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**Palladium-catalyzed allylation and deacylative allylation of 3-acetyl-2-oxindoles with allylic alcohols**

Aitor Ortega-Martínez, Rocco de Lorenzo, José M. Sansano,* and Carmen Nájera*
Palladium-catalyzed allylation and deacylative allylation of 3-acetyl-2-oxindoles with allylic alcohols

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ARTICLE INFO

Article history:
Received
Received in revised form
Accepted
Available online

Keywords:
oxindoles
allylic alcohols
palladium
catalysis
decacylation

ABSTRACT

The Pd-catalyzed allylation of 3-acetyl-2-oxindoles with allyl alcohol is performed using 3 mol% of Pd(dba)2, rac-BINAP and BINOL phosphoric acid as catalytic mixture. This procedure allows the in situ synthesis of 3-allyl-2-oxindole by adding Triton B to the reaction mixture. The deacylative allylation of 3-acetyl-3-methyl-2-oxindoles with allylic alcohols is carried out with 3 mol% of Pd(OAc)2, dppp and 1.5 equiv. of LiOEtBu as base affording the corresponding 3,3-disubstituted 2-oxindoles in good yields. Both methodologies can be combined for the preparation of unsymmetrical 3,3-diallylated 2-oxindoles such as compound 7. The DaA must be carried out in the absence of oxygen in order to avoid the competitive formation of 3-alkyl-3-hydroxy-2-indoles. The later compounds can be easily obtained by deacylative oxidation of 3-alkylated 3-acetyl-2-oxindoles with LiOEt at rt under air.

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1. Introduction

Pd-catalyzed allylation of nucleophiles with allylic alcohols is a direct methodology for the formation of C-C bonds. Allylic alcohols are commercially available compounds and their direct use avoids the preparation of their derivatives, normally acetates, carbonates and phosphates, to generate the corresponding allylic Pd electrophilic intermediates. Due to the poor leaving group ability of the OH group it has to be activated by means of Lewis or Brønsted acids or by forming in situ the corresponding esters. Alternatively, two main strategies can be used for the Pd-catalyzed allylation of active methylene derivatives: (a) decarboxylative allylation (DcA)² of allyl esters and (b) deacetylation allylation (DaA)³ with allylic alcohols of acylated substrates (Scheme 1). Intramolecular DcA requires an anion stabilizing group for the decarboxylative metalation of the starting allyl esters, which has to be previously formed by transesterification with Otera’s catalyst⁴ (XR₂SnOSnX₂R₂) using a large excess of the allylic alcohol. Intermolecular deacetylation metalation needs the introduction of the acetyl or a carboxylate group, which react with the alcoholate under basic conditions generating, in situ, the acetate or carbonate, respectively. This DaA takes place in THF or DMSO at 60 °C and has been studied with α-nitro and α-cyano ketones, 1,3-diketones, and α-cyanoacetates.

![Scheme 1](image)

Scheme 1. Pd-Catalyzed allylation of active methylene compounds by DcA and DaA

3,3-Disubstituted 2-oxindoles are important class of heterocyclic compounds occurring in natural alkaloids and biologically active compounds,⁵ for instance the alkaloid horsfiline⁶ and also esermethole,⁷ which is an intermediate for the synthesis of acetylcholinesterase inhibitors physostigmine and phenserine⁸ (Figure 1). This family of compounds have been synthesized from 3-allyl-3-methyloxindoles. The Pd-catalyzed prenylation and geranylation of 3-substituted 2-oxindoles has been performed with the corresponding allylic carbonates of the monoallylated oxindole.⁹ The resulting compounds are synthetic intermediates of fluspiramides A and B with skeletal and smooth muscle relaxant activity.

![Figure 1](image)

Figure 1. Biologically active 3,3-disubstituted oxindoles

For the Pd-catalyzed synthesis of 3-allyl-2-oxindoles, two alternative methodologies have been described: (a) one intramolecular process based on the Meerwein–Eschenmoser Claisen rearrangement of 2-allyloxyindoles¹⁰; (b) direct allylic alkylation of oxindoles with simple allylic alcohols co-catalyzed by Pd(OAc)₂/Ph₃P and PhCO₂H,¹¹ and (c) the DaA of 3-acyl-2-oxindoles with allylic alcohols¹² (Scheme 2).

