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Serendipitous Discovery of a New Method for the Catalytic Synthesis of Indole-fused Benzazepanes

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ABSTRACT
We report here on our investigations into the application of 1,5-hydride transfer cyclization mechanisms to the synthesis of 2,3-disubstituted benzofurans and indoles from alkyne substrates. We found that PtI4 in MeCN at 120 °C was indeed capable of activating the alkyne, however, the expected 2,3-disubstituted indole product was not observed. Instead we isolated an indolyl-3-benzazepane via an unexpected intramolecular Steven’s rearrangement/ring expansion. While this transformation has been previously reported, our method may prove to have increased substrate scope and more practical reaction conditions. Further studies are underway to optimize the reaction conditions and to fully explore the scope and mechanism of the transformation.

INTRODUCTION
Hydrogen-carbon bonds are among the most common bonds in organic chemistry, but they can only be converted by using harsh reaction conditions. While hydrocarbons, molecules composed primarily of hydrogen and carbon are fairly unreactive under mild reaction conditions, reactions that enable the conversion of C–H bonds to C–C, C–N, and C–O bonds are incredibly valuable.1 Such reactions allow for the construction of complex value-added molecules from simple abundant feedstocks. Throughout the past 30 years, C–H bond functionalization has been a rapidly growing field.2 Novel synthetic methods for enhancing molecular complexities have been explored, but this area of research is far from complete.3 The studies described in this report focus on the development of new methods for the synthesis of aromatic heterocycles, in particular indoles and benzofurans, which are common motifs in biologically active compounds (Figure 1).

We sought to construct the 5-membered ring of these heterocycles via a novel hydride-transfer cyclization that would result in a 2,3-disubstituted indole or benzofuran through a 1,5 hydride shift cyclization cascade (Figure 2). This

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method would streamline the process of synthesis, and potentially minimize the number of consecutive chemical reactions to achieve the necessary architecture of molecules of biological and medicinal significance. Through the hydride-transfer cyclization mechanism an activated C–H bond (I, C–H bond highlighted in red) can be functionalized using a metal catalyst. Through the activation of a polarizable functional group, such as an alkyne, by a Lewis acid an intramolecular 1,5-hydride-transfer can be triggered, resulting in cleavage of the C–H bond (I, Figure 2). The newly generated carbocation is then attacked by an internal nucleophile, here the metal-alkenyl species (II), forming a new C-C bond while simultaneously forming a new ring. Alkynes have been used as hydride-acceptors in similar transformations, which provide precedence for this theoretical method of C–H bond functionalization. However, previous studies did not examine aryl-alkynes as proposed above, which would provide novel methods of synthesizing functionalized molecules with indole or benzofuran cores.

Figure 1: Indole as a Privileged Structure in Medicinally Active Pharmaceuticals. This figure shows representative indole-containing drugs including anti-cancer, anti-inflammatory, and anti-psychotic compounds.

Figure 2: C–H Bond Functionalization via Hydride-Transfer Cyclization Cascade of Aryl Alkynes. This figure shows the functionalization of a C-H bond and the 1,5 hydride shift mechanism.
Methods

General Considerations

Nuclear Magnetic Resonance (NMR) spectra were recorded at room temperature on a Bruker 300 MHz Fourier transform spectrometer. $^1$H NMR spectra recorded in CDCl$_3$ were referenced to tetramethylsilane (TMS, 0.00 ppm). Mass spectrometry (MS) spectra were recorded with an HP 6890 series gas chromatography (GC) system and an Agilent Technologies 5975 mass spectrometer. Mass spectra were recorded in DCM using a low-resolution instrument (LRMS). Flash column chromatography was conducted on silica gel using diethyl ether and hexanes. All reactions were monitored by TLC analysis using ethyl acetate/hexanes and/or diethyl ether/hexanes mixtures as the eluent, and visualization was performed using UV light followed by a potassium permanganate stain and/or a ninhydrin stain. Experimental spectra can be seen in the Appendix (Figures A1 – A6).

