Synthesis of Enynoindoles Via Vinyl and Ethynyl Indoles

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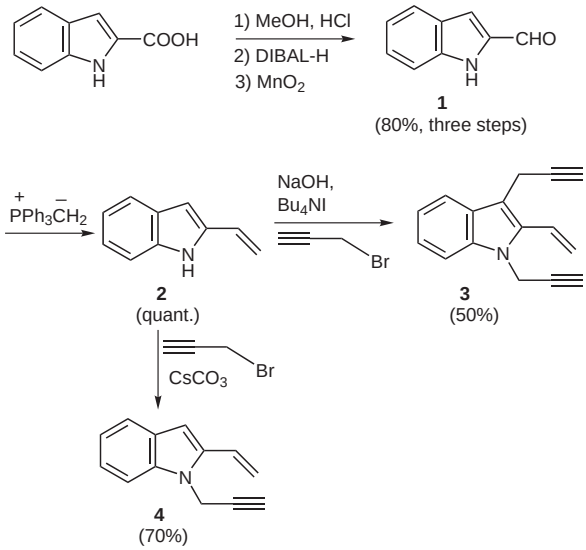
Abstract: A convenient synthesis of indoles bearing allyl, ethynyl, and/or propargyl moieties is described starting from indole or indole-2-carboxylic acid.

Key words: indoles, tandem reactions, enynes, Wittig reactions, alkynes

Suitable functionalised indoles are essential blocks in the synthesis of many natural products containing this nucleus. Indoles bearing unsaturated moieties are excellent precursors for cyclization reactions.[1] We have shown the use of these compounds in Pauson–Khand[2] and metathesis reactions.[3] The synthesis of vinylindoles, which have been used in Diels–Alder reactions,[4] has been reported although 2-vinylindole is described normally in moderate yields.[5] On the other hand 2-ethynylindole, another interesting starting material, has not been described. We herein report the syntheses of a group of indoles bearing unsaturated substituents in good global yields and from non-expensive commercial indoles. The methodology involves the use of reactions which most times do not need purification.

We first describe the synthesis of 2-vinylindole (**2**), which we intended to develop to both a 1-allyl and 1-propargyl derivative. Thus, from indole-2-carboxylic acid, a quantitative esterification was achieved with boiling methanol saturated with HCl. The reduction of the ester was carried out with DIBAL-H and gave also quantitatively the alcohol. None of the tested reaction conditions (slow addition at –78 °C of the hydride or keeping the reaction at low temperature) gave directly the aldehyde. Other reduction conditions with $LiAlH_4$ as described in the literature[6] gave poor yields in our hands (<20%). The subsequent oxidation was done with MnO_2 which gave the aldehyde in 80% overall yield (three steps) and after purification. Other reagents like PCC gave 50% yield in the oxidation step. The synthesis of this aldehyde has been thoroughly reported in the literature although we believe these tandem reactions in which no intermediates are purified are very efficient. Then, a Wittig reaction was used to obtain compound **2**. The ylide was generated using KHMDS at room temperature and then was cannulated to a solution of the aldehyde. These conditions were essential to obtain quantitative yields. 2-Vinylindole can be chromatographed and stored in the fridge without any tendency to decomposition.

For the alkylation of the indole nitrogen we used two different conditions: a phase transfer method using NaOH (30% solution)–toluene and Bu_4NI, or treatment with the alkyl bromide using $CsCO_3$ as the base. With propargyl bromide, the first conditions gave dipropargylated compound **3** in 50% yield. The desired compound **4** was obtained with the latter conditions in 70% yield. On the other hand both conditions gave decomposition products when using allyl bromide (Scheme 1).



Scheme 1

Therefore, the synthesis of 1-allyl-2-vinylindole was carried out following Scheme 2. Thus, allylation of the ester using the phase transfer conditions, followed by the same reduction–oxidation sequence gave compound **6** in 70% yield after 4 steps from indole-2-carboxylic acid. The subsequent Wittig reaction finally gave the desired compound **7** with 75% yield.

Finally, we carried out the synthesis of 1-allyl-2-ethynyl indole starting from indole. We followed Bergman's work[7] to obtain 2-iodoindole (**8**), which, without purification, was submitted to Sonogashira coupling with trimethylsilylacetilene to give **9** in 85% yield. This compound was air stable and can be kept in the fridge without decomposition. Allylation of **9** using $CsCO_3$ as base led directly to product **10** with loss of the trimethylsilyl group in the same reaction (Scheme 3).