![Scheme 2](image)

Scheme 2. Synthesis of 3-allyl-2-oxindoles by Pd-catalyzed methodologies

We have recently described the synthesis of 3,3-disubstituted 2-oxindoles by deacetylation alkylation of 3-acyl-2-oxindoles with alkyl halides and electrophilic alkenes under basic conditions.¹² Independently, Bisai and co-workers published a palladium-catalyzed alkylation of 3-acyl-2-oxindoles during the elaboration of this manuscript.¹³ Herein, we report our findings about the synthesis of 3,3-disubstituted 2-oxindoles by Pd-catalyzed direct alkylation of 3-acyl-2-oxindoles and by deacetylation alkylation. The main objectives of this study are: a) evaluate the possible palladium-catalyzed monoalkylation of 3-acyl-1-methyl-2-oxindole 1a; b) study the DaA using similar conditions from 3-acyl-1,3-methyl-2-oxindole (4a); c) the oxidation of heterocycles 4 under a mild process avoiding oxidizing agents.

2. Results and Discussion

Initially studies about the alkylation of 3-acyl-1-methyl-2-oxindole (1a)¹² were performed with allyl alcohol in the presence of different additives (Table 1). The selection of the N-methyalted structure obeyed to this arrangement is present in many natural compounds (Figure 1). Using the Tamara reaction conditions for the alkylation of active methylene compounds,¹³ 3 mol% of Pd(OAc)₂ and 1,3-bis(diphenylphosphino)propane (dppp), in the presence of triethylborane (60 mol%), gave compound 2aa in 99% isolated crude yield (Table 1, entry 1). In order to diminish the amount of additive 3 mol% of p-toluenesulfonic acid (TsOH) was employed instead of Et₃B affording 2aa in only 3% yield (Table 1, entry 2). Next, Pd(dba)₃ was employed instead of Pd(OAc)₂; without success (Table 1, entry 3). However, by changing the dppp ligand by rac-BINAP product 2aa was obtained in 66% yield (Table 1, entry 4). Using rac-BINOL phosphoric acid instead of TsOH gave a 98% of product 2aa (Table 1 entry 5). These reaction conditions: 3 mol%
of Pd(dba)2/rac-BINAP//rac-BINOL phosphoric acid in THF at rt, were used for the allylation of 3-acetyl-2-oxindoles 1b and 1c providing the corresponding allylated compounds 2ba and 2ca in 61 and 89% yield, respectively (Table 1, entries 6 and 7). To the best of our knowledge, this is the first palladium-catalyzed allylation of 3-acetyl-1-methyl-2-oxindoles from allyl alcohol.

**Table 1. Pd-Catalyzed allylation of 3-acetyl-2-oxindoles**

<table>
<thead>
<tr>
<th>R1</th>
<th>R2</th>
<th>Product</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Me</td>
<td>H</td>
<td>2aa</td>
<td>99</td>
</tr>
<tr>
<td>Me</td>
<td>OMe</td>
<td>2ba</td>
<td>3</td>
</tr>
<tr>
<td>H</td>
<td>OMe</td>
<td>2ca</td>
<td>-</td>
</tr>
</tbody>
</table>

The synthesis of 3-allyl-1-methyl-2-oxindole (3ab) was carried out by in situ addition of a solution of benzyltrimethylammonium hydroxide (Triton B) (40% in MeOH) (1 equiv) followed by addition of AcOH (0.85 mL) in 61% yield (Scheme 3). Attempts to prepare this compound by allylation of N-methyl-2-oxindole with allyl bromide and Triton B as base gave the corresponding 3,3-dialkylated 2-oxindole.12 Therefore, this one-pot procedure can be used for the synthesis of 3-monoallylated oxindoles instead of using LiHMDS at -78 °C during the allylation of N-alkyloxindole or sodium hydride at different temperatures.14

![Scheme 3. One-pot synthesis of 3-allyl-1-methyl-2-oxindole (3ab).](image)

