

Palladium-catalysed cyclization of 2-alkynylanilines to 2-substituted indoles under an acidic two-phase system

Sandro Cacchi

Dipartimento di Studi di Chimica e Tecnologia delle Sostanze Biologicamente Attive, Università degli Studi "La Sapienza", P. le A. Moro 5, I-00185 Roma (Italy)

Veronica Carnicelli and Fabio Marinelli

Dipartimento di Chimica, Ingegneria Chimica e Materiali, Università degli Studi, V. Vetoio-località Coppito, I-67100 L'Aquila (Italy)

(Received January 14, 1994)

Abstract

The cyclization of 2-alkynylanilines in the presence of PdCl_2 and $^n\text{Bu}_4\text{NCl}$ under an acidic CH_2Cl_2 – HCl two-phase system affords 2-substituted indoles in good to high yield, at room temperature. The reaction is particularly suited to the one-flask preparation of 2-substituted indoles from 2-ethynylaniline.

Key words: Palladium; Two-phase catalysis; Indole

1. Introduction

Because of their potential as synthetic intermediates for the preparation of many alkaloids and pharmacologically active compounds [1,2], 2-substituted indoles represent a target of current interest. Amongst the methods reported in the literature, the palladium-catalysed cyclization of 2-alkynylanilines [3] or 2-anilides [3b,4] appear to play a valuable role in the synthesis of this class of compounds and our report on the utilization of this reaction in combination with the palladium-catalysed coupling of 2-ethynylaniline with vinyl and aryl triflates or halides [3a] provided a significant widening of the scope of the methodology. A crucial step in the cyclization mechanism requires the protolytic cleavage of the carbon–palladium bond of the supposed σ -vinylpalladium intermediate **1** (Scheme 1). Under widely used conditions (acetonitrile; 60–80°C; PdCl_2L_2 [3,4]; neutral conditions from now on) protons necessary for that arise from the hydrochloric acid generated in the conversion of the starting 2-alkynylanilines or 2-anilides into the σ -vinylpalladium complex **1**.

We have previously found that, under acidic CH_2Cl_2 –3 N HCl two-phase conditions, the PdCl_2 – $^n\text{Bu}_4\text{NCl}$ combination can successfully promote the formation of conjugate addition-type products from arylmercury or aryltin compounds and α,β -enones and α,β -enals [5] as well as the conversion of 4-hydroxy-1-alkynes into γ -hydroxy- α,β -enones [6] at room temperature, most probably favouring the protic cleavage of σ -vinylpalladium intermediates. Therefore, as part of our continuing effort to develop synthetic procedures for the preparation of the indole nucleus [3a,7] and speculating that the acidic medium could favour the protic cleavage of the σ -vinylpalladium intermediates **1** as well, we decided to explore the possible utilization of this catalytic system in the cyclization of 2-alkynylanilines **2** to 2-substituted indoles **3**.

In the following, we report the results of this study.

2. Results and discussion

2-Alkynylanilines **2**, prepared through the palladium-catalysed coupling of readily available 2-ethynyl-

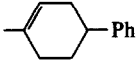
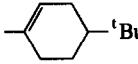
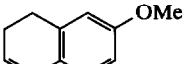
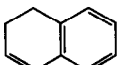
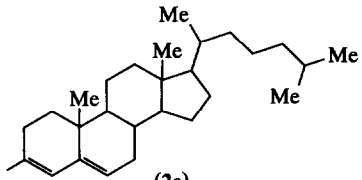
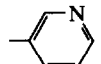
Correspondence to: Professor S. Cacchi or Dr. F. Marinelli.

aniline and a variety of vinyl and aryl halides or triflates [3a], have been reacted in the presence of the $\text{PdCl}_2\text{-}^n\text{Bu}_4\text{NCl}$ combination under an acidic $\text{CH}_2\text{-Cl}_2\text{-HCl}$ two-phase system at room temperature to

give 2-substituted indoles **3** with a good to high yield. Our results are summarized in Table 1.

The hydrochloric acid concentration was found to affect the reaction outcome. For example, **2d** gave the

TABLE 1. Palladium-catalysed cyclization of 2-alkynylanilines **2** to 2-substituted indoles **3** in an acidic $\text{CH}_2\text{Cl}_2\text{-HCl}$ two-phase system (Scheme 2)^a

Number	2-Alkynylaniline 2 R	Reaction time (h)	Aqueous HCl (N)	Yield of 3 ^b (%)
1		20	0.5	3a 98
2		3	–	3a 87 ^c
3		20	0.5	3a 62 ^d
4		20	0.5	3a 40 ^e
5	 (2a)	20	–	3a 10
6	 (2b)	16	0.5	3b 97
7	 (2c)	72	2.0	3c 70
8		3.5	–	3c 64 ^c
9	 (2d)	36	–	3d 92
10		3.5	–	3d 76 ^c
11	 (2e)	10	0.5	3e 89 ^f
12	–C ₆ H ₄ –4-Me (2f)	48	3.0	3f 82
13	–C ₆ H ₄ –4-Me (2f)	3	–	3f 80 ^c
14	–C ₆ H ₄ –4-OMe (2g)	21	3.0	3g 68
15	–C ₆ H ₄ –3-F (2h)	72	3.0	3h 45
16	–C ₆ H ₄ –3-F (2h)	6	–	3h 51 ^c
17	–C ₆ H ₄ –3-F (2h)	72	3.0	3h 22 ^d
18	–C ₆ H ₄ –3-F (2h)	72	3.0	3h 14 ^e
19	–C ₆ H ₄ –4-COOMe (2i)	72	3.0	–
20	–CH=CH–Ph (2j)	72	3.0	3j 57
21	–CH=CH–Ph (2j)	2.5	–	3j 74 ^c
22	 (2k)	48	3.0	3k –
23		36	–	3k 38 ^c
24		5	–	3k 56 ^g

^a Unless otherwise stated, reactions were carried out at room temperature under an argon atmosphere, using the following molar ratios: **2**: PdCl_2 : $^n\text{Bu}_4\text{NCl}$ = 1:0.05:0.01.