Synthesis of ether $5$ (Method 1):

2-iodophenol (1.1012 g, 4.9 mmol, 1 equiv.) was reacted with benzyl bromide (0.624 mL, 5.2 mmol, 1.05 eq) and K$_2$CO$_3$ (2.0731 g, 15 mmol, 3 equiv.) in MeCN under reflux according to a known procedure.$^5$ Following an aqueous workup with ethyl acetate extraction and water washes, the organic layer was dried with MgSO$_4$ and dried using a rotary evaporator with a 69% yield based off the crude NMR spectrum, which showed pure product. $^1$H-NMR (CDCl$_3$, 300 MHz) $\delta$ 5.15 (s, 2H), 6.72 (td, 1H), 6.85 (dd, 1H), 7.25–7.75 (m, 6H), and 7.81 (dd, 1H).

Following a known procedure, TMS-protected alkyne $6$ was prepared from $7$ (1.0719 g, 3.5 mmol). The aryl iodide ($7$) was mixed with PdCl$_2$(PPh$_3$)$_2$ (61 mg, 0.09 mmol, 0.025 equiv.) and Cul (16.5 mg, 0.09 mmol, 0.025 equiv. with triethylamine as the solvent.$^6$ Next, ethynyltrimethylsilane (0.73 mL, 5.2 mmol, 1.5 equiv.) was added to the reaction mixture. Using thin layer chromatography, the starting material was determined to be completely consumed, although there were many impurities present. The resulting reaction mixture was dried using a rotary evaporator and subsequent purification was done. Purification was performed by column chromatography using 2.5% diethyl ether and hexanes. After purification, the product ($6$) was isolated with a 26% yield. $^1$H-NMR (CDCl$_3$, 300 MHz) $\delta$ 5.15 (s, 2H), 6.72 (td, 1H), 6.85 (dd, 1H), 7.25–7.75 (m, 6H), and 7.81 (dd, 1H).
MHz) $\delta$ 0.26 (s, 16H), 0.52 (s, 2H), 6.91 (s, 3H), and 7.26-7.54 (m, 16H). LRMS m/z calc. for $\text{C}_{18}\text{H}_{20}\text{OSi} [\text{M}^+ ]$ 280.43, found 280.

Compound 6 was then deprotected using 0.2M tetrabutylammonium fluoride (TBAF) in tetrahydrofuran (THF, 0.9 mL, 1.1 equiv.) and an ice bath to afford the ether substrate 5 after aqueous work up. Ethyl acetate was used to extract the product after washing with water, drying with MgSO$_4$, and drying using a rotary evaporator. The percent yield was determined to be 30%. $^1$H-NMR (CDCl$_3$, 300 MHz) $\delta$ 1.28 (t, 1H), 3.36 (s, 1H), 5.23 (s, 2H), 6.95 (t, 3H), and 7.28-7.54 (m, 12H). LRMS m/z calc. for $\text{C}_{15}\text{H}_{12}\text{O}$ [M$^+$] 208.26, found 207.

The overall scheme for method 1 is shown in Figure 4.

**Synthesis of ether 5 (Method 2):**

![Figure 5: Ether 5 Synthesis (Method 2). The molecules synthesized and yield are shown. The yield of ether 5 was not determined (n.d.) due to impurities.](image)

Salicyladehyde (1.07 mL, 10 mmol, 1 equiv.) was reacted with benzyl bromide (1.25 mL, 10 mmol, 1.05 equiv.) and K$_2$CO$_3$ (4.1463 g, 30 mmol, 3 equiv.) in MeCN (0.3 M) under reflux according to a known procedure. Following an aqueous workup with ethyl acetate extraction and water washes, the organic layer was dried with MgSO$_4$ and rotovaped to dryness with a 12% yield based off the crude NMR, which showed pure product. $^1$H-NMR (CDCl$_3$, 300 MHz) $\delta$ 5.20 (s, 2H), 7.05 (d, 2H), 7.26-7.43 (m, 8H), 7.85 (t, 1H), and 10.57 (s, 1H).

A Gilbert-Seyferth homologation was done by generating 1-diazo-2-oxopropylphosphonate in-situ by reacting dimethyl-2-oxopropylphosphosphate (199 mg 1.2 mmol, 1.2 equiv.) and H$_2$SO$_4$-ImSO$_2$N$_3$ (353 mg 1.3 mmol, 1 equiv.) in 0.1 M MeCN and K$_2$CO$_3$ (622 mg, 4.5 mmol, 4.5 equiv.). Substrate 4 was subjected to the reaction mixture in 0.1 M MeOH, yielding terminal alkyne 5 after 15 hours reaction time at room temperature. The percent yield of this reaction was not determined due to unresolvable impurities following column chromatography using 2.5% diethyl ether and hexanes, although synthesis was confirmed by NMR and GC-MS data. $^1$H-NMR (CDCl$_3$, 300 MHz) $\delta$ 3.31 (s, 1H), 5.19 (s, 2H), 6.89 (q, 2H), 7.26-7.45 (m, 10H). LRMS m/z calc. for $\text{C}_{15}\text{H}_{12}\text{O}$ [M$^+$] 208.26, found 207, 354 (impurity). The overall scheme for method 2 is shown in Figure 5.

