Synthetic Methods

Rapid Assembly of Functionalised Spirocyclic Indolines by Palladium-Catalysed Dearomatising Diallylation of Indoles with Allyl Acetate

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Abstract: Herein, we report the application of allyl acetate to the palladium-catalysed dearomatising diallylation of indoles. The reaction can be carried out by using a readily available palladium catalyst at room temperature, and can be applied to a wide range of substituted indoles to provide access to the corresponding 3,3-diallylindolinines. These compounds are versatile synthetic intermediates that readily undergo Ugi reactions or proline-catalysed asymmetric Mannich reactions. Alternatively, acylation of the 3,3-diallylindolinines with an acid chloride or a chloroformate, followed by treatment with aluminium chloride, enables 2,3-diallylindoles to be prepared. By using ring-closing metathesis, functionalised spirocyclic indoline scaffolds can be accessed from the Ugi products, and a dihydrocarbazole can be prepared from the corresponding 2,3-diallylindole.

Introduction

Medicinal chemistry has traditionally focused on the synthesis of aromatic heterocycles and related derivatives as lead compounds due to their drug-like physical properties and synthetic accessibility. However, it is widely considered that an increasing focus on three-dimensional structures, which incorporate a greater proportion of sp3 carbons, is probably desirable[1] in order for medicinal chemistry programmes to be successful against more complex drug targets. Whilst natural products can provide suitable three-dimensional functionalised architectures, such compounds are often highly complex, difficult to synthesise, and display undesirable physical properties. As a consequence, there is considerable interest in the development of synthetic routes to access small chiral saturated rings including cyclopropanes,[2] oxetanes[3–4], and azetidines,[5] as well as benzfused heterocyclic systems, such as indolines[6] and dihydrobenzofurans.[7] In addition, the incorporation of these motifs into spirocyclic frameworks can lead to increased molecular complexity whilst maintaining a relatively low molecular weight.[4,8] Such systems can potentially provide a structurally rigid three-dimensional core, which can be functionalised at several sites to provide a library of drug-like compounds. Herein, we report a short synthetic route to convert readily available indoles into polyfunctionalised spirocyclic indolines,[9] which enables the incorporation of functional groups at a variety of different positions in the scaffold.

We envisaged that introduction of two allyl groups at the 3 position of an indole core, with concomitant dearomatisation, would enable the formation of a diallylindoline. Such a compound is potentially a very versatile synthetic intermediate that can undergo reactions with a variety of nucleophiles and electrophiles at the imine moiety, cross-coupling/C–H functionalisation reactions on the aromatic ring, and can be readily converted into a spirocyclic alkaloid-like structure by ring-closing metathesis (Scheme 1). Given the large number of indoles

Scheme 1. Proposed synthetic route to spirocyclic indolines (RCM = ring-closing metathesis).

that are readily available commercially, a diverse range of functionalised spirocyclic scaffolds could readily be constructed. The spirocyclic ring structure embedded in these scaffolds has not been widely explored in existing drugs,[10] though it forms part of the polycyclic frameworks of the ajmaline alkaloid natural-product family,[11] which contains compounds possessing antiarrrhythmic[12] and antiplasmodial activity,[13] some of which have found application in medical treatment.

Our synthetic plan involved the development of a Pd-catalysed alllylation procedure to achieve regioselective introduc-
tion of the allyl groups in a dearomatising reaction, to generate the desired isoindolinine. Whilst there is good precedent for the Pd-catalysed allylation of indoles with a range of allyl sources\cite{14–18}, and even for the dearomatising allylation of 3-substituted indoles with allyl carbonates, with allyl alcohols in combination with organoboranes\cite{15} or by rearrangement of N-alloc protected indoles\cite{14, 19–22}, the direct use of allyl acetate in such reactions has proved challenging to date\cite{23}. Although highly activated allylic esters containing two conjugated aromatic rings can be successfully used in Pd-catalysed allylation reactions\cite{24}, there is only a single report of the Pd-catalysed reaction of indole 1a with allyl acetate 2, and the reaction was reported to produce a relatively complex mixture of N and C allylated products 3a–6a from which 3-allylindole 4a was isolated in up to 54% yield\cite{23}. Allyl acetate is a considerably cheaper starting material than the carbonates and carbamates typically employed, because it is a bulk chemical that can be prepared on an industrial scale by direct acetoxylation of propene\cite{25}. Therefore, we decided to explore whether it could be successfully employed in the direct Pd-catalysed diallylation of indole.