^b Yields refer to single runs and are given on pure isolated products.

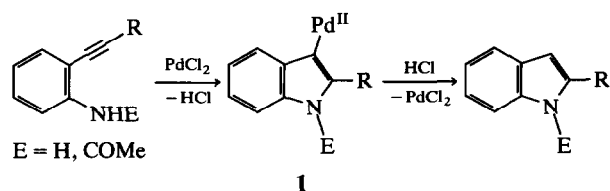
^c Carried out at 70°C in acetonitrile in the presence of PdCl_2 (5 mol.%) [**3a**].

^d Carried out in the presence of NaAuCl_4 (5 mol.%).

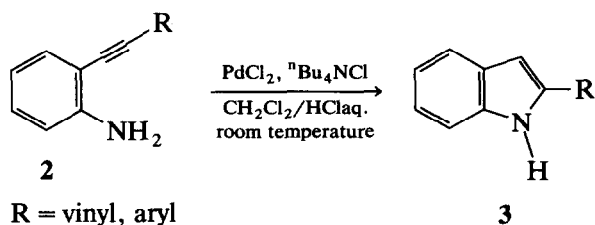
^e Carried out in the presence of NaAuCl_4 (5 mol.%) and $^n\text{Bu}_4\text{NCl}$ (10 mol.%).

^f In the presence of PdCl_2 (10 mol.%) and $^n\text{Bu}_4\text{NCl}$ (20 mol.%).

^g Carried out at 80°C in acetonitrile in the presence of NaAuCl_4 (5 mol.%) [**3b**].



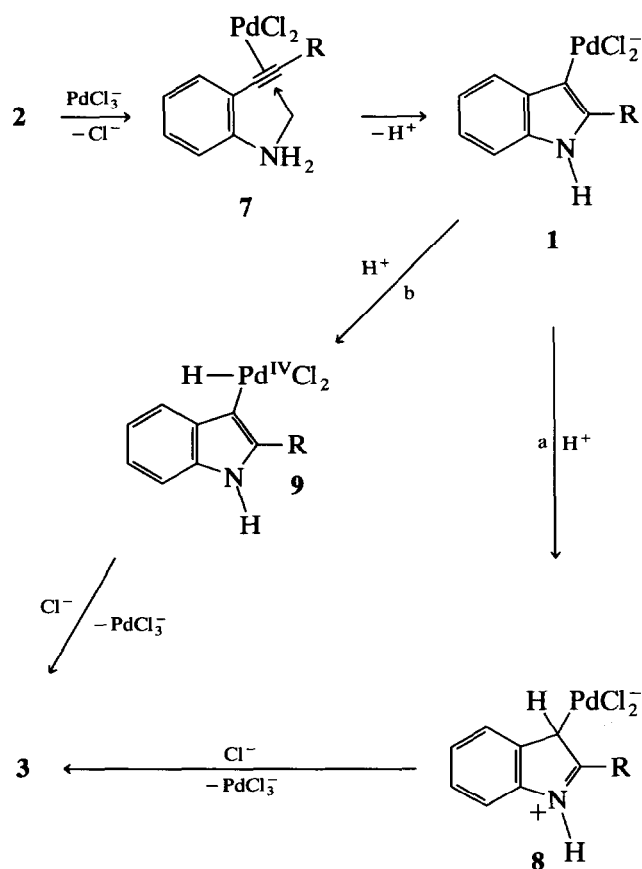
Scheme 1.



Scheme 2.

highest yield of the corresponding indole derivative in the presence of 2 N HCl (Table 2). In many cases, however, 0.5 N HCl provided good results.

Usually our acidic two phase conditions (room temperature) gave yields comparable with or higher than those obtained with PdCl₂ in acetonitrile (60–80°C) (Table 1, compare numbers 1, 7 and 9 with numbers 2, 8 and 10 respectively). The use of NaAuCl₄ with or without ⁿBu₄NCl under the same two-phase conditions afforded lower yields (Table 1, numbers 3, 4, 17 and 18). Limitations on the generality of the methodology arise when 2-alkynylanilines containing electron-withdrawing substituents are subjected to cyclization conditions (Table 1, numbers 19 and 22). With these substrates the use of neutral conditions was found to afford better results (Table 1, compare number 15 with 16 and number 22 with 23). In the effect, the highest yield with **2k** was obtained by using NaAuCl₄ under neutral conditions [3b] (Table 1, number 24). Since it seems likely that electron-withdrawing substituents may exert a closely similar influence on the step(s) leading



Scheme 3.