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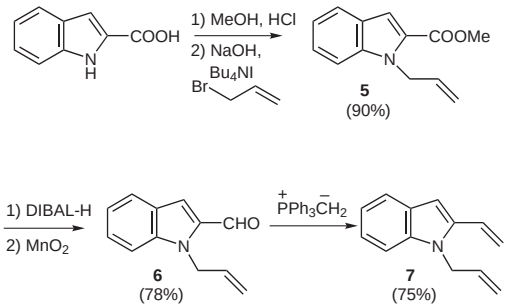
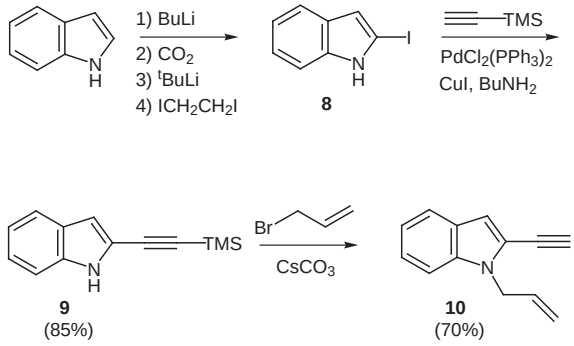


Scheme 2



Scheme 3

Melting points were taken on a Büchi 530 apparatus and are uncorrected. ^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker AM-300 instrument at 300 MHz and 75.43 MHz, respectively. NMR spectra were registered in $CDCl_3$ and chemical shifts are given in ppm relative to TMS (^{1}H, 0.00 ppm) or $CDCl_3$ (^{13}C, 77.00 ppm). IR spectra were recorded on a Perkin–Elmer 1330 infrared spectrophotometer. Elemental analyses were performed in the UCM Microanalysis Service (Facultad de Farmacia, Universidad Complutense de Madrid, Spain). For purification of crude reaction mixtures flash chromatography was applied in all cases. Silica gel (230–400 mesh) and basic alumina were used as the stationary phase.

1*H*-Indole-2-carbaldehyde (1)

A solution of indole-2-carboxylic acid (10.0 g, 62.1 mmol) in MeOH (200 mL) was saturated with HCl (g). The mixture was heated under reflux for 24 h. The solvent was evaporated under vacuum. Without further purification, a solution of DIBAL-H (1.5 M in toluene;103.5 mL, 0.15 mol) in anhyd THF (400 mL) and under argon was added dropwise to a solution of this 1*H*-indole-2-carboxylic acid methyl ester in anhyd THF (300 mL) at –78 ºC. The mixture was stirred for 24 h. The reaction was then quenched by addition of sat. aq sodium tartrate (700 mL) and extracted with EtOAc (3 × 500 mL). The combined organic extracts were dried ($MgSO_4$) and evaporated under vacuum. This alcohol was dissolved in MeCN (300 mL) without further purification and manganese oxide (54.0 g, 0.62 mol) was added to the solution. The reaction mixture was stirred for 24 h. The solution was filtered through Celite and the solvent evaporated under vacuum. The crude product was purified by flash chromatography (hexane–EtOAc, 4:1) to obtain **1**.

Yield: 7.2 g (80%, three steps); yellow solid; mp 141–143 °C (hexane–EtOAc) (lit.[8] 139–140 °C).

IR (KBr): 3200, 2920, 1670 cm^{-1}.

^{1}H NMR ($CDCl_3$): δ = 7.18 (t, 1 H, *J* = 7.7 Hz), 7.28 (d, 1 H, *J* = 1.6 Hz), 7.42 (m, 2 H), 7.75 (d, 1 H, *J* = 7.7 Hz), 9.03 (br s, 1 H), 9.85 (s, 1 H).

^{13}C NMR ($CDCl_3$): δ = 182.6, 138.3, 127.3, 127.2, 123.3, 121.1, 115.3, 115.3, 112.6.

