Tetrahedron Lett.* **1989**, *30*, 1135. (b) Zhang, Y.; Negishi, E-I *J. Am. Chem. Soc.* **1989**, *111*, 3454. (c) Negishi, E-I; Noda, Y.; Lamaty, F.; Vawter, E. J. *Tetrahedron Lett.* **1990**, *31*, 4393. (d) Wang, R-T; Chou, F-L; Luo, F-T *J. Org. Chem.* **1990**, *55*, 4846. (e) Cheung, W. S.; Patch, R.; Player, M. R. *J. Org. Chem.* **2005**, *70*, 3741. (f) Bour, C.; Blond, G.; Salem, B.; Suffert, J. *Tetrahedron* **2006**, *62*, 10567, and references therein.

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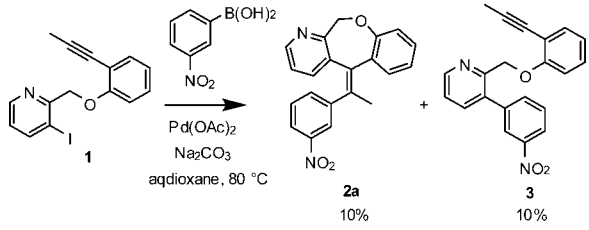
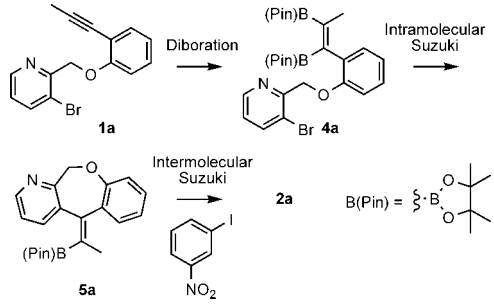
To continue the study of the dibenzoxepine structure−activity relationship (SAR) as NHR modulators, it was our initial desire to apply a route utilizing the key Heck-Suzuki step for the preparation of pyridine analogues. However, to our disappointment, under the ligandless conditions optimal for the phenyl analogues, the palladium-catalyzed reaction of alkyne-tethered aryl iodide **1** in the presence of 3-nitrophenyl boronic acid afforded a low yield of desired pyridyloxepine **2a**(10%) along with direct coupling product **3** (Scheme 1). Based upon mass balance after column chromatography, apparent oligomerization was the main outcome of the reaction.[6] To circumvent the issue of a low yielding cyclization step for the preparation of NHR modulator targets, we then envisioned a route highlighted by an intramolecular Suzuki coupling to synthesize the seven-membered ring containing the geometrically pure exocyclic alkene. A similar approach involving an intramolecular Stille coupling to trisubstituted exocyclic alkenes of benzopyridyloxepines was reported by Finch and co-workers.[7] Scheme 2 illustrates the new sequence commencing with a platinum-catalyzed syn diboration of tethered alkynyl aryl pyridyl bromide **1a**with bis(pinacolato)diboron to cleanly give bis vinylpinacol boronic ester **4a**, which was used in the next step without further purification.[8] It should be noted that the use of bromopyridine is required as an attempted diboration of the aryl iodide **1** resulted in recovery of starting material due to the likely C−I insertion of the platinum. With the bis boronic ester **4a** in hand, we investigated conditions for the intramolecular Suzuki cross coupling to give vinyl boronic ester **5a** (Scheme 2). Optimization of this step revealed that dilute (0.01 M **4a** in anhydrous dioxane) conditions, using $PdCl_2(dppf)\cdot CH_2Cl_2$ and K_3PO_4, delivered the desired vinyl boronic ester **5a**. To complete the synthesis of **2a**, we were faced with the challenge of coupling a bulky boronic ester with an aryl iodide. Prior art reveals that cross coupling of aryl halides with sterically hindered boronic esters under standard Suzuki conditions (e.g., $Pd(PPh_3)_4$, aqueous weak base, polar aprotic solvents, 80 °C) results in slow reaction times and low yields.[9] However, both Armstrong and Begtrup have shown that one could cross couple in a crowded environment similar to **5a** to afford tamoxifen derivatives by utilizing the electron rich 3,5-dimethoxyphenol (3,5-DMP) as an additive. Thus, under these conditions ($Pd(PPh_3)_4$, aqueous KOH, 3,5-DMP, dioxane, 80 °C), the reaction of vinyl boronic ester **5a** (Scheme 2) with 3-iodonitrobenzene gave 5-benzylidenyl- benzopyridyloxepine **2a** as a geometrically pure isomer in 45% isolated yield from tethered alkynyl aryl pyridyl bromide **1a**.[11]