Next, the Pd-catalyzed deacylative allylation of 3-acetyl-1,3-methyl-2-oxindole (4a) was attempted. The reaction conditions study was carried out with compound 4a12 and hex-2-en-1-ol (Table 2). Using Pd(OAc)2 and dppp (3 mol%) as catalysts and KOtBu (1.1 equiv) as base in THF, after 15 h at rt under Ar atmosphere, a 3:1 mixture of 5ab and also the oxidized 3-hydroxy-1,3-dimethyl-2-oxindole 6aa were obtained, compound 5ab being isolated after flash chromatography in 54% yield (Table 2, entry 1). The same process was repeated in the absence of oxygen (freezing-pump) and using LiOttBu instead of KOtBu giving a 95:5 mixture of both products, but also a 17% of 1,3-dimethyl-2-oxindole (3aa) (Table 2, entry 2). After increasing the amount of dppp to 6 mol% a 60:40 mixture of product 5ab and 3aa was formed (Table 2, entry 3). Changing Pd(OAc)2 by Pd2(dba)3 increased the amount of deacetylated product (Table 2, entry 4). Finally increasing the amount of LiOttBu to 1.5 equiv the formation of a mixture of 86% of the expected product 5ab together with 10% of 3aa and only 3% of 6aa was observed (Table 2, entry 5).

**Table 2. Reaction conditions study for the Pd-catalyzed DaA of 3-acetyl-1-methyl-2-oxindole (4a).**

<table>
<thead>
<tr>
<th>Entry</th>
<th>Cat (3 mol%)</th>
<th>Base (equiv)</th>
<th>Products ratio (%)</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Pd(OAc)2</td>
<td>KOtBu (1.1)</td>
<td>5ab (76), 6aa (24)</td>
<td>54</td>
</tr>
<tr>
<td>2</td>
<td>Pd(OAc)2</td>
<td>LiOttBu (1.1)</td>
<td>5ab (79), 3aa (17), 6aa (4)</td>
<td>66</td>
</tr>
<tr>
<td>3</td>
<td>Pd(OAc)2</td>
<td>LiOttBu (1.1)</td>
<td>5ab (61), 3aa (39)</td>
<td>-</td>
</tr>
<tr>
<td>4</td>
<td>Pd2(dba)3</td>
<td>LiOttBu (1.1)</td>
<td>5ab (49), 3aa (51)</td>
<td>-</td>
</tr>
<tr>
<td>5</td>
<td>Pd(OAc)2</td>
<td>LiOttBu (1.5)</td>
<td>5ab (86), 3aa (10), 6aa (3)</td>
<td>70</td>
</tr>
</tbody>
</table>

For the scope studies of this DaA process, different substituted oxindoles 4 and allylic alcohols were assayed using the optimal reaction conditions described on Table 2, entry 5 but 17 h instead of 15 h were needed as reaction time (Table 3). The reaction of 4a with primary allylic alcohols such as allyl alcohol, hex-2-enol and methallyl alcohol gave the corresponding products 5aa, 5ab and 5ac in good yields (Table 3, entries 1-3). The same occurred with geraniol giving product 5af in moderate 45% yield (Table 3, entry 6). However, 1-methylallyl alcohol afforded a ca. 2:1 inseparable mixture of the γ- and α-allylated products 5ad and 5at in 45% overall yield (Table 3, entry 4). Similar results were observed with prenyl alcohol affording a separable mixture of the γ- and α-products 5ae and 5af in 51% and 16% yields, respectively (Table 3, entry 5). In the case of pent-1,4-dien-3-ol, a 8:1 mixture of γ- and α-products 5ag and 5at was obtained in 62% overall yield (Table 3, entry 7). The DaA of 4a with cyclohex-2-ol gave dialkylated 2-
oxindole 5ah in 75% yield as a 1:1 mixture of diastereomers (Table 3, entry 8). Primary alcohols such as (−)-myrtenol and cinnamyl alcohol provided compounds 5ai and 5aj in 56 and 51% yields, respectively (Table 3, entries 9 and 10). Compound 5ai was obtained as an inseparable 5:5:1 mixture of diastereomers. Reactions of allyl alcohol with oxindoles 4b and 4c gave the corresponding products 5ba and 5ca in 72% and 77% yields, respectively (Table 3, entries 11 and 12). It is remarkable that compounds 5ab, 5ad, 5af, 5ag and 5aj were isolated as unique E-stereoisomers.