**Results and Discussion**

An initial test reaction of indole with Pd catalyst, 1,1’-bis(diphenylphosphino)ferrocene (dppf) ligand, allyl acetate 2 and K₂CO₃ led to the formation of a mixture of the desired product 3a, 3-allylindole 4a, as well as traces of 1,3-diallylindole 6a (Scheme 2; Table 1, entry 1). By increasing the number of equivalents of allyl acetate, a higher conversion was observed (entry 2), though large quantities of allyl acetate appeared to significantly slow down the reaction (entry 3). In the absence of base, no conversion to either 3a or 4a was seen (entry 4). By increasing the quantity of base in the reaction to three equivalents, and by employing five equivalents of allyl acetate, almost complete conversion of indole into 3a and 4a was observed with 3a becoming the major product (entry 5). The choice of ligand proved to be critical to controlling both the reactivity and the product distribution. A range of bidentate phosphines were explored, with ethylenebis(diphenylphosphine) (dppe) proving to be very ineffective (entry 6) and both (2,2’-bis(diphenylphosphino)-1,1’-binaphthyl) (BINAP) and 4,5-bis(diphenylphosphino)-9,9-dimethylxanthene (Xantphos) leading to lower conversions and selectivity in comparison to dppf (entries 7 and 8). However, with bis(2-(diphenylphosphino)phenyl)ether (DPEPhos), we were able to obtain an excellent conversion to the desired diallylindolinine 3a with very high selectivity (entry 9). Pleasingly, an 82% isolated yield of 3a could be obtained with only 5 mol% palladium catalyst at room temperature.

With practical conditions in hand, we went on to explore the scope of this dearomatising double allylation reaction (Scheme 3). A wide range of substituted indoles 1a–o were

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**Table 1. Screening of reaction conditions.**

<table>
<thead>
<tr>
<th>Entry</th>
<th>K₂CO₃ [equiv]</th>
<th>2 [equiv]</th>
<th>Ligand (5 mol%)</th>
<th>Conv. [%] (yield [%]) 3a/4a</th>
<th>Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>1a[1]</td>
<td>2</td>
<td>1.5</td>
<td>dppf</td>
<td>53 (15)</td>
<td>1:2</td>
</tr>
<tr>
<td>2a[1]</td>
<td>2</td>
<td>2.2</td>
<td>dppf</td>
<td>62</td>
<td>1:1</td>
</tr>
<tr>
<td>3a[1]</td>
<td>2</td>
<td>7</td>
<td>dppf</td>
<td>29</td>
<td>1:5</td>
</tr>
<tr>
<td>4a[1]</td>
<td>0</td>
<td>5</td>
<td>dppf</td>
<td>0</td>
<td>–</td>
</tr>
<tr>
<td>5a[2]</td>
<td>3</td>
<td>5</td>
<td>dppf</td>
<td>&gt;95</td>
<td>2:1</td>
</tr>
<tr>
<td>6a[2]</td>
<td>3</td>
<td>5</td>
<td>dppf</td>
<td>13</td>
<td>–</td>
</tr>
<tr>
<td>7a[2]</td>
<td>3</td>
<td>5</td>
<td>rac-BINAP</td>
<td>63 (45)</td>
<td>1:1</td>
</tr>
<tr>
<td>8a[2]</td>
<td>3</td>
<td>5</td>
<td>Xantphos</td>
<td>76 (47)</td>
<td>5:3</td>
</tr>
<tr>
<td>9a[2]</td>
<td>3</td>
<td>5</td>
<td>DPEPhos</td>
<td>&gt;95 (82)</td>
<td>&gt;10:1</td>
</tr>
</tbody>
</table>