Upon optimization of the intra/intermolecular Suzuki route for the preparation of pyridyloxepine **2a**, we wanted to expand the structural diversity of this series. In the Heck-Suzuki route, **1** was prepared by conducting a Mitsunobu reaction between iodopyridyl methanol **6** and alkynyl phenol **7**, an intermediate that required three steps to prepare from

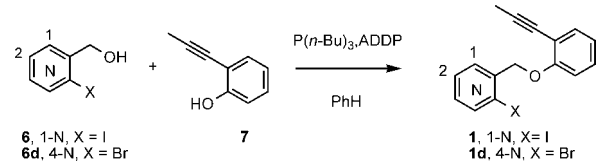
Scheme 1



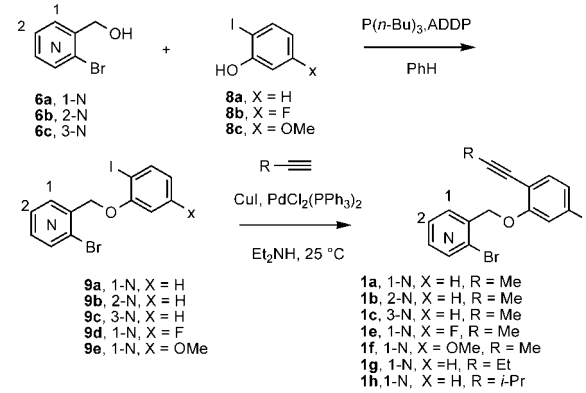
Scheme 2



Scheme 3

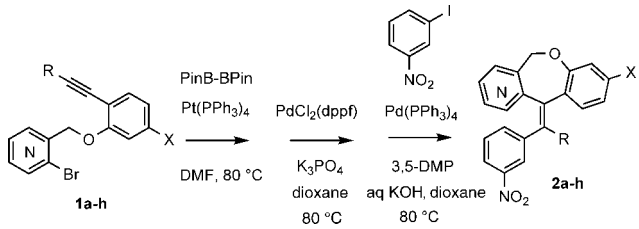


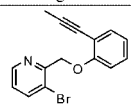
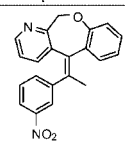
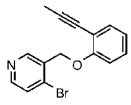
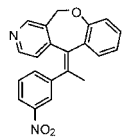
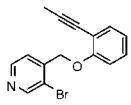
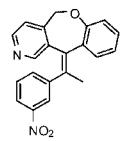
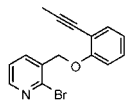
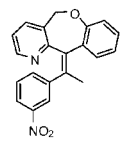
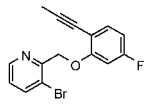
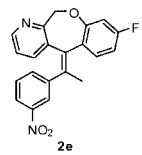
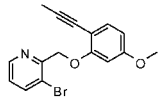
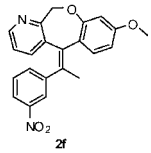
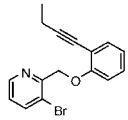
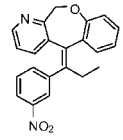
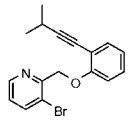
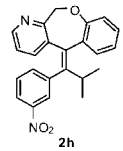
Scheme 4