Table 3. Palladium-catalyzed DaA of 3-acetyl-2-oxindoles 4. a

<table>
<thead>
<tr>
<th>Entry</th>
<th>4</th>
<th>Allylic Alcohol</th>
<th>No.</th>
<th>Product</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>4a</td>
<td>4a</td>
<td>5aa</td>
<td><img src="image" alt="Structure of 5aa" /></td>
<td>80</td>
</tr>
<tr>
<td>2</td>
<td>4a</td>
<td>nC₃H₇–OH</td>
<td>5ab</td>
<td><img src="image" alt="Structure of 5ab" /></td>
<td>70</td>
</tr>
<tr>
<td>3</td>
<td>4a</td>
<td>4a</td>
<td>5ac</td>
<td><img src="image" alt="Structure of 5ac" /></td>
<td>74</td>
</tr>
<tr>
<td>4</td>
<td>4a</td>
<td>4a</td>
<td>5ad</td>
<td><img src="image" alt="Structure of 5ad" /></td>
<td>45'</td>
</tr>
<tr>
<td>5</td>
<td>4a</td>
<td>4a</td>
<td>5ae</td>
<td><img src="image" alt="Structure of 5ae" /></td>
<td>51</td>
</tr>
<tr>
<td>6</td>
<td>4a</td>
<td>4a</td>
<td>5af</td>
<td><img src="image" alt="Structure of 5af" /></td>
<td>45</td>
</tr>
</tbody>
</table>
The synthesis of the unsymmetrically disubstituted 3,3-diallylated oxindole 7 was performed first by allylation of 1a affording product 2aa followed by Pd-catalyzed deacylative allylation with methallyl alcohol affording product 7 in 72% overall yield (Scheme 4).

Scheme 4. Sequential synthesis of 3-allyl-3-methallyl-1-methyl-2-oxindole (7).
Table 4. Synthesis of 3-alkyl-3-hydroxy-2-oxindoles 6, a

<table>
<thead>
<tr>
<th>Entry</th>
<th>R^1</th>
<th>R^2</th>
<th>R^3</th>
<th>Product</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Me</td>
<td>H</td>
<td>Me</td>
<td>6aa</td>
<td>70</td>
</tr>
<tr>
<td>2</td>
<td>Me</td>
<td>H</td>
<td>Bn</td>
<td>6ab</td>
<td>68</td>
</tr>
<tr>
<td>3</td>
<td>Me</td>
<td>H</td>
<td>allyl</td>
<td>6ac</td>
<td>68</td>
</tr>
<tr>
<td>4</td>
<td>Me</td>
<td>H</td>
<td>propargyl</td>
<td>6ad</td>
<td>70</td>
</tr>
<tr>
<td>5</td>
<td>Me</td>
<td>OMe</td>
<td>Me</td>
<td>6ba</td>
<td>57</td>
</tr>
<tr>
<td>6</td>
<td>Bn</td>
<td>OMe</td>
<td>Me</td>
<td>6ca</td>
<td>58</td>
</tr>
</tbody>
</table>

a Reaction conditions: 4 (0.15 mmol), LiOEt (0.15 mmol), THF (1.5 mL), 12 h, rt under air.

3. Conclusions

The Pd-catalyzed allylation of 3-acyl-2-oxindoles with allyl alcohol can be performed under BINOL-derived phosphoric as co-catalyst in THF at rt in good yields. This methodology allows the synthesis of monoallylated 2-oxindoles by in situ deacetylation with Triton B. For the deacetylation of 3-acyl-3-methyl-2-oxindoles with allylic alcohols, Pd(OAc)_{2}/dppp and LiOrBu as base (1.5 equiv) gave the best results affording the corresponding 3,3-disubstituted 2-oxindoles in moderate to good yields. The mildness of both transformations allows to prepare no-easily accessible unsymmetrical 3,3-diallylated-1-methyl-2-oxindoles as has been demonstrated for compound 7. By treatment of 3-alkyl-3-acetyl-2-oxindoles with LiOEt under air the corresponding 3-alkyl-3-hydroxy-2-oxindoles can be easily prepared. These reaction conditions are very mild, the selective substitution and the high tolerance of the reagents to many functional groups convert this process in an a priori useful tool for the synthesis of natural products.

