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ABSTRACT

The reaction of (2-aminobenzyl) triphenylphosphonium bromide with aromatic aldehydes or \( \alpha,\beta \)-unsaturated aldehydes under microwave-assisted conditions constitutes a new synthesis of 2-substituted indoles in high yields (81–97%) in a one-pot reaction. The adduct from indole-4-carboxaldehyde was an advanced intermediate in the synthesis of arcyriacyanin A.

Many 2-aryl and 2-vinylindoles are key subunits of a variety of biologically active molecules. The 2-vinylindole moiety can function as a heterocyclic diene for stereocontrolled annulation of the indole skeleton. The traditional methods include Fischer indole synthesis, Batcho–Leimgruber synthesis from \( \alpha \)-nitrotoluene, Gassman synthesis from \( N \)-haloanilines, reductive cyclization of \( \alpha \)-nitrobenzyl ketones, and Madelung cyclization of \( N \)-acyl-o-toluidines. Transition-metal-catalyzed reactions, using palladium or copper, for the direct arylation of indoles and related heterocycles have been widely reported. The Wittig cyclizations of \( N \)-acylated 2-aminobenzyl phosphonium salts also provide versatile syntheses of quinolines and 2-aryl or vinylindoles. Despite the fact that these reactions are synthetically useful, they suffer from several disadvantages: (i) high temperatures and long times (above 125 °C and 12 h), (ii) expensive transition-metal catalysts, (iii) multistep and moderate yields as well as high sensitivity to moisture. We report herein a new approach that can successfully afford 2-aryl or vinylindoles in high yields in one pot under very mild conditions.

In an approach to the indoloquinoline alkaloids, we condensed commercially available phosphonium salt 1 with isatin 2 to form imine 3 under the conditions shown in Scheme 1. Treatment of imine 3 with potassium tert-butoxide in either THF or toluene provided adduct 5 in around 21% yield.

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2-substituted indoles

Although we had expected the product to be compound 4, an intermediate in the synthesis of cryptolepine, our proton, and carbon NMR spectra did not match the published spectra. After considering its mass spectrum (which showed the mass of 4 plus an oxygen atom) and the $^{13}$C NMR (which showed a resonance at 99 ppm as the most downfield resonance), we tentatively assigned structure 5. Compound 5 had been reported, and its major mass spec fragmentation patterns were identical to those in our adduct.

We reasoned that if a spirow compound such as 5 had formed such an intermediate might be employed in a general synthesis of 2-substituted indoles. Since these compounds are intermediates for the synthesis of indole natural products, a one-pot synthesis from commercially available starting materials would be useful. The strategy for the formation of 2-substituted indoles 9 from 1 via 7 and 8 is illustrated in Scheme 2.

### Scheme 2

![Scheme 2](image)

It is notable that our initial studies used the traditional methods to form an imine by boiling overnight in methanol or toluene with a catalytic amount of acetic acid with a low yield. Application of microwave energy as a nonconventional activation source in organic syntheses is increasing rapidly, and its benefits have been well documented. Microwave-assisted organic synthesis has proven to be a valuable tool to increase efficiency in the synthesis of heterocyclic compounds. This prompted us to synthesize the 2-unsubstituted indoles under the microwave conditions. The results presented in Table 1 show that under microwave-assisted

### Table 1. Reaction of 1 with Isatin to Generate Compound 5

<table>
<thead>
<tr>
<th>entry</th>
<th>solvent</th>
<th>temperature (°C)</th>
<th>time (h)</th>
<th>yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>methanol</td>
<td>65</td>
<td>12</td>
<td>25</td>
</tr>
<tr>
<td>2</td>
<td>toluene</td>
<td>111</td>
<td>12</td>
<td>21</td>
</tr>
<tr>
<td>3</td>
<td>methanol</td>
<td>80</td>
<td>10</td>
<td>87</td>
</tr>
</tbody>
</table>

*Reaction conditions: phosphonium salt 1 (1 mmol), isatin (1 mmol), AcOH (0.4 mmol), solvent (2 mL).” Isolated yield. “Microwave assisted conditions the reaction proceeds very efficiently within a few minutes, and the yield also increased from 21% to 87%.