(6) This result is reminiscent of our previous findings in which we conducted exploratory Heck-Suzuki reactions of phenyl analogues in the presence of a ligand. The fact that the pyridine resulted in much lower yields than the phenyl analogue under the ligandless conditions suggests that another molecule of **1**or resultant intermediates function as a ligand. In other words, the complexation of the pyridyl nitrogen to organopalladium intermediates disfavors the desired intramolecular Heck-Suzuki compared to side reactions such as 1) direct coupling to give **3** and; 2) intermolecular Heck reaction leading to high molecular weight products.

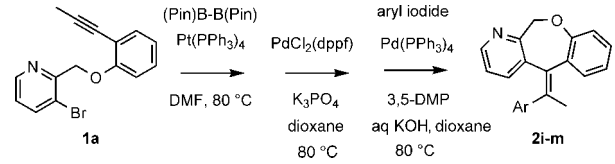
Table 1. Synthesis of Benzopyridyloxepines **2a**−**h** from Tethered Alkynyl Aryloxy Pyridyl Bromides **1a**−**h**[a]

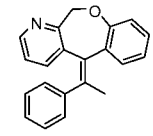
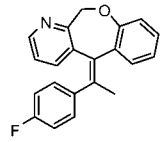
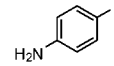
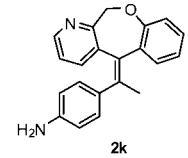
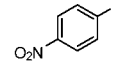
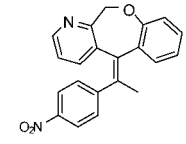
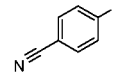
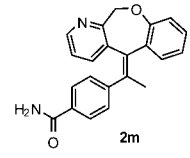


entry	starting material	product	% yield[b]
1	 **1a**	 **2a**	45
2	 **1b**	 **2b**	32
3	 **1c**	 **2c**	30
4	 **1d**	 **2d**	0
5	 **1e**	 **2e**	40
6	 **1f**	 **2f**	38
7	 **1g**	 **2g**	45
8	 **1h**	 **2h**	45

[a] Diboration: 1.1 equiv of bis(pinacolato)diboron and 8 mol % of $Pt(PPh_3)_4$ in DMF (0.1 M) at 80 °C for 24 h. Intramolecular Suzuki: 10 mol % $PdCl_2(dppf)\cdot CH_2Cl_2$ and 3 equiv of K_3PO_4 in dioxane (0.01 M) at 80 °C for 24 h. Intermolecular Suzuki: 1.5 equiv of 3-iodonitrobenzene, 5 mol % of $Pd(PPh_3)_4$, 6 M aqueous KOH (0.4 M), and 5 equiv of 3,5-dimethoxyphenol in dioxane (0.15 M) at 80 °C for 18 h. [b] Isolated yields (**1** to **2**, three steps) after column chromatography.

Table 2. Synthesis of Benzopyridyloxepine Derivatives **2i**−**m** from **1a**[a]



entry	aryl iodide	product	% yield[b]
1		 **2i**	36
2		 **2j**	42
3		 **2k**	31
4		 **E-2l** + **Z-2l**	37[c]
5		 **2m**	22

[a] Diboration: 1.1 equiv of bis(pinacolato)diboron and 8 mol % of $Pt(PPh_3)_4$ in DMF (0.1 M) at 80 °C for 24 h. Intramolecular Suzuki: 10 mol % $PdCl_2(dppf)\cdot CH_2Cl_2$ and 3 equiv of K_3PO_4 in dioxane (0.01 M) at 80 °C for 24 h. Intermolecular Suzuki: 1.5 equiv of aryl iodide, 5 mol % of $Pd(PPh_3)_4$, 6 M aqueous KOH (0.4 M), and 5 equiv of 3,5-dimethoxyphenol in dioxane (0.15 M) at 80 °C for 18 h. [b] Isolated yields (**1** to **2**, three steps) after column chromatography. [c] (*E*)-**2l** and (*Z*)-**2l** were isolated as single isomers via column chromatography in 21% and 16% yield, respectively.

