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A [4+1] annulation protocol is developed for the synthesis of various 2-alkenylindole derivatives starting from aminobenzyl phosphonium salts and cinnamaldehydes. This process, the reaction proceeds efficiently without the usage of any metal catalysts or base, which is featured with easily available starting materials, broad substrate scope, excellent yields and simple reaction conditions.

Introduction

Indole derivatives, known as a class of significant and ubiquitous heterocyclic compounds, are commonly found in the application of medicals,2 agrochemicals,3 and dyestuffs4 due to their unique biological activity and chemical properties. Therefore, the synthesis of indole compounds has always been becoming a hot topic and widely studied by researchers all long.4 In particular, the 2-alkenylindole core5 is a vital structural constituent of several biologically relevant molecules, such as Flinderole C, Fluvastain, and SB-242784 osteoclast inhibitor, which exhibit significant pharmacological properties (Figure 1). In addition, these indoles have also played an important role in building architecturally complicated organic materials.6

![Figure 1](https://example.com/figure1.png)

**Figure 1.** Biologically Relevant Molecules with a 2-Alkenylindole Unit

Recently, significant efforts have been devoted in the preparation of 2-alkenylindoles. Transition metals, such as Mn,7 Fe,8 Co,9 and Ni10 were employed extensively for the synthesis of such compounds through direct functionalization of indoles (Scheme 1, eq a). Later, several noble metal-catalyzed procedures have been developed for the synthesis of 2-alkenylindoles through annulation of aniline derivatives with enones11 or propargyl alcohols12 (Scheme 1, eq b). Despite of these advances, there are still some disadvantages to limit their application, such as the use of expensive metal catalysts, not easily available starting materials, narrow substrate scope and relatively low yields.

**Scheme 1.** Represented Protocols for the Synthesis of 2-Alkenylindoles

The development of synthetic strategies that efficiently construct diverse and complex molecules has attracted considerable attention. In this regard, the exploration and utilization of various active building blocks represents one of the most attractive and challenging issues in organic chemistry community, especially annulation reactions in constructing various bioactive heterocycles.13 In the past years, our group has focused on the synthesis of quinolines through annulation of anthranils with a series of synthons, such as 1,3-diketones,14a phenylacetaldehydes,14b sulfoxonium ylides,14c enaminones14d and ammonium salts.14e As part of our continuing work on the synthesis of heterocycles,14,15 herein, we report a concise and
green method for the synthesis of 2-alkenylindoles through [4+1] annulation of aminobenzyl phosphonium salts with cinnamaldehydes (Scheme 1, eq c).16

Results and discussion

The initial optimization of the reaction conditions was conducted with aminobenzyl phosphonium salt 1a and cinnamaldehyde 2a as substrates and all the results were summarized in Table 1 (For details see Supporting Information). To our delight, when we used 1a and 2a in EtOH at a 1.5:1 ratio without any additive, the desired product 3 was isolated in 45% yield after stirring at 110 °C for 6 h (Table 1, entry 1). Then the effect of solvents was investigated and the use of DMSO instead of EtOH almost led to no formation of product 3 (Table 1, entry 2). Further screening of solvents showed that THF was the best solvent, providing product 3 in 72% yield (Table 1, entries 3-11). Subsequently, the reaction was tested at different reaction temperatures and a better yield of 87% was achieved at 80 °C (Table 1, entries 12-15). At last, the yield could be raised to 92% after extending the reaction time to 12 hours (Table 1, entry 16).