When phosphonium salt 1 was allowed to react with benzaldehyde to form the imine and then potassium tert-butoxide was added, 2-phenylindole (8) was formed as the only product in 95% yield. In view of this promising result, several aromatic and α,β-unsaturated aldehydes were reacted with 1. The results of these experiments are collected in Table 2.

As the results in Table 2 indicate, a wide range of functionalized aldehydes react effectively with phosphonium salt 1, including a variety of electron-donating and electron-withdrawing substituents, such as aromatic ethers, halides, nitro and aryl groups (entries 2, 3, 4, and 5), and also heterocyclic aldehydes (entries 6 and 7). In addition, the reactions with α,β-unsaturated aldehydes (entries 8 and 9) also proceed very smoothly and gave high yields under these conditions. Unfortunately, the alkyl aldehydes such as isobutyraldehyde did not form the imine intermediates with phosphonium salt 1 under the same microwave conditions. Adduct 11 is an advanced intermediate in the synthesis of the natural product acryciyanin A.

Arcyriacyanin A, a pigment of the slime mold of *Arcyria obvelata Onsberg*, is an effective inhibitor of protein kinase C and protein tyrosine kinase.\(^{13}\) Since compound 11 has been transformed into 12 with 3,4-dibromomaleimide as shown in Scheme 3,\(^{12}\) the synthesis of compound 11 constitutes a formal *two-step* total synthesis of 12 from commercially available starting materials.

In conclusion, we have established a new method for the preparation of 2-aryl and 2-vinyl indoles from commercially available starting materials. These reactions proceed under very mild conditions (often at room temperature) and remarkably short times (less than 2 h) in one pot with high yields (81–97%). The adduct from indole-4-carboxaldehyde was an advanced intermediate in the synthesis of arcyriacyanin A, which can be synthesized in two steps in 35% overall yield.

**Acknowledgment.** We thank the Iowa State University Department of Chemistry for support of this work.

**Supporting Information Available:** Detailed synthetic procedures, characterization data, and \(^1\)H NMR, \(^13\)C NMR, and HRMS spectra of these synthesized compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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**Table 2. Reaction of 1 with Aldehydes to Generate 2-Aryl and 2-Vinyl Indoles**

<table>
<thead>
<tr>
<th>entry</th>
<th>6</th>
<th>product</th>
<th>yield (%)</th>
<th>melting point (°C) (Lit. mp)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1-CHO</td>
<td>12</td>
<td>95</td>
<td>188-190 (188-189)(^{13})</td>
</tr>
<tr>
<td>2</td>
<td>Br-CH=O</td>
<td>12</td>
<td>95</td>
<td>211-213 (208-212)(^{13})</td>
</tr>
<tr>
<td>3</td>
<td>4-CH=O</td>
<td>12</td>
<td>81</td>
<td>82.5-83 (83)(^{13})</td>
</tr>
<tr>
<td>4</td>
<td>3-NO(_2)-CH=O</td>
<td>12</td>
<td>86</td>
<td>248-250 (249-251)(^{13})</td>
</tr>
<tr>
<td>5</td>
<td>2-CHO</td>
<td>12</td>
<td>93</td>
<td>97-99 (98-102)(^{13})</td>
</tr>
<tr>
<td>6</td>
<td>2-CH=O</td>
<td>12</td>
<td>86</td>
<td>120-123</td>
</tr>
<tr>
<td>7</td>
<td>3-NO(_2)-CH=O</td>
<td>12</td>
<td>85</td>
<td>175-176 (170-175)(^{13})</td>
</tr>
<tr>
<td>8</td>
<td>5-CH=O</td>
<td>12</td>
<td>97</td>
<td>202-204 (197-199)(^{13})</td>
</tr>
<tr>
<td>9</td>
<td>2-CHO</td>
<td>12</td>
<td>83</td>
<td>164-165</td>
</tr>
<tr>
<td>10</td>
<td>2-NO(_2)-CH=O</td>
<td>12</td>
<td>87</td>
<td>202-203 (199-202)(^{23})</td>
</tr>
</tbody>
</table>

* Reaction conditions: (i) phosphonium salt 1 (1 mmol), aldehydes (1 mmol), AcOH (0.4 mmol), methanol (2 mL); (ii) t-BuOK (1.6 mmol), THF (2 mL). \(^a\) Isolated yield.