Brønsted Acid Catalyzed Intramolecular Friedel-Crafts Addition of Tertiary Allylic Alcohols to Indoles

Bryan H. Wakefield¹, Romie Barnes², Traeannah Brown³, Ashley M. Jones⁴, Victoria A. Knotts¹, Christina Martinetti⁵

¹Coastal Carolina University, ²Prisma Health Richland Hospital, ³Medical University of South Carolina, ⁴Northeast Ohio Medical University, ⁵Syracuse University School of Law

An intermolecular Friedel-Crafts alkylation of indole and tertiary allylic alcohols has been developed. The allylic alcohols were synthesized using a two-step procedure, then exposure of these alcohols to diphenyl phosphate facilitated the desired annulation reaction. This reaction tolerated a variety of indole substitutions to yield 1H,2H,3H,4H-pyrido[1,2-a]indoles.

Introduction

Due to their importance in natural products and pharmaceuticals,¹⁴ the reactivity of indole and indole-containing compounds is frequently studied.¹⁻¹² In particular, indoles readily undergo electrophilic aromatic substitution reactions. The electrophiles used in these reactions can be generated from many different stable precursors, including allylic alcohols.¹³⁻¹⁷ Recent reports have shown that allylic alcohols readily undergo Friedel-Crafts reactions with indoles in the presence of catalytic amounts of InCl₃, InBr₃, FeCl₃, AuCl₃ or CsF·B(OH)₂.¹³⁻¹⁷ While Brønsted acids have been shown to be effective catalysts for this transformation and others,¹⁸⁻¹⁹ the use of diphenyl phosphoric acid as a catalyst has not been reported.²⁰⁻²⁶ Furthermore, these examples focus on intermolecular reactions though there is one example of an intramolecular reaction.²⁷ We sought to develop a method for the synthesis of 1H,2H,3H,4H-pyrido[1,2-a]indoles and related structural motifs which could be used in the synthesis of natural products, such as flinderoles A-C, and their analogues (Figure 1).²⁸⁻³⁰ This could be accomplished by tethering the allylic alcohol to the indole nitrogen and promoting the electrophilic addition at the C-2 position. Herein, we report diphenyl phosphate-catalyzed intramolecular Friedel-Crafts reactions of indoles with tertiary allylic alcohols.

Chemistry

The allylic alcohols required for this study were synthesized in two steps (Scheme 1). First, treatment of indoles with different substituents with KOH and 5-bromo-1-pentene provided the N-alkylation product (n = 2) in moderate to good yield (Table 1, Entries 1-10).³¹⁻³⁴ The chain length could be changed to n = 1 or n = 3 by using 4-bromo-1-butene or 6-bromo-1-hexene, respectively. (Table 1, Entries 11-12). Cross-metathesis with Grubbs second generation catalyst and 2-methyl-3-buten-2-ol provided the allylic alcohols, 5.³⁵ This two-step procedure was effective in constructing indole-tethered allylic alcohols with different functionality on the indole ring.

With the allylic alcohols in hand, the diphenyl phosphate-catalyzed Friedel-Crafts reaction could be explored (Scheme 2). Treatment of 5a with 10 mol% diphenyl phosphate in dichloromethane yielded the desired product in 73% yield. Introduction of various electron-donating groups on the indole ring was tolerated. Substitution at the C-3 position of the ring provided an increase in yield (Figure 1, 6b and 6c). Methyl or methoxy substituents could be added to the indole ring and the reaction proceeded in moderate to good yield in most cases, 6d-i. Use of allylic alcohol 5k, which contains bromine, led to the generation of an inseparable mixture of non-polar compounds, indicating that electron-withdrawing groups are not compatible with these reaction conditions. The effects of changing the tether length from n = 2 to n = 1 (5k) or 3 (5l) to provide access to 5- or 7-membered rings, respectively, were also examined. This change provided little of the desired annulation product, but instead yielded the dehydration products, 7a or b, in low yield. Compound 7a was isolated as a 4:5:1 of mixture with desired cyclization product. The yield was the annulation product could not be improved. The dehydration reaction was not

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Table 1. Results of alkylation and cross-metathesis reactions

<table>
<thead>
<tr>
<th>Entry</th>
<th>n</th>
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<th>Compound (Yield %)</th>
<th>Compound (Yield %)</th>
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<td>5a (82)</td>
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<tr>
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<td>2</td>
<td>3-methyl</td>
<td>3b (56)</td>
<td>5b (56)</td>
</tr>
<tr>
<td>3</td>
<td>2</td>
<td>3 CH₂CH₂OTBDPS</td>
<td>3c (32)</td>
<td>5c (68)</td>
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<tr>
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<td>2</td>
<td>4-methoxy</td>
<td>3d (76)</td>
<td>5d (72)</td>
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<tr>
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<td>2</td>
<td>5-methoxy</td>
<td>3e (61)</td>
<td>5e (61)</td>
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<tr>
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<td>1</td>
<td>H</td>
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<td>5k (57)</td>
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<tr>
<td>12</td>
<td>3</td>
<td>H</td>
<td>3l (33)</td>
<td>5l (61)</td>
</tr>
</tbody>
</table>

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Figure 1. Structure of the flinderoles