4. Experimental section

4.1. General

Melting point was determined with a Marienfeld melting point apparatus and are uncorrected. For flash chromatography, silica gel 60 (40-60 μm) was employed. 300 and 400 MHz 1H NMR and 75 and 101 MHz 13C NMR spectra were recorded using Bruker AV300 and Bruker AV400, respectively, with CDCl₃ as solvent and TMS as internal standard for 1H NMR, and the own chloroform signal for 13C NMR, and chemical shifts are given in ppm. IR spectra were recorded using a Perkin-Elmer PE 11400 Fourier Transform IR Spectrometer and a Nicolet Avatar 380 FT-IR Spectrometer. Low-resolution electron impact (GC-EI) mass spectra were obtained at 70 eV using a Agilent 6890N Network GC system and Agilent 5973 Network Mass Selective Detector. High-resolution mass spectra (GC-EI) were recorded using a QTOF Agilent 7200 instrument for the exact mass and Agilent 7890B for the GC. Analytical TLC was performed using ALUGRAM® Xtra SIL G/UV254 silica gel plates, and the spots were determined under UV light (λ=254 nm). Allylic alcohols were purchased as pure E- stereoisomers.

4.2. General procedure for the synthesis of 3-acetyl-3-allyl-2-oxindoles 2.

To a round-bottom flask was added Pd(dba)₂ (3 mol%, 5.2 mg, 0.009 mmol), rac-BINAP (3 mol%, 5.6 mg, 0.009 mmol), and dry THF (1.5 mL) and the mixture stirred for 30 min. Then, the oxindole 1 (0.3 mmol), the BINOL derived phosphoric acid (3 mol%, 3.1 mg, 0.009 mmol) and allyl alcohol (31 μL, 0.45 mmol) were added. The resulting mixture was stirred at rt for 60 h and afterwards extracted with EtOAc (3x10 mL) and the organic phases washed with H₂O (10 mL), dried (MgSO₄) and evaporated to dryness. The residue was purified by flash chromatography (EtOAc/hexane) affording pure products 2.

3-Acetyl-3-allyl-1-methylindolin-2-one (2aa): Yield 96%; Orange oil; Rf 0.19 (hexane/EtOAc 9/1); IR (neat) ν : 3521, 3410, 3078, 3057, 3006, 2923, 1738, 1724, 1609 cm⁻¹; 1H NMR (400 MHz) δH : 7.36 (td, J = 7.7, 1.3 Hz, 1H), 7.19–7.17 (m, 1H), 7.10 (td, J = 7.5, 0.9 Hz, 1H), 6.91 (d, J = 7.8 Hz, 1H), 5.30 (ddd, J = 16.9, 10.1, 7.8, 6.7 Hz, 1H), 5.00 (dq, J = 17.0, 1.3 Hz, 1H), 4.90–4.87 (m, 1H), 3.28 (s, 3H), 2.95 (ddt, J = 13.8, 6.7, 1.1 Hz, 1H), 2.86 (dd, J = 13.9, 7.9 Hz, 1H), 1.99 (s, 3H); 13C NMR (101 MHz) δC : 200.7, 174.5, 144.3, 131.5, 129.3, 127.0, 124.2, 123.2, 119.5, 108.5, 66.4, 37.5, 26.6; LRMS (EI) m/z (%): 229 (8) (M⁺), 188 (14), 187 (100), 186 (24), 172 (14), 160 (24), 158 (16), 144 (13), 143 (13), 130 (12), 128 (10); HRMS (ESI): calcd. for C₁₄H₁₃NO₂ 229.1103; found 229.1101.

3-Acetyl-3-allyl-5-methoxy-1-methylindolin-2-one (2ba): Yield 61%; Orange oil; Rf 0.10 (hexane/EtOAc 9/1); IR (neat) ν : 3077, 3003, 2941, 2836, 1745, 1729, 1601 cm⁻¹; 1H NMR (400 MHz) δH : 6.88 (dd, J = 8.5, 2.5 Hz, 1H), 6.82–6.79 (m, 2H), 5.31 (ddd, J = 16.9, 10.1, 7.8, 6.7 Hz, 1H), 5.04–4.99 (m, 1H), 4.91–4.88 (m, 1H), 3.79 (s, 3H), 3.25 (s, 3H), 2.96–2.83 (m, 2H), 2.00 (s, 3H); 13C NMR (101 MHz) δC : 200.8, 174.2, 156.4, 137.8, 131.5, 128.2, 119.5, 113.8, 111.2, 108.9, 66.8, 55.9, 37.6, 26.7, 26.6; LRMS (EI) m/z (%): 259 (28) (M⁺), 218 (15), 217 (100), 216 (21), 202 (37), 190 (12), 188 (16), 176 (10), 174 (29), 173 (11), 144 (18), 115 (21), 77 (11); HRMS (ESI): calcd. for C₁₅H₁₄NO₃ 259.1208; found 259.1206.