[a] Determined by ‘H NMR. [b] Reaction was performed at 40 °C. [c] Reaction was performed at RT. [d] Small quantities of 6a were also observed.
converted to the corresponding diallylindolenines 3a–o in generally good to excellent yield. Notably, the reaction was tolerant of alkoxy or alkyl substituents at any position on the benzene ring (3b–g). However, the allylation reactions of several haloindoles were somewhat sluggish at room temperature, requiring heating at 50 °C in order to obtain reasonable yields of the desired product (3h–j).\(^1\) Pleasently, the presence of a substituent at C-2 did not impair the reaction, despite the potential steric crowding around the reaction site (3l–o). The presence of a tert-butyl(dimethyl)silyl(TBS)-protected alcohol at C-2 was compatible with the reaction, giving a good yield of the diallylindoline 3o considering the presence of this relatively large substituent so close to the newly formed quaternary carbon centre. As was anticipated, electron-rich indoles were generally better substrates for the reaction (3b, d, f, m).

In contrast, highly electron-deficient systems did not form the diallylindoline at all, with the N-allylindoles 3a and 3b being obtained as the major product from reactions of 5-nitroindole and 2-methyl-5-nitroindole, respectively. No allylation or diallylation of N-methylindole was observed under these conditions, demonstrating that a free NH is essential for the reaction to take place.

Given the difficulties initially encountered with achieving selectivity in the indole allylation reaction, we recognised that several different reaction pathways may be operative (Scheme 4). A likely possibility is that the reaction proceeds directly through allylation at C-3 to give 4a, followed by a second allylation at C-3 to give the diallylindoline 3a. However, it was also possible that 4a might undergo N-allylation to give 6a, followed by a (potentially Pd-catalysed) rearrangement to generate diallylindoline 3a. Conversely, the by-product 6a may be formed by rearrangement of 3a. In this latter case, the yield of 3a would be eroded during prolonged exposure to the reaction conditions as it was gradually converted into the undesired by-product 6a. Furthermore, initial N-allylation of 1a to give 5a, could be followed by (potentially Pd-catalysed) rearrangement to generate 4a. Therefore, we synthesised pure samples of 4a,\(^2\) 5a,\(^2\) and 6a and resubmitted them to the reaction conditions to determine, which of these compounds, if any, are plausible reaction intermediates. Neither 5a nor 6a apparently underwent rearrangement under the reaction conditions, but small quantities of 6a were produced from 5a. This indicates that 5a and 6a are not plausible intermediates in the formation of diallylindoline 3a. However, 3-allylindole 4a was completely converted into a mixture of 3a and 6a upon resubmission to the reaction conditions. The diallylindoline 3a did not undergo conversion into 6a upon resubmission to the reaction conditions, but some degradation of 3a did take place suggesting that prolonged exposure of the product to the reaction conditions will have a detrimental effect on the reaction yield. These observations suggest that only 4a is an intermediate in the reaction, and that the formation of by-products 5a and 6a is solely a result of competing N-allylation on reaction of 1a or 4a with the electrophilic π-allyl complex. The use of K₂CO₃ as base in related reactions has been reported to promote N-allylation over C-allylation due to the formation of a looser ion pair,\(^3\) but this is obviously not a significant factor in our reaction. It should be noted that the use of lithium or sodium carbonates in this diallylation reaction was ineffective.

With these useful diallylindoline building blocks in hand, we then began to investigate the reactivity of these compounds in further transformations (see Scheme 5). To rapidly

![Scheme 4. Identification of possible reaction pathways by resubmission of potential intermediates to the reaction conditions. Conditions: [Pd(allyl)(Cl)]₂ (2.5 mol %), 2 (5 equiv), DPEPhos (5 mol %), K₂CO₃ (3 equiv), MeCN, 24 h, RT.](https://doi.org/10.1002/chem.201400833)