to the protic cleavage of the carbon–palladium bond of σ -vinylpalladium intermediates **1** under both neutral and acidic conditions, a reasonable working hypothesis accounting for the differences in reactivity observed with 2-alkynylanilines containing acetylenic π electrons conceivably less prone to coordinate palladium can be based on the assumption that they arise in the step leading to the formation of the π -alkynylpalladium complex **7** (Scheme 3). The idea is that in the presence of PdCl₂ and ⁿBu₄NCl this step involves a palladium(II) species less reactive than that operating under neutral conditions. In this respect, it may be worth mentioning that PdCl₂ and ⁿBu₄NCl have been reported to react in dichloromethane to produce a palladium complex whose minimal chemical structure may be represented as ⁿBu₄NPdCl₃ [8]. The possible presence of this dichloromethane soluble complex along the reaction coordinate leading to 2-substituted indoles appears to reconcile our results.

Based on these considerations, the reaction may be supposed to proceed through (a) nucleophilic attack of nitrogen on the complexed carbon–carbon triple bond, (b) protonation of the σ -vinylpalladium complex **1** and

TABLE 2. Acid concentration and synthesis of **3d** from **2d** in a CH₂Cl₂–HCl two-phase system in the presence of PdCl₂–ⁿBu₄NCl ^a

Acid concentration (N)	Recovered 2d yield ^b (%)	3d yield ^b (%)
0.1	55	9
0.5	26	35
1.0	17	45
2.0	–	92 ^c

^a Unless otherwise stated, reactions were carried out at room temperature (48 h), under a nitrogen atmosphere, using the following molar ratios: **2d**:PdCl₂:ⁿBu₄NCl = 1:0.05:0.10.

^b Yields refer to single run and are given on pure isolated products.

^c 36 h.



^c The crude mixture obtained from the palladium-catalysed coupling of **10** with **11a** was reacted, after evaporation at the rotary evaporator, with PdCl₂ in acetonitrile (80°C for 3.5 h).

two-phase system (room temperature for 14 h), again after evaporation under vacuum at the rotary evaporator, led to the isolation of **3a** with 98% yield.

Our results are summarized in Table 3.

In conclusion, we have shown that our protocol, based on the utilization of the $\text{PdCl}_2\text{-}^n\text{Bu}_4\text{NCl}$ combination in a $\text{CH}_2\text{Cl}_2\text{-HCl}$ two-phase system, allows an easy access to 2-substituted indole derivatives from 2-alkynylanilines under mild conditions. No protection of the amino group is needed. The possibility of preparing 2-substituted indoles through an efficient one-flask process from 2-ethynylaniline is of particular interest from a synthetic standpoint. In the most favourable cases, it is possible to synthesize 2-substituted indoles from 2-ethynylaniline at room temperature.

3. Experimental details

Melting points were determined with a Büchi apparatus and are uncorrected. PdCl_2 , NaAuCl_4 and $^n\text{Bu}_4\text{NCl}$ are commercially available and were used as purchased, without further purification. 2-Alkynylanilines **2** were prepared as reported in reference [3a]. Vinyl triflates **11a**, **m** [10], **n** [11], **o** and **p** [6] were prepared according to reference [12] and purified by flash chromatography on silica gel eluting with *n*-hexane–EtOAc mixtures. Palladium-catalysed cyclization of 2-alkynylanilines and one-flask conversion of 2-ethynylaniline into 2-substituted indoles were carried out on a 0.3–1.2 mmol scale. The products were purified by flash chromatography on silica gel eluting with *n*-hexane–EtOAc mixtures.

NMR spectra (CDCl_3 , unless otherwise indicated; tetramethylsilane as internal standard) were recorded with a Bruker AC 200 spectrometer. IR spectra (KBr, unless otherwise indicated) were recorded with a Perkin–Elmer 683 spectrometer. Electron impact (EI) and chemical ionization (CI) (CH_4) mass spectra were recorded on a HP 59970 spectrometer workstation formed by an HP 5890 gas chromatograph equipped with a methyl silicone capillary column and by an HP 5970 mass detector. All the isolated products gave satisfactory microanalyses.

3.1. 2-Alkynylanilines **2a–2k**

3.1.1. 2-(4-Phenylcyclohex-1-enyl)ethynylaniline (**2a**)

M.p., 125–127°C. IR: ν 3500, 3400, 2190 cm^{-1} . ^1H NMR: δ 7.35–7.15 (m, 6H), 7.10–7.03 (m, 1H), 6.69–6.62 (m, 2H), 6.25 (bs, 1H), 4.15 (bs, 2H), 2.82–2.73 (m, 1H), 2.48–2.26 (m, 4H), 2.01–1.76 (m, 2H). ^{13}C NMR: δ 147.5, 146.3, 134.0, 131.9, 129.2, 128.4, 126.8, 126.2, 120.6, 117.7, 114.2, 108.3, 96.2, 83.8, 39.1, 33.8, 30.1,

29.5. Mass spectroscopy (MS) (CI): m/e (relative intensity) 274 (MH^+ , 100).

3.1.2. 2-(4-*tert*-Butylcyclohex-1-enyl)ethynylaniline (**2b**)

M.p., 93–94°C. IR: ν 3450, 3350, 2180 cm^{-1} . ^1H NMR: δ 7.25 (d, J = 7.8 Hz, 1H), 7.10–7.02 (m, 1H), 6.68–6.61 (m, 2H), 6.18 (bs, 1H), 4.16 (bs, 2H), 2.31–2.10 (m, 3H), 1.95–1.75 (m, 2H), 1.30–1.20 (m, 2H), 0.87 (s, 9H). ^{13}C NMR: δ 147.5, 135.0, 131.9, 129.1, 120.5, 117.8, 114.1, 108.5, 96.4, 83.3, 43.2, 32.2, 31.0, 27.5, 27.1, 23.8. MS (CI): m/e (relative intensity) 254 (MH^+ , 100).