2-Vinyl-1*H*-indole (2)

To a solution of methyltriphenylphosphonium bromide (5.54 g, 15.51 mmol) in anhyd THF (75 mL) under argon, KHMDS (0.5 M in toluene; 26.9 mL, 13.44 mmol) was added. The mixture was stirred at r.t. for 0.5 h. The ylide formed was added dropwise to a solution of **1** (1.5 g, 10.34 mmol) in anhyd THF (50 mL). The reaction was stirred at r.t. for 2 h. The resulting suspension was poured into Et_2O –H_2O (1:1, 200 mL). The organic layer was separated and the aq layer extracted with Et_2O (3 × 50 mL). The combined organic phases were dried ($MgSO_4$) and the solvent was evaporated under vacuum. The crude was purified by flash chromatography (hexane–EtOAc, 5:1) to obtain **2**.

Yield: 1.46 g (quantitative); pale yellow solid; mp 85–86 °C (hexane–EtOAc).

IR (KBr): 3380, 3020, 1450 cm^{-1}.

^{1}H NMR ($CDCl_3$): δ = 5.26 (d, 1 H, *J* = 11.0 Hz), 5.54 (d, 1 H, *J* = 18.0 Hz), 6.51 (d, 1 H, *J* = 1.6 Hz), 6.74 (dd, 1 H, *J* = 18.0, 11.0 Hz), 7.08 (t, 1 H, *J* = 8.2 Hz), 7.18 (t, 1 H, *J* = 7.7 Hz), 7.33 (d, 1 H, *J* = 7.7 Hz), 7.56 (d, 1 H, *J* = 8.2 Hz), 8.16 (br s, 1 H).

^{13}C NMR ($CDCl_3$): δ = 136.5, 136.2, 128.6, 127.4, 122.7, 120.7, 120.0, 112.2, 110.7, 102.9.

1,3-Di-(2-propynyl)-2-vinyl-1*H*-indole (3)

To a solution of **2** (0.75 g, 5.24 mmol) in toluene (25 mL), aq NaOH (30%; 25 mL), propargyl bromide (0.68 mL, 0.86 mmol) and tetrabutylammonium iodide (0.19 g, 0.52 mmol) were added. The reaction mixture was vigorously stirred at r.t. for 5 h. The organic layer was dried ($MgSO_4$) and the solvent evaporated under vacuum. The crude product was purified by flash chromatography (hexane) to obtain **3**.

Yield: 0.57 g (50%); white solid; mp 100–101 °C (hexane–EtOAc).

IR (KBr): 3250, 3040, 2910, 2100 cm^{-1}.

^{1}H NMR ($CDCl_3$): δ = 2.04 (t, 1 H, *J* = 2.8 Hz), 2.30 (t, 1 H, *J* = 2.2 Hz), 3.72 (d, 2 H, *J* = 2.8 Hz), 4.86 (d, 2 H, *J* = 2.2 Hz), 5.67 (dd, 1 H, *J* = 11.5, 1.1 Hz), 5.78 (dd, 1 H, *J* = 17.6, 1.1 Hz), 6.86 (dd, 1 H, *J* = 17.6, 11.5 Hz), 7.17 (t, 1 H, *J* = 7.7 Hz), 7.27 (t, 1 H, *J* = 8.2 Hz), 7.38 (d, 1 H, *J* = 8.2 Hz), 7.73 (d, 1 H, *J* = 7.7 Hz).

^{13}C NMR ($CDCl_3$): δ = 136.4, 134.1, 127.3, 124.9, 122.8, 120.7, 120.1, 119.1, 109.3, 109.0, 82.6, 78.4, 72.5, 68.2, 33.3, 14.6.

Anal. Calcd for $C_{16}H_{13}N$: C, 87.64; H, 5.98; N, 6.39. Found: C, 87.79; H, 6.09; N, 6.52.

1-(2-Propynyl)-2-vinyl-1*H*-indole (4)

To a solution of **2** (0.44 g, 3.08 mmol) in anhyd DMF (100 mL) was added under argon caesium carbonate (3.01 g, 9.24 mmol) and propargyl bromide (1.02 mL, 9.24 mmol). The mixture was heated at 60 ºC for 24 h. The solution was diluted with EtOAc (50 mL) and washed with water (2 × 50 mL). The combined organic extracts were dried ($MgSO_4$) and evaporated under vacuum. The crude product was purified by flash chromatography (hexane–EtOAc, 24:1) to obtain **4**.