**Synthesis of amine 9 (method 3):**

![Figure 6: Amine 9 Synthesis. The molecules synthesized and the two-step yield are shown.](image)

2-fluorobenzaldehyde (3.14 mL, 30 mmol, 1 equiv.) was reacted with 1,2,3,4-tetrahydroisoquinoline (3.76 mL, 30 mmol, 1 equiv.) and K$_2$CO$_3$ (4.9734 g, 36 mmol, 1.2 equiv.) in 0.5 M DMF under reflux. Following workup including washing with water and brine, substrate 10 was extracted using ethyl acetate. Crude $^1$H NMR showed pure product, thus the subsequent reaction immediately followed. $^1$H-NMR (CDCl$_3$, 300 MHz) $\delta$ 3.05 (t, 2H), 3.46 (t, 2H), 4.34 (s, 2H), 7.12 - 7.26 (m, 10H), 7.52 (m, 1H), 7.84 (d, 1H), and 10.33 (s, 1H).

A Gilbert-Seyferth homologation was done by generating 1-diazo-2-oxopropylphosphonate in-situ by reacting dimethyl-2-oxopropylphosphate

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(1.1 mL, 1.2 mmol, 7.7 equiv.) and H$_2$SO$_4$-ImSO$_2$N$_3$ (2.2566 g, 8.3 mmol, 1 equiv.) in 0.1 M MeCN and K$_2$CO$_3$ (622 mg, 4.5 mmol, 4.5 equiv.). Substrate 10 was subjected to the reaction mixture in 0.1 M MeOH, yielding terminal alkyne 9 after 15 hours reaction time at room temperature. This reaction mixture was rotovaped and column chromatography immediately done using 5% ethyl acetate and hexanes. There was a 54% yield of substrate 9. 

1H-NMR (CDCl$_3$, 300 MHz) $\delta$ 3.02 (t, 2H), 3.39 (s, 1H), 3.60 (t, 2H), 4.36 (s, 2H), 6.93-7.29 (m, 7H), and 7.49 (d, 1H). LRMS $m/z$ calc. for C$_{17}$H$_{15}$N $[M +]$ 233.12, found 232. The overall scheme for method 3 is shown in Figure 6.

**Synthesis of indolyl-3-benzazepane 13:**

![Figure 7: Catalytic Synthesis of the Indolyl-benzazepane 13 from Aryl-alkyne 9. This figure shows the conversion from a terminal alkyne into an alkene forming a polycyclic ring. Platinum tetraiodide in acetonitrile at 120 ºC was used in this transformation. The percent yield was 12%.](image)

Substrate 9 (23 mg, 0.1 mmol, 1 equiv.) was dissolved in MeCN (2 mL, 0.05 M), followed by the addition of PtI$_4$ (3.5 mg, 0.005 mmol, 5 mol%). There was a color change from pale yellow to a darker brown. Upon consumption of the starting material as determined by TLC (silica, 2.5 % diethyl ether/hexanes) the reaction mixture was rotovaped and purified via column chromatography (silica gel, from 1-2% diethyl ether/hexanes) with a 12% yield of product 13. 1H-NMR (CDCl$_3$, 300 MHz) $\delta$ 3.41 (t, 2H), 4.25 (s, 2H), 4.32 (t, 2H), 6.31 (s, 1H), 7.06-7.27 (m, 7H), and 7.56 (d, 1H). LRMS $m/z$ calc. for C$_{17}$H$_{15}$N $[M +]$ 233.31, found 233. The overall scheme for the synthesis of compound 14 is shown in Figure 7.