commercially available iodophenol (Scheme 3). However, the intra/intermolecular Suzuki route allowed us to target bromopyidines as intermediates which shortened the syntheses and allowed for later structural divergence. As shown in Scheme 4, Mitsunobu reaction between bromopyridyl methanols **6a**−**c** and iodophenols **8a**−**c** afforded bromobenzyl iodoaryl ethers **9a**−**e** which undergo regioselective Sonogashira reactions at the C−I locus to give alkynes **1a-h**.

It should be noted that bromopyridines with reactive C−Br bonds (see **6d**) were outside the scope of the selective Sonogashira reaction, therefore Mitsunobu between **6d** and

7 using tri*n*-butylphine and 1,1′-(azodicarbonyl)-dipiperidine (ADDP)afforded the desired bromopyridine **1d** (Scheme 3).

With intermediates **1a**−**h** in hand, we applied the intra/intermolecular Suzuki technology to prepare compounds for the SAR studies. The methodology worked in moderate yields, calculated at the end of the three-step diboration, intra/intermolecular coupling sequence, to afford the 1,2, and 3-pyridyl isomers **2a**−**c** (Table 1, entries 1−3). To our disappointment, the sequence failed in the case of the 4-pyridyl analogue **1d** (Table 1, entry 4). Both the fluoro and methoxy substituted examples (Table 1, entries 5−6) resulted in similar yields suggesting a lack of electronic effect in the alkynyl phenyl ring. We successfully expanded the series to propylidenyl **2g** and isobutylidenyl **2h** analogues as well (Table 1, entries 7−8) resulting in yields similar to the ethylidenyl analogue **2a** (Table 1, entry 1).

The intra/intermolecular Suzuki route allowed for access to substituted aryl rings at the vinyl position with late divergence in the synthesis. Analogues phenyl **2i**, *p*-fluorophenyl **2j**, and *p*-aminophenyl **2k** were prepared in moderate yields (Table 2, entries 1−3). However, the conditions of the coupling reaction in some cases gave undesired results. For example, unlike the *m*-NO_2 analogue **2a** (Table 1, entry 1), the coupling of **5a** with 4-iodonitrobenzene afforded both the E- and Z- isomers of **2l** (Table 2, entry 4). We attempted to synthesize the *p*-cyanophenyl derivative, but could only isolate the primary amide **2m** in low yield (Table 2, entry 5). Despite the aforementioned limits, one could conclude that the three-step diboration, inter/intramolecular Suzuki cross coupling methodology has the potential to be a viable alternative to the intramolecular carbometalation for the stereoselective preparation of tetra-substituted exocyclic alkenes.

In summary, a diboration, inter/intramolecular Suzuki cross-coupling sequence enabled the synthesis of pyridylbenzoxepines with a highly substituted stereodefined olefinic moeity at the five-position. Highlights of the sequence include (1) an intramolecular Suzuki cross coupling to give a seven-membered ring and (2) an example of an intermolecular Suzuki in a sterically congested environment. The route allowed us to synthesize a diverse set of targets for our NHR program, and it serves as complimentary route to the Heck−Suzuki cascade. In future work, we will expand the scope of this technology to biologically active exocyclic alkenes outside the scope of dibenzoxepines.

Supporting Information Available: Detailed experimental procedures and NMR of products. This material is available free of charge via the Internet at http://pubs.acs.org.

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(11) Due to instability, boronic acid intermediates **4a** and **5a** as well as analogous intermediates (*vide*infra) were difficult to purify, therefore the material was used in subsequent steps in crude form and the yield was calculated over three steps.