Yield: 0.37 g (70%); yellow solid; mp 77–78 °C (hexane–EtOAc).

IR (KBr) 3250, 3040, 2910, 2100 cm^{-1}.

^{1}H NMR ($CDCl_3$): δ = 2.31 (t, 1 H, *J* = 2.7 Hz), 4.91 (d, 2 H, *J* = 2.7 Hz), 5.43 (dd, 1 H, *J* = 11.0,1.1 Hz), 5.87 (dd, 1 H, *J* = 17.6, 1.1 Hz), 6.71 (s, 1 H), 6.85 (dd, 1 H, *J* = 17.6, 11.0 Hz), 7.12 (t, 1 H,

J = 8.2 Hz), 7.23 (t, 1 H, *J* = 7.7 Hz), 7.37 (d, 1 H, *J* = 8.2 Hz), 7.58 (d, 1 H, *J* = 7.7 Hz).

^{13}C NMR ($CDCl_3$): δ = 137.6, 136.9, 127.9, 125.4, 122.2, 120.7, 120.3, 117.0, 109.2, 100.2, 78.2, 72.5, 32.6.

Anal. Calcd for $C_{13}H_{11}N$: C, 86.15; H, 6.12; N, 7.73. Found: C, 86.30; H, 6.28; N, 7.85.

1-Allyl-1*H*-indole-2-carboxylic Acid Methyl Ester (5)
Following the same procedure used for the synthesis of **3**, from 1*H*-indole-2-carboxylic acid methyl ester (1.0 g, 5.71 mmol), aq NaOH (30%; 65 mL), allyl bromide (0.74 mL, 8.56 mmol) and tetrabutyl ammonium iodide (0.21 g, 0.57 mmol) and after purification by flash chromatography (hexane–EtOAc, 9:1), **6** was obtained.

Yield: 1.1g (90%); colourless oil.

IR (neat): 3040, 2940, 1710, 1515 cm^{-1}.

^{1}H NMR ($CDCl_3$): δ = 3.90 (s, 3 H), 4.88 (m, 1 H), 5.11 (m, 1 H), 5.24 (m, 2 H), 5.99 (m, 1 H), 7.20 (m, 2 H), 7.34 (m, 2 H), 7.69 (m, 1 H).

^{13}C NMR ($CDCl_3$): δ = 162.3, 139.1, 133.8, 126.9, 125.9, 125.1, 122.6, 120.7, 115.9, 110.7, 110.6, 51.6, 46.7.

1-Allyl-1*H*-indole-2-carbaldehyde (6)[1e]
Following the same procedure employed for the synthesis of **1**, from **5** (1.0 g, 4.65 mmol), DIBAL-H (1.5M in toluene; 7.75 mL, 11.63 mmol) and then by treatment of the crude product with manganese oxide (3.97 g, 46.5 mmol) and purification by flash chromatography (hexane–AcOEt, 9:1), **6** was obtained.

Yield: 0.67 g (78%); colourless oil.

IR (neat): 2800, 1665, 1515 cm^{-1}.

^{1}H NMR ($CDCl_3$): δ = 4.91 (dd, 1 H, *J* = 17.0, 1.1 Hz), 5.11 (dd, 1 H, *J* = 10.0, 1.1 Hz), 5.23 (m, 2 H), 5.93–6.05 (m, 1 H), 7.19 (td, 1 H, *J* = 8.2, 2.2 Hz), 7.30 (s, 1 H), 7.41 (m, 2 H), 7.75 (d, 1 H, *J* = 8.2 Hz), 9.89 (s, 1 H).

^{13}C NMR ($CDCl_3$): δ = 182.7, 140.3, 133.4, 133.3, 127.0, 123.4, 121.0, 118.1, 118.0, 116.3, 110.8, 46.7.

1-Allyl-2-vinyl-1*H*-indole (7)
Following the same procedure used for the synthesis of **2**, from methyltriphenylphosphonium bromide (0.87 g, 2.43 mmol), KHMDS (0.5M in toluene; 4.22 mL, 2.1 mmol) and **6** (0.3 g, 1.62 mmol) and after purification by flash chromatography (basic alumina; hexane), **7** was obtained.

Yield: 0.22 g (75%); colourless oil.

IR (neat): 3060, 2920, 1630 cm^{-1}.