Scheme 1. Synthesis of allylic alcohols from indoles
Scheme 2. Brønsted Acid catalyzed intramolecular Friedel-Crafts Addition

Figure 2. Products from the Friedel-Crafts Addition. Reaction time 8 h\(^b\) 10% dehydration product isolated\(^c\) 1:4.5 Ratio of 6:7
3.03 (t, 2 H, 1H) heated to 40 °C overnight. The mixture was cooled, filtered through a pad of a 1:1 mixture of silica gel and celite, which was washed with ethyl acetate. The filtrate was concentrated in vacuo. The residue was purified by chromatography on SiO2 (0.8% EtOAc/Hexanes) to yield 95 mg (37% yield) of 3I as a yellow-brown oil: IR (KBr) 3038, 3005, 2963, 2921, 2854, 2838, 1490, 1427 cm\(^{-1}\); 1H NMR (300 MHz, CDCl3) d 7.68-7.61 (m, 4 H), 7.44-7.31 (m, 8 H), 7.14 (dddd, 1 H, J = 8.3, 7.1, 1.4, 0.7 Hz), 7.02 (dddd, 1 H, J = 7.7, 6.9, 0.8 Hz), 6.90 (s, 1 H), 5.79 (dddd, 1 H, J = 17.0, 10.7, 6.6, 6.6 Hz), 5.04 (dddd, 1 H, J = 7.7, 1.4, 1.4, 1.4 Hz), 4.99 (dddd, 1 H, J = 1.4, 1.4 Hz), 4.05 (ddd, 2 H, J = 6.9 Hz), 3.92 (t, 2 H, J = 7.4 Hz), 3.03 (t, 2 H, J = 7.1 Hz), 2.05 (dddd, 2 H, J = 6.9, 6.9, 6.9, 1.8 Hz), 1.89 (dddd, 2 H, J = 6.9, 6.9, 6.9, 1.06 (s, 9 H); 13C NMR (75 MHz, CDCl3) d 137.6, 136.3, 135.8, 134.2, 129.7, 128.3, 127.8, 126.2, 121.4, 119.2, 118.7, 117.5, 116.1, 109.4, 64.7, 45.5, 31.0, 29.4, 28.8, 27.0, 19.4; MS (EI) m/z (relative intensity) 467 (M+1, 15), 412 (10), 311 (40), 310 (100), 310 (52), 198 (25), 158 (10), 144 (25), 130 (10); HRMS (EI) Calcd for C14H20NOSi 467.2644, found 467.2635.

### Sample Cross Metathesis Procedures

(3E)-7-(3-2-[(tert-butyldiphenylsiloxy)ethyl]-1H-indol-1-yl)2-methylhept-3-en-2-ol (5e): A solution of 60 mg (0.12 mmol) of 3e in 1.2 mL of CH2Cl2 was added 144 mg (1 mmol) of 2-methyl-3-buten-2-ol (4) and 5.5 mg (0.0064 mmol) of Grubbs II. The mixture was then heated to 40 °C overnight. The mixture was cooled, filtered, then a pad of silica gel and celite, which was washed with ethyl acetate. The filtrate was concentrated in vacuo. The residue was purified by chromatography on SiO2 (0.8% EtOAc/Hexanes) to yield 43 mg (68%) of 5e as a colorless oil: IR (Neat) 3390, 3070, 2984, 2929, 2856, 1613, 1580, 1468, 1428 cm\(^{-1}\); 1H NMR (300 MHz, Acetone-d6) d 7.68-7.62 (m, 4 H), 7.47-7.33 (m, 8 H), 7.11 (dd, 2 H, J = 6.9, 6.9, 0.8 Hz), 6.94 (dddd, 1 H, J = 8.0, 8.0, 1.1 Hz), 5.59 (dddd, 2 H, J = 4.7, 2.8 Hz), 4.13 (t, 2 H, J = 6.9 Hz), 3.93 (t, 2 H, J = 7.1 Hz), 3.38 (s, 1 H), 3.03 (t, 2 H, J = 7.1 Hz), 1.99 (dddd, 2 H, J = 7.7, 7.7, 3.3 Hz), 1.85 (dddd, 2 H, J = 6.9, 6.9, 6.9, 1.2 Hz), 1.21 (s, 6 H), 1.04 (s, 9 H); 13C NMR (75 MHz, Acetone-d6) d 141.0, 137.4, 136.4, 134.7, 130.6, 129.3, 128.7, 127.3, 125.6, 121.9, 119.7, 119.3, 119.1, 110.3, 70.1, 65.4, 45.9, 30.9, 30.5, 30.1, 29.5, 27.3, 19.7; MS (EI) m/z (relative intensity) 525 (M+1, 2), 509 (10), 508 (25), 507 (75), 451 (25), 450 (65), 252 (20), 239 (15), 238 (100), 225 (10), 199 (10), 183 (10), 144 (10), 67 (10); HRMS (EI) Calcd for C28H30NO3Si 525.3063, found 525.3058.
formations of 5 and 7-membered rings. In the addition, this approach could extend to pyrrole or other heterocycles or the use of chiral phosphoric acid catalysts could render this reaction enantioselective.

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Notes and References

*Corresponding author email: bwakefiel@coastal.edu