3-Acetyl-3-allyl-1-benzyl-5-methoxyindolin-2-one (2ca): Yield 89%; Pale orange oil; Rf 0.21 (hexane/EtOAc 9/1); IR (neat) ν : 3065, 3032, 2922, 2836, 1745, 1723, 1600 cm⁻¹; 1H NMR (300 MHz)
After performing the Pd-catalyzed allylation of compound 1a (see, Section 4.2), a solution of benzyltrimethylammonium hydroxide (Triton B) in MeOH (40 wt%, 136 mL, 0.3 mmol) was added and, immediately, acetic acid (0.85 mL, 15 mmol) was added and degassed by three cycles of freeze-pump-thaw and filled with Ar before the addition of LiOrBu (36 mg, 0.45 mmol). The solution was stirred at rt for 14 h and then extracted with EtOAc (3×10 mL). The organic phases were washed with H2O (10 mL), dried with MgSO4, filtered and concentrated. The resulting crude was purified by flash chromatography (hexane/EtOAc) to afford pure compound 3ab in 61% yield.

### 4.4. General procedure for the Pd-catalyzed deacetylation of allylation of compounds 4

To a mixture of Pd(OAc)2 (3 mol%, 2.0 mg, 0.009 mmol) and 1,3-bis(diphenylphosphino)propane (3 mol%, 3.7 mg, 0.009 mmol) was added dry THF (1 mL) under Ar and stirring continued for 30 min. This mixture was added to a solution of oxindole 4 (0.3 mmol) in dry THF (0.5 mL). Finally, the allylic alcohol (0.45 mmol) was added and the mixture was degassed by three cycles of freeze-pump-thaw and filled with Ar before the addition of LiOrBu (36 mg, 0.45 mmol). The solution was stirred at rt for 14 h and then extracted with EtOAc (3×10 mL). The organic phases were washed with H2O (10 mL), dried over MgSO4, and evaporated under vacuum. The pure compounds 5 were obtained after flash chromatography (hexane/EtOAc).

Compounds 5aa, 5ac, 5ae, 5af, 5aj, 5ag, 5ah, and 5ca are known, and new compounds follow:

(E)-3-(3,7-Dimethylcyclohexa-2,4-dien-1-yl)-1,3-dimethylindolin-2-one (5ag): Mixture of isomers (major trans isomer); Yield 55%; Pale yellow wax; Rf: 0.24 (hexane/EtOAc: 9/1); IR (KBr): ν: 2924, 2852, 1713, 1612 cm⁻¹; 1H NMR (300 MHz) δ: 7.26 (td, J = 7.9, 1.3 Hz, 1H), 7.21–7.16 (m, 1H), 7.06 (td, J = 7.5, 1.0 Hz, 1H), 6.83 (d, J = 7.8 Hz, 1H), 6.21–5.96 (m, 2H), 5.36 (dt, J = 15.0, 7.7 Hz, 1H), 5.09–5.02 (m, 1H), 4.96–4.92 (m, 1H), 3.19 (s, 3H), 2.53 (d, J = 7.7 Hz, 2H), 1.37 (s, 3H); 13C NMR (75 MHz) δ: 180.2, 143.2, 139.8, 134.2, 131.5, 127.7, 124.3, 123.1, 122.3, 118.3, 107.8, 48.7, 39.9, 36.8, 26.8, 26.2, 25.8, 22.4, 17.8, 16.4; LRMS (EI, m/z %): 227 (5) (M⁺), 174 (9), 161 (13), 160 (100), 132 (11), 131 (13), 117 (7), 67 (5); HRMS (ESI) calculated for C17H16NO: 227.1310; found 227.1309.

