Gold(III)-Catalyzed Annulation of 2-Alkynylanilines: A Mild and Efficient Synthesis of Indoles and 3-Haloindoles

Antonio Arcadi, Gabriele Bianchi, Fabio Marinelli*

Dipartimento di Chimica, Ingegneria Chimica e Materiali, Facoltà di Scienze, via Vetoio, 67100 L'Aquila, Italy
Fax +39(0862)433753; E-mail: fmarinel@univaq.it

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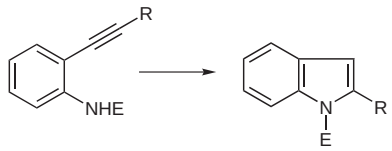
Abstract: Gold(III)-catalyzed annulation of 2-alkynylanilines in EtOH or EtOH–water mixtures at room temperature gives indoles derivatives in good yields. One-flask protocol for the gold-catalyzed conversion of 2-alkynylanilines to 3-bromo and 3-iodoindoles is also reported.

Key words: 2-alkynylanilines, indoles, 5-*endo*-dig cyclization, gold catalysis, halogenations

The indole nucleus is found in many natural and synthetic products that display a wide range of interesting biological activity[1] and is currently object of great synthetic efforts.[2] Besides classical methods (e.g. Fischer, Reissert and Madelung reactions),[3] many transition metals-assisted protocols have been developed in the last two decades,[2c,10] with remarkable improvements in terms of efficiency and functional group compatibility. In this area, one of the most investigated approach to indoles is represented by the cyclization of 2-alkynylanilines **1** or their N-substituted derivatives **2** (Scheme 1). Many reaction conditions have been reported for this purpose.



1 or **2** **3**

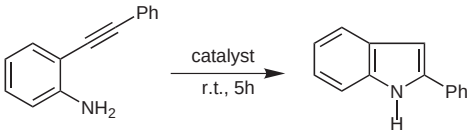
1 E = H
2 E = $COCH_3$, $COCF_3$, Tosyl, Mesyl

Scheme 1

Base-promoted cyclizations of 2-alkynylanilines[4] **1** or their N-protected derivatives[5] **2** have been developed. Nevertheless, many protocols rely on transition metal-catalyzed processes. Pd(II)-catalyzed cyclizations of **1** and **2** to 2-substituted indoles **3** have been widely explored.[6] Cu(II)-catalyzed cyclization of **1** and **2** occurs in refluxing dichloroethane in the presence of 10% of catalyst,[7] and a Cu(I)-promoted conversion of 2-[(trimethylsilyl)ethynyl]anilines to 2-unsubstituted indoles requires 2 equivalents of CuI in DMF at 100 °C.[8] Microwave-assisted solid-phase organic synthesis has been demonstrated to significantly facilitate the Cu(II) or Pd(II)-mediated ring closure of the resin-bound 2-alkynylanilides.[9] Syntheses of 2-substituted indoles through copper[10] or palladium[11] catalyzed domino reactions of N-protected *o*-iodoaniline derivatives with 1-alkynes have been also developed. 2,3-Disubstituted indoles could be readily available by electrophilic cyclization of 2-alkynylaniline derivatives assisted by I_2[12] or by σ-palladium complexes.[13]

Our interest towards the development of resource-saving and safe chemical processes[14] led us to explore gold salts as green catalysts.[15] Until now, little attention has been paid to gold-catalyzed cyclization of 2-alkynylanilines derivatives. Only few examples of $NaAuCl_4$-catalyzed cyclization of **1** or **2** in THF have been previously reported by Utimoto and co-workers;[16] moreover, it has been recently shown that this catalyst is scarcely efficient in the cyclization of 2-alkynyl-*N*-(alkoxycarbonyl)aniline to indoles in 1,2-dichloroethane at 100 °C (only one substrate was tested).[17] Consequently, the use of gold catalysis in the conversion of *o*-alkynylanilines **1** to indoles **3** remains largely unexplored.

Here we describe that a gold catalyst in EtOH or EtOH–water mixture at room temperature can lead to indoles in a very simple fashion. Indeed, with the aim to develop a synthetic protocol involving the use of more environmentally benign solvents and avoiding the need of protecting groups and or harsh reaction conditions, we selected 2-(phenylethynyl)aniline **1a** as a model substrate to attempt its cyclization in EtOH or EtOH–water mixtures at room temperature by means of a variety of catalysts (Equation 1). The results of this investigation are reported in Table 1.