![Scheme 5. Ugi reactions of the diallylindolines (d.r. = diastereomeric ratio).](https://doi.org/10.1002/chem.201400833)
introduce diverse functionality onto the indoline core, we explored the use of the diallylindolinines 3 in multicomponent reactions. Multicomponent reactions offer a highly efficient route to construct functionalised molecules based on a central core structure.[24] The use of imines and their derivatives, in combination with isonitriles and a range of different nucleophiles, has often proved to be a highly effective strategy for constructing bioactive small molecules of potential interest. Indeed, the classical Ugi reaction and closely related processes have proved to be of great value in the synthesis of a vast array of medicinally relevant structures containing an α-aminoamide core.[25] We envisaged that the highly stable imine unit present in the indolinine core should be an excellent building block for use in Ugi reactions, and surprisingly, the use of such compounds in these multicomponent reactions does not seem to have previously been explored. The dialyl indolinines 3 proved to be excellent substrates for Ugi reactions under standard conditions (Scheme 5). Reaction of selected indolinines with a diverse selection of carboxylic acids and isocyanides in MeOH gave access to a wide range of multicomponent products 8a–n (Scheme 5). As well as simple aliphatic and aromatic groups (8a–d), products containing heterocyclic rings (8e–g), primary amides (8h), activated chlorides (8i) and carbamate-protected amines (8j–k) could be prepared. Remarkably, even unprotected α-aminoacids (8l–m) and α-hydroxyacids (8n) could be used directly in the multicomponent reactions, although, as with many other Ugi reactions using chiral components, only low levels of diastereoselectivity were observed.[26]

An alternative strategy for functionalisation of the indoline was devised by reaction of the imine unit with a chloroformate or acid chloride[31] to give access to 2-chloroindolines, which after hydrolysis during work-up gave the corresponding 2-hydroxyindolines 10a–c in good yield (Scheme 6). Alternatively, acylation with an acid chloride, followed by quenching with methanol could be used to access a 2-methoxyindoline 11d. Acylation of 2-methylindoline 31 with methyl chloroformate resulted in the formation of N-acylaniline 12 in good yield. The 2-hydroxyindolines 10a and 10c readily underwent rearrangement to the corresponding 2,3-diallylindoles 13a and 13c upon treatment with aluminium trichloride, providing a convenient route to an alternative structural motif. The acylation and rearrangement reactions could be conveniently combined into a single process to provide access to the 2,3-diallylindoles 13f without the need to isolate the intermediate 2-hydroxyindolines.

A strategy for desymmetrising the achiral diallylindolinones 3 through asymmetric addition of a nucleophile to the imine group was also explored (Scheme 7). Gratifyingly, we found that L-proline-catalysed Mannich reaction of acetonitrile with three diallylindolinones (3a, d, j) gave the corresponding 3-aminoketones 14a–c in good yield and with very high enantiomeric purity. During the preparation of this manuscript, similar conditions were reported for the asymmetric Mannich reaction of closely related 3,3-disubstituted indolines,[32] so this reaction was not explored in further detail. With a range of different substituted indolines in hand, the synthesis of the corresponding spirocycloc indolines via ring closing metathesis was studied (Scheme 8).[33] A selection of the Ugi products (8a–c, e, i–k, n) underwent efficient ring-closing metathesis by using Grubbs’ first-generation catalyst in dichloromethane as solvent. The corresponding spirocyclic indolines 15 were isolated in good to excellent yield. The 2-hydroxyindolines 10a and b could also be smoothly converted into the corresponding spirocyclic indolines 16 in good yield. A dihydrocarbazole 17 could also be accessed by a ring-closing metathesis reaction of 2,3-diallylindole 13d.

Conclusion

We have described the application of the bulk chemical allyl acetate to the palladium-catalysed deoxygenating dimerization of indoles. The choice of ligand was found to be critical to con-
trolling the product distribution, and under the optimised conditions, the reaction proceeds efficiently and selectively at room temperature by using 5 mol% of a readily available palladium catalyst. This procedure enables the rapid assembly of a range of substituted indolines from readily available indoles by short synthetic sequences, including a selection of compounds containing the spirocyclic indoline motif. A diverse array of functional groups can be introduced into the scaffold through Ugi multicomponent reactions, and the achiral scaffold can also be desymmetrised by an asymmetric Mannich reaction. Many of these molecules incorporate hydrogen-bond donor and acceptor groups and possess potentially useful drug-like properties (Figure 1). Furthermore, the indolines generated from the diallylation reaction can also be used to access a variety of 2,3-diallylindoles via acylation and rearrangement.