3.1.3. 2-(6-Methoxy-3,4-dihydro-1-naphthyl)ethynylaniline (**2c**)

Oil. IR (neat): ν 3460, 3370, 2200 cm^{-1} . ^1H NMR: δ 7.59 (d, J = 8.4 Hz, 1H), 7.38–7.26 (m, 1H), 7.15–7.04 (m, 1H), 6.77–6.64 (m, 4H), 6.38 (t, J = 4.8 Hz, 1H), 4.20 (bs, 2H), 3.76 (s, 3H), 2.77 (t, J = 8.4 Hz, 2H), 2.42–2.31 (m, 2H). ^{13}C NMR: δ 159.1, 147.8, 136.9, 132.8, 132.1, 129.5, 126.2, 125.8, 121.3, 117.9, 114.3, 113.2, 111.2, 108.2, 92.8, 86.5, 55.2, 27.6, 23.6. MS (CI): m/e (relative intensity): 276 (MH^+ , 100).

3.1.4. 2-(3,4-Dihydro-1-naphthyl)ethynylaniline (**2d**)

Oil. IR (neat): ν 3500, 3400, 2200 cm^{-1} . ^1H NMR: δ 7.66 (d, J = 7.3 Hz, 1H), 7.37–7.33 (m, 1H), 7.24–7.03 (m, 4H), 6.70–6.60 (m, 2H), 6.48 (t, J = 4.8 Hz, 1H), 4.20 (bs, 2H), 2.76 (t, J = 8.0 Hz, 2H), 2.40–2.29 (m, 2H). ^{13}C NMR: δ 135.3, 135.1, 132.6, 132.1, 129.5, 127.7, 127.4, 126.6, 124.9, 121.7, 117.8, 114.3, 108.0, 92.5, 86.8, 27.1, 23.6. MS (CI): m/e (relative intensity): 246 (MH^+ , 100).

3.1.5. 2-(Cholesta-3,5-dien-3-yl)ethynylaniline (**2e**)

M.p., 207–209°C. IR: ν 3350, 3450 cm^{-1} . ^1H NMR: δ 7.29–7.24 (m, 1H), 7.09 (t, J = 7.7 Hz, 1H), 6.71–6.63 (m, 2H), 6.36 (s, 1H), 5.55 (bs, 1H), 4.20 (bs, 2H). ^{13}C NMR: δ 147.5, 141.4, 135.2, 131.9, 129.2, 126.5, 117.9, 117.1, 114.2, 108.6, 97.0, 85.5. MS (CI): m/e (relative intensity) 484 (MH^+ , 100).

3.1.6. 2-(4-Methylphenyl)ethynylaniline (**2f**)

M.p., 100–102°C. IR: ν 3400, 3500, 2210 cm^{-1} . ^1H NMR: δ 7.44–7.32 (m, 3H), 7.21–7.07 (m, 3H), 6.74–6.66 (m, 2H), 4.25 (bs, 2H), 2.35 (s, 3H). ^{13}C NMR: δ 147.7, 138.3, 132.0, 131.3, 129.5, 129.1, 120.2, 117.9, 114.3, 108.1, 94.8, 85.2, 21.5. MS (CI): m/e (relative intensity) 208 (MH^+ , 100).

3.1.7. 2-(4-Methoxyphenyl)ethynylaniline (**2g**)

M.p., 104–106°C. IR: ν 3500, 3400 cm^{-1} . ^1H NMR: δ 7.45 (AA' part of an AA'BB' system, J = 8.6 Hz, 2H),

7.35 (d, $J = 7.4$ Hz, 1H), 7.11 (t, $J = 7.8$ Hz, 1H), 6.86 (BB' part of an AA'BB' system, $J = 8.6$ Hz, 2H), 6.74–6.66 (m, 2H), 4.03 (bs, 2H), 3.80 (s, 3H). ^{13}C NMR: δ 159.5, 147.6, 132.9, 131.9, 129.4, 117.9, 115.4, 114.3, 114.0, 108.2, 94.6, 84.5, 55.2. MS (CI): m/e (relative intensity) 224 (MH^+ , 100).

3.1.8. 2-(3-Fluorophenyl)ethynylaniline (2h)

M.p., 70–72°C. IR 3500, 3400, 2190 cm^{-1} . ^1H NMR: δ 7.37–6.99 (m, 6H), 6.73–6.66 (m, 2H), 4.27 (bs, 2H). ^{13}C NMR: δ 162.4 (d, $J = 246$ Hz), 147.9, 132.2, 130.1, 129.9, 127.3, 127.2, 118.1 (d, $J = 23$ Hz), 118.0, 115.5 (d, $J = 21$ Hz), 114.4, 107.3, 93.4, 86.9. MS (CI): m/e (relative intensity): 212 (MH^+ , 100).