Table 1. Optimization of the Reaction Conditions

<table>
<thead>
<tr>
<th>Entry</th>
<th>Solvent</th>
<th>Temp. (°C)</th>
<th>Time (h)</th>
<th>Yield (%)</th>
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<tr>
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<td>45</td>
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<td>2</td>
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<td>110</td>
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<tr>
<td>4</td>
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<td>110</td>
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<td>43</td>
</tr>
<tr>
<td>5</td>
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<td>110</td>
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</tr>
<tr>
<td>6</td>
<td>THF</td>
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<td>6</td>
<td>65</td>
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<td>110</td>
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</tr>
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<td>110</td>
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<td>12</td>
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<tr>
<td>16</td>
<td>THF</td>
<td>80</td>
<td>12</td>
<td>92</td>
</tr>
</tbody>
</table>

*Reaction conditions: Aminobenzyl phosphonium salt 1a (0.3 mmol), cinnamaldehyde 2a (0.2 mmol), solvent (1 mL), 80 °C, 12 h. Yields based on 2a.

With the optimized reaction conditions in hand (Table 1, entry 16), the scope of the reaction of aminobenzyl phosphonium salts 1a was investigated and the results were summarized in Scheme 2. Substrates bearing various electron-donating or electron-withdrawing substituents were applied to the reaction to prepare a series of 2-alkenylindoles. For substrates containing halogen groups (–F, –Cl and –Br) on the para-position of right benzene ring unit of substrate 1, products 4-6 were obtained in 85%, 91% and 92% yields, respectively. Next, the reaction was turned to substrates bearing substituents –Cl and –Br at other positions of left benzene ring unit of substrate 1, affording products 7 and 8 in the 92% and 96% yields, respectively. To our delight, this reaction system could also be efficiently applied to one substrate with two substituents –F and –Cl, giving product 9 in 94% yield.

Scheme 2. Substrate Scope for Aminobenzyl Phosphonium Salts 1a

To further extend the scope of the reaction, the reaction of various cinnamaldehydes 2 with aminobenzyl phosphonium salt 1a were performed and the results were shown in Scheme 3. At first, substrates bearing electron-donating groups –Me and –OMe at the ortho-position were investigated in the reaction, giving the desired products 10 and 11 in 90% and 89% yields, respectively. Next, for substrates containing halogen groups –Cl and –Br, products 12 and 13 were obtained in 94% and 95%, respectively. For the substrates with electron-withdrawing substituent –NO2, the reaction could also proceed smoothly, affording product 14 in 83% yield. In addition, substrates bearing –Me, –F, –Cl, and –CF3 groups at the meta-position of the olefin were tested in the reaction, giving products 15-18 in yields ranging from 76% to 96%. Furthermore, for substrates containing electron-donating groups –Me, –OMe, and –Me2 at the para-position of the benzene ring, products 19, 20, and 21 were prepared in 95%, 95%, and 62% yields, respectively. Replacement with halogen groups –F, –Cl, and –Br at the same position, products 22-24 were obtained in yields ranging from 84% to 91%. To our delight, substrates bearing –Me, Cl, and –Br groups at the ortho-position of the aldehyde were also employed successfully in the reaction, affording products 25, 26, and 27 in 76%, 87%, and 95% yields, respectively. Substrates containing a heterocycle (thienyl) also reacted well with 1a, giving products 28 in 50% yield. Moreover, the reaction of one substrate containing an anthracene group could also proceed well, affording product 29 in 92% yield.

Furthermore, we wondered the reaction activity of aliphatic acroleins instead of cinnamaldehydes. As shown in scheme 3, a series of aliphatic acroleins were reacted smoothly with 1a, providing the corresponding products 30-34 in yields ranging from 42% to 76%. It should be noteworthy that two additional types of aliphatic compounds 35 and 36 were also synthesized successfully in 88% and 96% yields. At last, an additional investigation was attempted with extended conjugate side chains, giving products 37-39 in yields ranging from 38% to 67%.
To demonstrate the synthetic effectiveness of our strategy, further investigations were conducted in Scheme 5. Gram-scale reaction was carried out under the standard conditions using 8.3 mmol of 1a and 5.5 mmol of 2a, affording product 3 in 82% yield (1.3356 g). After that, we started to explore synthetic transformations of product 3. Firstly, the alkylation or acylation of product 3 were conducted with CH₃I or Ac₂O under the promotion of base, providing compounds 52 and 53 in 96% and 75% yields, respectively. In addition, the protection of the amino group of product 3 could also be achieved smoothly with the use of (Boc)₂O or TsCl, giving the corresponding products 54 and 55 in 93% and 82% yields, respectively. Finally, an attempt on the reduction of alkene at 2-position of indole was finished, yielding the desired compound 56 in 86% yield.