Experimental Section

General methods

All chemicals were purchased from Sigma–Aldrich, Acros, Alfa Aesar or Santa Cruz Biotechnology and used without further purification. Samples of functionalised carboxylic acids for the Ugi reactions were provided by GlaxoSmithKline. 1-Allyl-1H-indole (5a), 3-allyl-1H-indole (4a), 1,3-diallyl-1H-indole (6a) were synthesized according to literature procedures. Anhydrous THF, dichloromethane and acetonitrile were purchased from Fisher Scientific. All other solvents were used as received. PE refers to petroleum ether. Flash-column chromatography was carried out by using normal-phase silica gel (33–70 μm) supplied by WVR. Thin-layer chromatography was carried out by using Merck TLC Silica gel 60 F 254 plates and products were visualized by using combinations of UV light (λ = 254 nm) and potassium permanganate (KMnO₄) when required.

General procedure A: Synthesis of 3,3-diallyl-3H-indolines (3)
The indole (1 equiv), [Pd(allyl)Cl]₂ (2.5 mol%), DPEPhos (5 mol%) and K₂CO₃ (3 equiv) were placed in an oven-dried carousel tube. After three vacuum/Ar cycles, acetonitrile (C₂/C₅ 0.025 mol L⁻¹) and allyl acetate (5 equiv) were successively added. The heterogeneous mixture was stirred at RT for 18–24 h before addition of water. The solution was extracted with Et₂O and washed with water. The combined organic layers were dried with Na₂SO₄, filtered, and volatiles were removed under vacuum. Purification by flash chromatography on SiO₂ gave the corresponding 3,3-diallyl-3H-indole compound 3.

General procedure B: Synthesis of Ugi products (8)
The carboxylic acid (1 equiv) and the isocyanide (1 equiv) were added to a solution of 3,3-diallyl-3H-indole (1 equiv) in MeOH (ca. 0.25 mol L⁻¹). The reaction mixture was stirred for 2–24 h at RT, before evaporation of the volatiles under vacuum. Pure compounds were obtained by washing the crude residue with PE, or by purification by column chromatography on SiO₂.

General procedure C: Synthesis of 3,3-diallyl-2-hydroxyindolines (10)
The chloroformate or acid chloride (1 equiv) was added to a solution of the 3,3-diallyl-3H-indole (1 equiv) in CH₂Cl₂ (ca. 0.07 mol L⁻¹), and the reaction was left to stir for 30 min at RT, before addition of saturated NaHCO₃. After extraction with CH₂Cl₂ (three times), the combined organic layers were washed with water, dried over Na₂SO₄ and filtered through cotton wool. Pure compounds were obtained by evaporation of the volatiles under reduced pressure or by purification by column chromatography on SiO₂.

General procedure D: Preparation of 2,3-diallylindoles (13) from 2-hydroxy-3,3-diallylindolines (10)
Aluminium chloride (1.1 equiv) was added to a solution 3,3-diallyl-2-hydroxyindoline (1.0 equiv) in CH₂Cl₂ (ca. 1 mol L⁻¹) at RT. The mixture was stirred for 30 min before addition of NET₃ (2 equiv).

Figure 1. Calculated properties of selected indolines.
After 5 min at RT, water was added, and the product was extracted with CH₂Cl₂ (three times). The combined organic layers were dried over Na₂SO₄. After evaporation, the crude material was purified by filtration through a small pad of SiO₂ to give the rearranged product.

Preparation of 2,3-diallylindolines (13) from 3,3-diallylindolines (3)

General procedure E: Using an acyl chloride

The acyl chloride (1 equiv) was added to a solution of 3,3-diallyl-3H-indole (1 equiv) in CH₂Cl₂ (ca. 0.3 mol L⁻¹) at room temperature. After 30 min, the reaction was quenched by addition of water and the mixture was extracted with CH₂Cl₂ (three times). The combined organic layers were dried over Na₂SO₄ and filtered. Evaporation of the volatiles gave the 3,3-diallyl-2-hydroxyindoline which was directly dissolved in CH₂Cl₂ (ca. 0.2 mol L⁻¹) and AlCl₃ (1.1 equiv) was added. After 30 min at room temperature, the reaction was quenched with saturated NaHCO₃ before extraction with CH₂Cl₂ (three times). The combined organic phases were washed with water, dried over Na₂SO₄ and filtered. After evaporation of the volatiles under vacuum, the crude residue was purified by a filtration on a small pad of SiO₂ using PE/Et₂O (100:0 to 90:10) as eluent.