3.1.9. 2-(4-Carbomethoxyphenyl)ethynylaniline (2i)

M.p., 127–129°C. IR: ν 3490, 3390, 2200, 1720 cm^{-1} . ^1H NMR: δ 8.02 (AA' part of an AA'BB' system, $J = 7.9$ Hz, 2H), 7.57 (BB' part of an AA'BB' system, $J = 7.9$ Hz, 2H), 7.39–7.35 (m, 1H), 7.21–7.12 (m, 1H), 6.76–6.69 (m, 2H), 4.30 (bs, 2H), 3.93 (s, 3H). ^{13}C NMR: δ 166.5, 150.0, 132.3, 131.3, 130.3, 129.5, 129.3, 128.0, 118.0, 114.4, 107.2, 94.0, 89.1, 52.2. MS (CI): m/e (relative intensity) 252 (MH^+ , 100).

3.1.10. 2-(2-Phenyleth-1-enyl)ethynylaniline (2j)

M.p., 95–97°C. IR: ν 3490, 3390, 2180 cm^{-1} . ^1H NMR: δ 7.44–7.26 (m, 6H), 7.16–7.08 (m, 1H), 7.02 (AA' part of an AA'BB' system, $J = 16.2$ Hz, 1H), 6.75–6.66 (m, 2H), 6.43 (BB' part of an AA'BB' system, $J = 16.2$ Hz, 1H), 4.20 (bs, 2H). ^{13}C NMR: δ 147.7, 140.6, 136.2, 132.0, 129.6, 128.7, 128.5, 126.2, 117.9, 114.3, 108.1, 94.2, 88.3. MS (CI): m/e (relative intensity) 220 (MH^+ , 100).

3.1.11. 2-(3-Pyridyl)ethynylaniline (2k)

M.p., 104–106°C. IR: ν 3470, 3330, 2200 cm^{-1} . ^1H NMR: δ 8.76–8.74 (m, 1H), 8.54–8.50 (m, 1H), 7.79–7.73 (m, 1H), 7.39–7.34 (m, 1H), 7.27–7.10 (m, 2H), 6.74–6.67 (m, 2H), 4.36 (bs, 2H). ^{13}C NMR: δ 151.9, 148.4, 148.0, 138.2, 132.3, 130.3, 123.1, 120.5, 117.9, 114.4, 106.9, 91.2, 89.4. MS (CI): m/e (relative intensity) 195 (MH^+ , 100).

3.2. General procedure for the cyclization of 2-alkynylanilines (2): synthesis of 2-(3,4-dihydro-1-naphthyl)indole (3d)

To a solution of **2d** (0.200 g, 0.81 mmol) in dichloromethane (15 ml) were added 2.0 N HCl (5 ml), PdCl_2 (0.007 g, 0.040 mmol) and $n\text{Bu}_4\text{NCl}$ (0.024 g, 0.081 mmol). The reaction mixture was stirred for 36 h at room temperature under nitrogen and poured into a separatory funnel containing diethyl ether and saturated NaHCO_3 . The organic layer was separated, and

the aqueous layer was extracted twice with diethyl ether. The combined organic layers were dried (Na_2SO_4) and evaporated under vacuum. The residue was separated on silica gel eluting with a 90/10 *n*-hexane/EtOAc mixture to afford 0.185 g of **3d** (92% yield).

3.3. General procedure for one-flask conversion of 2-ethynylaniline (10) into 2-substituted indoles (3): synthesis of 2-(3 α -acetoxyandrost-16-en-17-yl)indole (3m)

To a stirred solution of 3 α -acetoxy-androst-16-en-17-yl triflate **11n** (0.230 g, 0.49 mmol) in dimethylformamide (0.5 ml) and diethylamine (2 ml) were added 2-ethynylaniline **10** (0.058 g, 0.49 mmol), $\text{Pd}(\text{PPh}_3)_4$ (0.011 g, 0.009 mmol) and CuI (0.004 g, 0.020 mmol). The reaction mixture was stirred for 6 h at room temperature under a nitrogen atmosphere, and then evaporated under vacuum at the rotary evaporator (warm water bath). The residue was dissolved in dichloromethane (13 ml) and 0.5 N HCl (5 ml), PdCl_2 (0.05 g, 0.028 mmol), and $n\text{Bu}_4\text{NCl}$ (0.015 g, 0.051 mmol) were added. The reaction mixture was stirred at room temperature for 48 h under a nitrogen atmosphere. Work-up as before afforded a residue which was purified by silica gel chromatography eluting with a 80/20 *n*-hexane/EtOAc mixture to give 0.205 g of **3m** (96% yield).

3.3.1. 2-(4-Phenylcyclohex-1-enyl)indole (3a)

M.p., 201–203°C. IR 3450 cm^{-1} . ^1H NMR: δ 8.08 (bs, 1H), 7.56 (d, $J = 7.5$ Hz, 1H), 7.36–7.02 (m, 8H), 6.47 (d, $J = 1.5$ Hz, 1H), 6.15 (bs, 1H), 2.95–2.80 (m, 1H), 2.61–2.36 (m, 4H), 2.15–1.85 (m, 2H). ^{13}C NMR: δ 146.5, 138.9, 136.2, 129.0, 128.9, 128.5, 126.9, 126.2, 122.1, 121.9, 120.4, 119.8, 110.4, 99.2, 39.8, 33.6, 29.6, 26.7. MS (EI): m/e (relative intensity): 273 (M^+ , 73).