(E)-3-(3,7-Dimethylcyclohexa-1,4-dien-1-yl)-1,3-dimethylindolin-2-one (5ah): Mixture of diastereoisomers; Yield 55%; Pale yellow oil; Rf: 0.28 (hexane/EtOAc: 9/1); IR (neat) ν: 3076, 2962, 2926, 1712.8, 1613 cm⁻¹; 1H NMR (300 MHz) δ: 7.31–7.25 (m, 1H), 7.22–7.20 (m, 1H), 7.05 (td, J = 7.5, 1.0 Hz, 1H), 6.82 (d, J = 7.8 Hz, 1H), 5.86 (dd, J = 17.0, 8.3 Hz, 1H), 5.39 (dd, J = 17.1, 10.2, 8.7 Hz, 1H), 5.19–5.01 (m, 3H), 4.93 (dd, J = 10.1, 1.9 Hz, 1H), 3.22–3.14 (m, 4H), 1.36 (s, 3H) ppm; 13C NMR (CDC13), 75 MHz δ: 179.9, 143.7, 135.7, 135.6, 132.4, 128.0, 123.7, 118.2, 117.4, 107.9, 55.6, 51.2, 26.2, 21.8; LRMS (EI, m/z %): 227 (5) (M⁺), 161 (11), 160 (100), 132 (10), 131 (11), 117 (7), 67 (5), 65 (5); HRMS (ESI) calculated for C17H16NO: 227.1310; found 227.1309.

To a solution of oxindole 4 (0.15 mmol) in dry THF (1.5 mL) was added dropwise a solution of LiOEt (0.1 M in THF, 150 μL, 0.15 mmol) and the mixture was stirred at rt for 12 h. Then it was extracted with EtOAc (3x10 mL), the organic phases were washed with water (10 mL), dried over MgSO4, and evaporated under vacuum. The pure compounds 6 were obtained after flash chromatography (hexane/EtOAc).

Compounds 6aa,20 6ab,21 6ac,22 6ad,23 and 6ba,24 are known, a new compound follow:

1-Benzyl-3-hydroxy-5-methoxy-3-methylindolin-2-one (6ca): Yield 58%; Orange solid; m.p. 135–137 °C (hexane/EtOAc); Rf 0.12 (hexane/EtOAc 7/3); IR (KBr) v : 3347, 3028, 2927, 2833, 1704 cm⁻¹; ¹H NMR (400 MHz) δ (7): 7.32–7.27 (m, 5H), 7.04 (d, J = 2.6 Hz, 1H), 6.70 (dd, J = 8.5, 2.6 Hz, 1H), 6.60 (d, J = 8.5 Hz, 1H), 4.93 (d, J = 15.7 Hz, 1H), 4.78 (d, J = 15.7 Hz, 1H), 3.75 (s, 3H), 3.17 (br s, 1H), 1.67 (s, 3H); ¹³C NMR (101 MHz) δ: 178.8, 156.6, 153.6, 135.1, 132.9, 128.9, 127.8, 127.3, 114.2, 110.6, 110.3, 74.3, 55.9, 43.9, 25.3; LRMS (EI) m/z (%): 283 (39) (M⁺), 267 (8), 192 (7), 174 (5), 146 (8), 106 (7), 92 (10), 91 (100), 89 (6), 77 (7), 65 (19) 63 (5), 51 (5); HRMS (ESI): calcd. for C₂₇H₂₃NO₂ 421.1647; found 421.1646.


The first step was carried out following the description of section 4.2. for the synthesis of intermediate 2aa. The second step was run according to section 4.4. and, after purification, product 7 was isolated in 72% yield.

Acknowledgments

We gratefully acknowledge financial support from the Spanish Ministerio de Economía y Competitividad (MINECO) (projects CTQ2013-43446-P and CTQ2014-51912-REDI), the Spanish Ministerio de Economía, Industria y Competitividad, Agencia Estatal de Investigación (AEI) and Fondo Europeo de Desarrollo Regional (FEDER, EU) (projects CTQ2016-76782-P and CTQ2016-81797-REDI), the Generalitat Valenciana (PROMETEO2009/039 and PROMETEOII/2014/017) and the University of Alicante. A. O.-M. thanks MINECO for a predoctoral fellowship.