General procedure F: Using a chloroformate

The chloroformate (1 equiv) was added to a solution of 3,3-diallyl-3H-indole (1 equiv) in CH₂Cl₂ (ca. 0.2 mol L⁻¹) at room temperature. After 30 min, the reaction was quenched by addition of saturated NaHCO₃, and the mixture was extracted with CH₂Cl₂ (three times). The combined organic layers were washed with water and dried over Na₂SO₄ and filtered. Evaporation of the volatiles gave the 3,3-diallyl-2-hydroxyindoline derivative which was directly dissolved in CH₂Cl₂ (ca. 0.2 mol L⁻¹) and AlCl₃ (1.1 equiv) was added. After 30 min at RT, NEt₃ (2 equiv) was added. The solution was left to stir for 5 min before addition of a saturated solution of K₂CO₃ and extraction with CH₂Cl₂ (three times). The combined organic phases were washed with water, dried over Na₂SO₄ and filtered. After evaporation of the volatiles under vacuum, the crude residue was purified by filtration through a small pad of SiO₂ using PE/Et₂O (100.0 to 90.10) as eluent.

Asymmetric synthesis of Mannich reaction products (15)

General procedure G

L-Proline (30 mol%) was added at 0 °C to a solution of 3,3-diallyl-3H-indole (1 equiv) in a mixture of acetone/CHCl₃ (4:5:1, ca. 0.022 mol L⁻¹). The reaction mixture was allowed to warm up slowly to RT and stirred for two days. Evaporation of the solvent followed by purification by column chromatography on SiO₂ gave the Mannich product.

General procedure H

L-Proline (30 mol%) was added at 0 °C to a solution of 3,3-diallyl-3H-indole (1 equiv) in a mixture of acetone/DMSO (4:1, ca. 0.016 mol L⁻¹). The solution was allowed to warm up to RT and stirred for two days. The reaction mixture was diluted with diethyl ether and washed with saturated NaHCO₃. The product was extracted with Et₂O (three times), and the combined organic layers were washed with water, brine and dried with MgSO₄. After filtration and removal of the solvents under reduced pressure, the crude product was purified by column chromatography on SiO₂.

General procedure I: Synthesis of spirocyclic indolines (16)

First-generation Grubbs’ catalyst (15 mol%) was added to a degassed solution of the corresponding Ugi product (1 equiv) in CH₂Cl₂ (ca. 0.06 mol L⁻¹) at 45 °C. The reaction mixture was heated at reflux for 24 h under argon before evaporation of the solvent under reduced pressure. The crude residue was purified by column chromatography on SiO₂ to give the desired product.

General procedure J: Synthesis of spirocyclic indolines (17)

The corresponding substituted 3,3-diallyl-2-hydroxyindoline compound was added to a refluxing solution of first generation Grubbs’ catalyst (15 mol%) in CH₂Cl₂ (ca. 0.04 mol L⁻¹) under argon. The reaction was heated at reflux for 24 h before evaporation of the volatiles under vacuum. The crude material was purified by column chromatography on SiO₂ to yield the desired product.

General procedure K: Synthesis of dihydro-1H-carbazole (18)

Grubbs’ first-generation catalyst (5 mol%) was added to a dried and degassed solution of 2,3-diallyl-1H-indole in CH₂Cl₂. The mixture was heated overnight at 55 °C before evaporation of the volatiles under reduced pressure. The residue obtained was purified by column chromatography on SiO₂.

Acknowledgements

We would like to acknowledge the UCL drug discovery PhD programme (PhD studentship to PD), the Engineering and Physical Sciences Research Council (EP/K001183/1, PDRA funding to LB) and GlaxoSmithKline (supply of selected functionalised carboxylic acids) for supporting this work.

Keywords: allylation · heterocycles · homogeneous catalysis · indoles · palladium


Received: June 12, 2014
Published online on August 29, 2014