3.3.2. 2-(4-tert-Butylcyclohex-1-enyl)indole (3b)

M.p., 148–150°C. IR 3390 cm^{-1} . ^1H NMR: δ 8.05 (bs, 1H), 7.55 (d, $J = 7.4$ Hz, 1H), 7.30–7.05 (m, 3H), 6.42 (s, 1H), 6.06 (t, $J = 2.8$ Hz, 1H), 2.70–2.55 (m, 1H), 2.45–2.15 (m, 2H), 2.10–1.90 (m, 2H), 1.40–1.20 (m, 2H), 0.92 (s, 9H). ^{13}C NMR: δ 139.2, 136.2, 128.9, 128.8, 122.8, 121.9, 120.3, 119.7, 110.4, 98.7, 43.9, 32.2, 27.5, 27.2, 27.1, 23.9. MS (EI): m/e (relative intensity) 253 (M^+ , 78).

3.3.3. 2-(6-Methoxy-3,4-dihydro-1-naphthyl)indole (3c)

M.p., 122–124°C. IR 3390 cm^{-1} . ^1H NMR: δ 7.98 (bs, 1H), 7.58 (d, $J = 7.7$ Hz, 1H), 7.31–7.03 (m, 4H), 6.76–6.75 (m, 1H), 6.67–6.61 (m, 1H), 6.53 (d, $J = 1.9$ Hz, 1H), 6.12 (t, $J = 4.8$ Hz, 1H), 3.75 (s, 3H), 2.74 (t, $J = 8$ Hz, 2H), 2.36–2.26 (m, 2H). ^{13}C NMR: δ 158.8,

138.8, 137.2, 135.8, 131.2, 128.6, 126.6, 126.5, 125.8, 121.8, 120.3, 119.8, 114.0, 110.8, 110.7, 101.7, 55.2, 28.4, 23.1. MS (EI): m/e (relative intensity) 275 (M^+ , 100).

3.3.4. 2-(3,4-Dihydro-1-naphthyl)indole (3d)

M.p., 157–159°C. IR: ν 3440 cm^{-1} . ^1H NMR: δ 8.01 (bs, 1H), 7.61 (d, $J = 8.0$ Hz, 1H), 7.40–7.28 (m, 2H), 7.22–7.08 (m, 5H), 6.58 (d, $J = 2.0$ Hz, 1H), 6.33 (t, $J = 4.8$ Hz, 1H), 2.82 (t, $J = 7.8$ Hz), 2.44–2.33 (m, 2H). ^{13}C NMR: δ 136.9, 135.8, 133.6, 131.7, 128.6, 128.5, 127.8, 127.5, 126.5, 125.3, 121.9, 120.4, 119.9, 110.7, 101.9, 28.0, 23.2. MS (EI): m/e (relative intensity) 245 (M^+ , 61).

3.3.5. 2-(Cholesta-3,5-dien-3-yl)indole (3e)

M.p., 213–216°C. IR: ν 3450 cm^{-1} . ^1H NMR: δ 8.17 (bs, 1H), 7.55 (d, $J = 7.5$ Hz, 1H), 7.32–7.28 (m, 1H), 7.14–7.05 (m, 2H), 6.53 (d, $J = 1.6$ Hz, 1H), 6.34 (s, 1H), 5.60 (bs, 1H). ^{13}C NMR: δ 141.7, 139.0, 136.5, 129.0, 125.7, 125.6, 123.8, 122.2, 120.3, 119.9, 110.4, 99.9. MS (EI): m/e (relative intensity) 483 (M^+ , 100).

3.3.6. 2-(4-Methylphenyl)indole (3f)

M.p., 212–214°C. IR: ν 3450 cm^{-1} . ^1H NMR (acetone- d_6): δ 10.60 (bs, 1H), 7.75 (AA' part of an AA'BB' system, $J = 8.1$ Hz, 2H), 7.55 (d, $J = 7.5$ Hz, 1H), 7.40 (d, $J = 7.7$ Hz, 1H), 7.26 (BB' part of an AA'BB' system, $J = 8.1$ Hz, 2H), 7.12–6.96 (m, 2H), 6.84 (d, $J = 2.1$ Hz, 1H), 2.34 (s, 3H). ^{13}C NMR (acetone- d_6): δ 137.9, 130.3, 125.8, 122.3, 120.9, 120.3, 111.9, 99.3, 21.1. MS (EI): m/e (relative intensity) 207 (M^+ , 100).

3.3.7. 2-(4-Methoxyphenyl)indole (3g)

M.p., 219–221°C. IR: ν 3450 cm^{-1} . ^1H NMR (DMSO- d_6): δ 11.43 (bs, 1H), 7.80 (AA' part of an AA'BB' system, $J = 8.7$ Hz, 2H), 7.49 (d, $J = 7.5$ Hz, 1H), 7.38 (d, $J = 7.8$ Hz, 1H), 7.10–7.00 (m, 4H), 6.76 (d, $J = 1.9$ Hz), 3.80 (s, 3H). ^{13}C NMR (DMSO- d_6): δ 158.7, 137.7, 136.9, 128.8, 126.3, 124.9, 121.0, 119.7, 119.2, 114.3, 111.1, 97.3, 55.1. MS (EI): m/e (relative intensity) 223 (M^+ , 100), 208 (45).