^{1}H NMR ($CDCl_3$): δ = 4.73–4.75 (m, 2 H), 4.87 (dd, 1 H, J_1 = 18.1, 1.1 Hz), 5.12 (dd, 1 H, *J* = 10.4, 1.1 Hz), 5.32 (dd, 1 H, *J* = 11.0, 1.6 Hz), 5.81 (dd, 1 H, *J* = 17.6, 1.6 Hz), 5.88–5.99 (m, 1 H), 6.66–6.75 (m, 2 H), 7.08 (td, 1 H, *J* = 7.7, 1.1 Hz), 7.16 (td, 1 H, *J* = 8.2, 1.1 Hz) 7.24 (d, 1 H, *J* = 8.2 Hz), 7.58 (d, 1 H, *J* = 7.7 Hz).

^{13}C NMR ($CDCl_3$): δ = 138.1, 137.3, 133.2, 127.8, 125.7, 121.8, 120.5, 119.9, 116.4, 116.3, 109.4, 99.2, 45.4.

Anal. Calcd for $C_{13}H_{13}N$: C, 85.21; H, 7.15; N, 7.64. Found: C, 85.39; H, 7.29; N, 7.78.

2-Trimethylsilanylethynyl-1*H*-indole (9)
The crude product obtained in the reaction of indole (1.17 g, 10.0 mmol) with BuLi (2.5 M in hexane; 4.2 mL), *t*-BuLi (1.7 M in pentane; 6.2 mL) and 1,2-diiodoethane (2.82 g, 10.0 mmol) following the method described by Bergman and Velemalm[7] was dissolved in toluene (25 mL). Then, a solution of $Pd(PPh_3)_2Cl_2$ (0.34 g, 0.56 mmol), butylamine (3.6 mL, 44.88 mmol), trimethylsilylacetylene (3.2 mL, 22.44 mmol) and copper(I) iodide (0.43 g, 2.24 mmol) in toluene (25 mL) was added and the mixture was stirred at r.t. for 4 h. The solvent was evaporated under vacuum and the crude was purified by flash chromatography (hexane) to obtain **9**.

Yield: 1.82 g (85%); yellow solid; mp 92–93 °C (hexane–EtOAc).

IR (KBr): 3490, 3040, 2140 cm^{-1}.

^{1}H NMR ($CDCl_3$): δ = 0.29 (s, 9 H), 6.79 (d, 1 H, *J* = 1.1 Hz), 7.13 (td, 1 H, *J* = 7.7, 1.1 Hz), 7.24 (td, 1 H, *J* = 8.2, 1.1 Hz), 7.31 (dd, 1 H, *J* = 8.2, 1.1 Hz), 7.59 (d, 1 H, *J* = 7.7 Hz), 8.18 (br s, 1 H).

^{13}C NMR ($CDCl_3$): δ = 135.8, 127.4, 123.6, 120.9, 120.4, 118.5, 110.7, 109.2, 98.4, 96.9, –0.19.

1-Allyl-2-ethynyl-1*H*-indole (10)
Following the same procedure used for the synthesis of **4**, from **9** (0.5 g, 2.7 mmol), caesium carbonate (0.88 g, 2.70 mmol) and allyl bromide (4.77 mL, 5.4 mmol) and after purification by flash chromatography (hexane), **10** was obtained.

Yield: 0.352 g (70%); pale yellow oil.

IR (neat): 3280, 3040, 2090 cm^{-1}.

^{1}H NMR ($CDCl_3$): δ = 3.46 (s, 1 H), 4.85–4.88 (m, 2 H), 4.97 (dd, 1 H, *J* = 17.0, 1.6 Hz), 5.15 (dd, 1 H, *J* = 9.9, 1.6 Hz), 5.90–6.02 (m, 1 H), 6.85 (s, 1 H), 7.09–7.15 (m, 1 H), 7.21–7.29 (m, 2 H), 7.59 (d, 1 H, *J* = 7.7 Hz).

^{13}C NMR ($CDCl_3$): δ = 136.4, 132.9, 126.9, 123.3, 121.1, 120.2, 116.6, 109.9, 108.7, 108.6, 83.4, 75.3, 46.4.

Anal. Calcd for $C_{13}H_{11}N$: C, 86.15; H, 6.12; N, 7.73. Found: C, 86.33; H, 6.26; N, 7.87.

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