Scheme 5. Gram-scale Reaction and Product Derivatization

To elucidate the possible mechanism of the reaction, several preliminary experiments were carried out (Scheme 6). Radical scavengers such as 2,6-bis(1,1-dimethylethyl)-4-methylphenol (BHT) or 2,2,6,6-tetramethyl-1-piperidinolxy (TEMPO) were added in the reaction, affording the desired product 3 in 90% and 87% yields, respectively, indicating that there might be no radical step in the process.

Scheme 6. Control Reactions

On the base of our results and previous work, a possible mechanism is proposed for the synthesis of 3 (Scheme 7). In the reaction process, we believe the imine formation is involved and intermediate A is obtained through the condensation of 1a and 2a. It is clear that the imine intermediate is conjugated with the olefin system, which makes it as very good acceptor. Next, intermediate A undergoes electron transfer followed by six-electron ring closure. In the meanwhile, bulky triphenylphosphine group eliminates readily in the process.

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*aReaction conditions: Aminobenzyl phosphonium salt 1a (0.3 mmol), acryaldehyde 2 (0.2 mmol), THF (1 mL), 80 °C, 12 h.

In order to further extend the substrate scope, several aromatic aldehydes were employed in the reaction and the results were shown in Scheme 4. Despite of relatively less efficiency, product 41 was prepared in 62% yield when the reaction of aminobenzyl phosphonium salt 1a was performed with benzaldehyde. The structure of compound 41 was unambiguously determined by X-ray crystallography. Then, two aminobenzyl phosphonium salts 1c and 1d were also reacted well with benzaldehyde, providing compounds 42 and 43 in 53% and 57% yields, respectively. At last, other aromatic aldehydes containing –Me, –OMe, –Cl, –Br and –CF₃ groups at the different positions were tested in the reaction, yielding products 44-51 in yields ranging from 45% to 96%.

Scheme 4. Annulation of Aminobenzyl Phosphonium Salts with Arylaldehydes

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The synthetic effectiveness of the reaction was further confirmed by the synthesis of 3 (Scheme 5). The standard reaction was carried out under the standard conditions using 8.3 mmol of 1a and 5.5 mmol of 2a, affording product 3 in 82% yield (1.3356 g). After that, we started to explore synthetic transformations of product 3. Firstly, the alkylation or acylation of product 3 were conducted with CH₃I or Ac₂O under the promotion of base, providing compounds 52 and 53 in 96% and 75% yields, respectively. In addition, the protection of the amino group of product 3 could also be achieved smoothly with the use of (Boc)₂O or TsCl, giving the corresponding products 54 and 55 in 93% and 82% yields, respectively. Finally, an attempt on the reduction of alkene at 2-position of indole was finished, yielding the desired compound 56 in 86% yield.

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producing intermediate B. At last, product 3 is formed through the tautomerism of intermediate B.

Scheme 7. Possible Reaction Mechanism

Conclusions

In conclusion, an alternative synthetic method for the preparation of 2-alkenylindoles has been developed through a [4+1] annulation of aminobenzyl phosphonium salts with acrylaldehydes. Various aryl or alkyl substituents could be tolerated for acrylaldehydes. Furthermore, aromatic aldehydes were also successfully tested in the reaction. In all, this concise and green protocol exhibited significant advantages in terms of no need of any catalyst or base, broad substrate scope, the use of easily available starting materials and high yields.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

The financial support from the Open Research Fund of School of Chemistry and Chemical Engineering, Henan Normal University (2022B01) and Talent Initiation Fund of Wuxi University (2023r032) are greatly appreciated.

References

Data Availability Statement

The data supporting this study's findings are available from the corresponding author (Dr. Lianghua Zou) upon reasonable request.