3.3.8. 2-(3-Fluorophenyl)indole (3h)

M.p., 127–130°C. IR: ν 3450 cm^{-1} . ^1H NMR: δ 8.26 (bs, 1H), 7.63 (d, $J = 7.4$ Hz, 1H), 7.38–7.10 (m, 7H), 6.81 (d, $J = 2.2$ Hz, 1H). ^{13}C NMR: δ 163.2 (d, $J = 245$ Hz), 130.7, 130.5, 122.8, 120.9, 120.7, 120.6, 120.5, 114.4 (d, $J = 21$ Hz), 112.0 (d, $J = 23$ Hz), 111.0, 100.9. MS (EI): m/e (relative intensity) 211 (M^+ , 100).

3.3.9. 2-(2-Phenyleth-1-enyl)indole (3j)

M.p., 198–201°C. IR: ν 3420 cm^{-1} . ^1H NMR (acetone- d_6): δ 10.60 (bs, 1H), 7.58–7.49 (m, 3H), 7.41–

7.21 (m, 6H), 7.15–6.96 (m, 2H), 6.62 (d, $J = 1.2$ Hz, 1H). ^{13}C NMR (acetone- d_6): 138.2, 129.6, 128.3, 127.9, 127.0, 123.1, 121.0, 120.3, 120.2, 111.6, 104.1. MS (EI): m/e (relative intensity) 219 (M^+ , 100).

3.3.10. 2-(3-Pyridyl)indole (3k)

M.p., 163–166°C. IR: ν 3170 cm^{-1} . ^1H NMR: δ 9.10 (bs, 1H), 9.00 (d, $J = 1.9$ Hz, 1H), 8.54–8.51 (m, 1H), 7.98 (dt, $J = 7.9$ Hz, $J = 1.8$ Hz, 1H), 7.65 (d, $J = 7.6$ Hz, 1H), 7.44–7.33 (m, 2H), 7.23–7.10 (m, 2H), 6.89 (d, $J = 1.5$ Hz, 1H). ^{13}C NMR: δ 148.2, 146.2, 137.3, 134.4, 132.6, 128.9, 128.7, 123.9, 123.0, 120.9, 120.6, 111.2, 101.3. MS (CI): m/e (relative intensity) 195 (MH^+ , 100).

3.3.11. 2-(17-Oxoandrosta-3,5-dien-3-yl)indole (3l)

M.p., 259–261°C. IR: ν 3480, 1730 cm^{-1} . ^1H NMR: δ 8.18 (bs, 1H), 7.56 (d, $J = 7.6$ Hz, 1H), 7.32 (d, $J = 7.6$ Hz, 1H), 7.19–7.02 (m, 2H), 6.55 (d, $J = 1.3$ Hz, 1H), 6.36 (s, 1H), 5.62 (bs, 1H), 1.03 (s, 3H), 0.93 (s, 3H). ^{13}C NMR: δ 221.1, 141.7, 138.7, 136.5, 129.0, 126.0, 124.4, 123.4, 122.3, 120.3, 119.9, 110.4, 100.1. MS (CI): m/e (relative intensity) 386 (MH^+ , 100).

3.3.12. 2-(3 β -Acetoxy-androst-16-en-17-yl)indole (3m)

M.p., 119–121°C. IR: ν 3400, 1740 cm^{-1} . ^1H NMR: δ 8.16 (bs, 1H), 7.55 (d, $J = 8.2$ Hz, 1H), 7.31–7.01 (m, 3H), 6.53 (d, $J = 1.6$ Hz, 1H), 5.95 (bs, 1H), 5.03 (bs, 1H), 2.05 (s, 3H), 1.03 (s, 3H), 0.86 (s, 3H). ^{13}C NMR: δ 170.8, 146.7, 136.0, 134.1, 129.0, 124.9, 122.1, 120.4, 119.8, 110.3, 99.9, 70.1. MS (EI): m/e (relative intensity) 431 (M^+ , 100), 372 (46).

3.3.13. 2-(3,3,5,5-Tetramethylcyclohex-1-enyl)indole (3n)

M.p., 79–82°C. IR: ν 3480 cm^{-1} . ^1H NMR: δ 8.15 (bs, 1H), 7.54 (d, $J = 6.9$ Hz, 1H), 7.30–7.00 (m, 3H), 6.45 (d, $J = 1.3$ Hz, 1H), 5.80 (s, 1H), 2.20 (d, $J = 1.1$ Hz, 2H), 1.43 (s, 2H), 1.11 (s, 6H), 1.04 (s, 6H). ^{13}C NMR: δ 139.4, 136.2, 131.4, 128.9, 125.4, 122.0, 120.3, 119.7, 110.3, 99.4, 49.6, 39.8, 33.0, 31.6, 30.6, 30.0.