**RESULTS**

With the lead substrates in hand, potential hydride-transfer cyclization reactions were examined. Initial studies began with alkynyl ether 5. Given the precedence for Pt salts to activate alkenes towards nucleophilic attack, including intramolecular hydride-transfer, we began with an established protocol of PtI$_4$ (5 mol%) at 0.05 M in MeCN (acetoniitrile) at 100 ºC. The 1H NMR of the crude reaction mixture indicated complete decomposition of the starting material. The following attempt was done at 80 ºC and decomposition was prevented, but again no product was observed in the 1H NMR spectrum.

We next shifted our attention to substrate 9. The tetrahydroisoquinoline motif has been shown to be an effective hydride-transfer partner in a variety of reactions. As such, this substrate was designed be a strong hydride donor in the presence of the alkyne. Subjecting substrate 9 to PtI$_4$ (5 mol%) at 0.05 M in MeCN at 120 ºC did lead to formation of a new compound as determined by thin-layer chromatography. The 1H NMR of the crude reaction mixture confirmed that a product formed, although not the intended cyclized product. The compound was isolated via column chromatography and determined to be the indolyl-benzazepane 13 (7). While the yield of 13 was low, 12%, the reaction ran to complete conversion, but with some decomposition occurring. In addition, the 1H NMR of the crude mixture was reasonably pure, suggesting a modification of the reaction conditions might afford the target in higher yield. Experiments at 80 ºC and 100 ºC were also done, but failed in the conversion into indolyl-benzazepane 13. Thus, higher temperatures were required, but optimization studies must still be done.

**DISCUSSION**

Figure 8 shows the proposed formation of 13 from 9. The proposed formation of this product begins, with activation of the alkyne by the Lewis acid PtI$_4$, which undergoes intramolecular hydride-transfer by the tertiary nitrogen, rather than hydride transfer, to form the quaternary ammonium species (I). This intermediate then undergoes a 1,2-Stevens rearrangement resulting in a ring expansion to form the benzazapane (II). The platinum-carbenoid that forms could undergo several processes, which may prove to be distinguishable by 1H NMR in future studies.
At this stage a 1,2-hydride-shift is proposed, generating III, followed by π-bond formation to yield 13 and regeneration of the platinum catalyst.

This transformation has been reported in the literature employing catalytic W(CO)₆ (10 mol %).¹² However, this method required photoirradiation to generate the reactive tungsten-centered catalyst. Attempts to affect the transformation without the use of light required a super-stoichiometric amount of W(CO)₆ (300 mol %), and only afforded the product in 14% yield. While the conversion of 9 to 13 by PtI₄ also proceeded in low yield, the yield may approach a more practical value with further optimization of the reaction conditions. Moreover, none of the successful substrates previously reported contained a terminal alkyne as we have employed here. The authors make no mention of the reactivity of terminal alkynes in their study. Thus, our system may prove to compliment the tungsten-catalyzed cyclization of internal alkynes and open new avenues for complex heterocycle synthesis.

**Conclusion**

We have reported the serendipitous discovery of a new method for the synthesis of an indolyl-benzazepane from a terminal alkynyl-amine. This method, while in the preliminary stage of investigation, has significant potential to provide access to highly functionalized nitrogen heterocycles. We are currently investigating alternative catalyst systems, and deuterium labeling experiments in order to further elucidate the mechanism of the transformation. Supplemental spectra for the molecules synthesized can be seen in the Spectra Appendices (Figures A1-A6).

**Figure 8:** Proposed rationale for the Formation of 13. This shows the intramolecular ring expansion mechanism that transformes an aryl alkyne into the indolyl benzazepane.

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**AUTHOR CONTRIBUTIONS**

P.V. designed the experiment and served as the faculty advisor throughout this process. E.G. ran the experiment, collected, and analyzed spectroscopic data. E.G. wrote the paper and P.V. provided subsequent revisions.

**REFERENCES**


Figure A1: $^1$H NMR Spectrum of Molecule 5.

*Note for all spectra: peaks at 2.0 ppm and lower are various impurities and solvent peaks unrelated to the molecule.
Figure A2: $^1$H NMR Spectrum of Molecule 9.
Figure A3: $^1$H NMR Spectrum of Molecule 13.
Figure A4: $^1$H-$^1$H COSY NMR Spectrum of Molecule 13 showing cross-peaks between protons a and b.
Figure A5: GC-MS Spectrum of Molecule 9.
Figure A6: GC-MS Spectrum of Molecule 13.