3.3.14. 2-(Cyclooct-1-enyl)indole (3o)

M.p., 88–90°C. IR: 3400 cm^{-1} . ^1H NMR: δ 8.05 (bs, 1H), 7.54 (d, $J = 8$ Hz, 1H), 7.22–7.04 (m, 3H), 6.46 (d, $J = 1.8$ Hz, 1H), 7.01 (t, $J = 8.2$ Hz, 1H), 2.63 (t, $J = 6.2$ Hz, 2H), 2.35–2.25 (m, 2H). ^{13}C NMR: δ 139.2, 136.4, 132.4, 129.1, 125.1, 122.0, 120.3, 119.7, 110.3, 99.6, 30.3, 29.4, 27.1, 27.0, 26.8, 26.0. MS (CI): m/e (relative intensity) 226 (MH^+ , 100).

Acknowledgments

The authors gratefully acknowledge the Ministero dell'Università e della Ricerca Scientifica (MURST)

for financial support. The authors are also greatly indebted to Dr. Luciana Turchetto of the Istituto Superiore di Sanità for obtaining the mass spectra of new products.

References

- 1 R.J. Sundberg, in A.T. Blomquist (ed.), *The Chemistry of Indoles*, Academic Press, New York, 1970; R.K. Brown, in W.J. Houlihan (ed.), *Heterocyclic Compounds*, Vol. 25, Wiley-Interscience, New York, 1972; J.E. Appleton, K.N. Dack, A.D. Green and J. Steele, *Tetrahedron Lett.*, **34** (1993) 1529; S.P. Modi, A.-H. Zayed and S. Archer, *J. Org. Chem.*, **54** (1989) 3084; C. Hashimoto and H.-P. Husson, *Tetrahedron*, **29** (1988) 4563; M.E. Kuhene, D.E. Podhorez, T. Mulamba and W.G. Bornmann, *J. Org. Chem.*, **52** (1987) 347; P. Leon, C. Garbay-Jaureguiberry, M.C. Barsi, J.B. Le Pecq and B.P. Roques, *J. Med. Chem.*, **30** (1987) 2074; G.W. Gribble and D.A. Johnson, *Tetrahedron Lett.*, **28** (1987) 5259.
- 2 For the use of 2-vinylindoles in Diels-Alder reactions see for example J.E. Macor, M.E. Newman and K. Ryan, *Tetrahedron Lett.*, **30** (1989) 2509; M.E. Kuehne and W.G. Bornmann, *J. Org. Chem.*, **54** (1989) 3407; U. Pindur, *Heterocycles*, **27** (1988) 1253; M.K. Eberle, M.J. Shapiro and R. Stucki, *J. Org. Chem.*, **52** (1987) 4661.
- 3 (a) A. Arcadi, S. Cacchi and F. Marinelli, *Tetrahedron Lett.*, **30** (1989) 2581; (b) K. Iritani, S. Matsubara and K. Utimoto, *Tetrahedron Lett.*, **29** (1988) 1799.
- 4 D.E. Rudisill and J.K. Stille, *J. Org. Chem.*, **54** (1989) 5856; E.C. Taylor, A.H. Katz, H. Salgado-Zamora and A. McKillop, *Tetrahedron Lett.*, **26** (1985) 5963.
- 5 S. Cacchi and G. Palmieri, *Tetrahedron*, **39** (1983) 3373, and references cited therein.
- 6 A. Arcadi, S. Cacchi and F. Marinelli, *Tetrahedron*, **49** (1993) 4955.
- 7 A. Arcadi, S. Cacchi, V. Carnicelli and F. Marinelli, *Tetrahedron*, **50** (1994) 437; A. Arcadi, S. Cacchi, F. Marinelli and P. Pace, *Synlett*, (1993) 743; A. Arcadi, S. Cacchi and F. Marinelli, *Tetrahedron Lett.*, **33** (1992) 3915.
- 8 S. Cacchi, F. La Torre and D. Misiti, *Tetrahedron Lett.*, **47** (1979) 4591.
- 9 For other reactions suggested to proceed through the formation of palladium(IV) complexes see for example R.C. Larock, M.J. Doty and S. Cacchi, *J. Org. Chem.*, **58** (1993) 4579; A.J. Canty, *Acc. Chem. Res.*, **25** (1992) 83; S.K. Meegalla, N.J. Taylor and R. Rodrigo, *J. Org. Chem.*, **57** (1992) 2422; D. Milstein and J.K. Stille, *J. Am. Chem. Soc.*, **101** (1979) 4981. For isolated palladium(IV) complexes see for example M. Catellani and G.P. Chiusoli, *J. Organomet. Chem.*, **346** (1988) C35; M. Crespo and R.J. Puddephatt, *Organometallics*, **6** (1988) 2548; P.K. Byers and A.J. Canty, *J. Chem. Soc., Chem. Commun.*, (1988) 639; P.K. Byers, A.J. Canty, M. Crespo, R.J. Puddephatt and J.D. Scott, *Organometallics*, **6** (1988) 1363.
- 10 A. Arcadi, A. Burini, S. Cacchi, M. Delmastro, F. Marinelli and B.R. Pietroni, *J. Org. Chem.*, **57** (1992) 976.
- 11 W. Harnich, E. Morera and G. Ortar, *J. Org. Chem.*, **50** (1985) 1990.
- 12 S. Cacchi, E. Morera and G. Ortar, *Org. Synth.*, **68** (1990) 138; P.J. Stang and W. Treptow, *Synthesis*, (1980) 283; P.J. Stang, M. Hanack and L.R. Subramanian, *Synthesis*, (1982) 85.