1a **3a**

Equation 1

According to our previous results,[15] gold(III) catalysts were very effective. From all catalysts screened, $NaAuCl_4 \cdot 2H_2O$ in EtOH was the most efficient (entries 1, 6, 7) for the preparation of **3a**. Other Pd, Pt or Cu catalysts were much less effective than Au in promoting the cyclization (entries 8–14). Interestingly, the reaction can be

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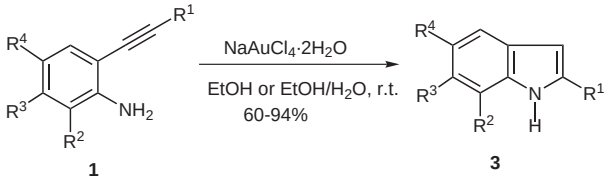
Table 1 Transition Metals-Catalyzed Synthesis of **3a** from **1a**[a]

Entry	catalyst	Solvent	Yield%[b]
1	$NaAuCl_4 \cdot 2H_2O$	EtOH	83
2	$NaAuCl_4 \cdot 2H_2O$	EtOH–H_2O, 95:5	80
3	$NaAuCl_4 \cdot 2H_2O$	EtOH–H_2O, 66:33	84
4	$NaAuCl_4 \cdot 2H_2O$	EtOH–H_2O, 50:50	82
5	$NaAuCl_4 \cdot 2H_2O$	EtOH–H_2O, 33:66	62
6	$KAuCl_4$	EtOH	76
7	AuCl	EtOH	50
8	$PtCl_4$	EtOH	20
9	$NaPdCl_4$	EtOH	7
10	$Pd(OAc)_2$	EtOH	8
11	$PdCl_2$	EtOH	6
12	$PdCl_2$	EtOH	5[c]
13	$Cu(OTf)_2$	EtOH	10
14	$Cu(OAc)_2$	EtOH	0

[a] Determined by GLC analysis.
[b] Reactions were carried out at r.t. under N_2 for 5 h on a 0.26 mmol scale with 0.01 mmol of catalyst in 1.5 mL of solvent.
[c] In the presence of 0.26 mmol of $CuCl_2 \cdot 2H_2O$

carried out in EtOH–water mixtures without loss of efficiency (entries 2–4); raising the amount of water of the EtOH–water mixtures over 50% can result in a less satisfactory yield of **3a** because of the decreasing solubility of **1a** (entry 5).

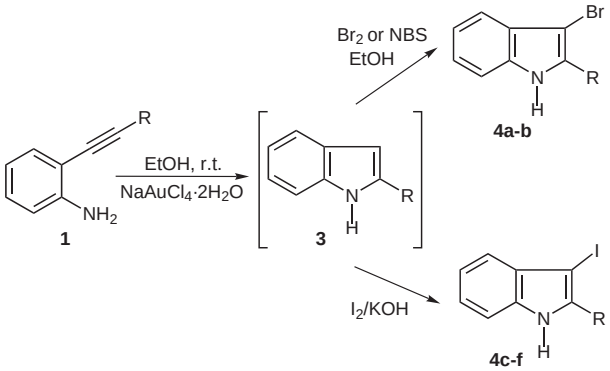
Subsequently this gold-catalyzed protocol has been extended to various alkynylanilines **1** (Equation 2).



Equation 2

The results of Table 2 show that $NaAuCl_4 \cdot 2H_2O$ in EtOH or EtOH–water mixtures affords indoles **3a**–**o** at room temperature in good to high yields. The gold-catalyzed annulation reaction of 2-alkynylanilines **1** is general and compatible with a large variety of functional groups. The isolation of products is simple and does not require extractive work-up. Interestingly, good results were obtained for the synthesis of 2-unsubstitued indoles **3l**–**o** (entries 15–19); it is worth noting that these products have been previously isolated from the corresponding 2-alkynylanilines in the presence of two-fold excess of CuI in hot DMF[8] or four-fold excess of *t*-BuOK in refluxing *t*-BuOH.[5b] The failure in the formation of **3l** by reacting **1l** with a catalytic amount (4 mol%) of $PdCl_2$ in refluxing MeCN for 7 hours gives further support to the advantage of the present protocol over the previously reported methodologies.[6]

Since 3-haloindoles **4** represents versatile building-blocks for the assembly of more complex structure,[18] we also attempted a one-flask gold-catalyzed conversion of 2-alkynylanilines **1** into 3-bromo and 3-iodoindoles **4**.[12] Considering that a variety of methods are available for the β-halogenation of indoles,[19] we found that the derivatives **4** can be conveniently prepared in a single, practical operation by adding the halogen source (NBS can also be used in place of Br_2) to the reaction mixture after that the conversion of **1** to **3** was observed by GC analysis (Scheme 2).



Scheme 2

The results of this latter protocol are summarized in Table 3. The alternative protocols[12] requires sophisticated iodonium source ($Ipy_2BF_4 \cdot HBF_4$) at temperatures between –20 °C and –60 °C or N-protecting groups and the use of excess of iodine (3 equiv), which could prove a disadvantage in relatively large scale preparations in terms of work-up and by-product disposal.

In conclusion, we have showen that gold catalysis can allow a mild and green procedure for the synthesis of indoles from 2-alkynylanilines. This approach is simple to perform and requires neither use of bases, acids nor N-protective group. One-flask gold-catalyzed conversion of 2-alkynylanilines into 3-haloindoles opens a clean and synthetically competitive alternative to the established procedures.

Table 2 Gold-Catalyzed Synthesis of Indoles **3** from 2-Alkynilanilines **1**[a]

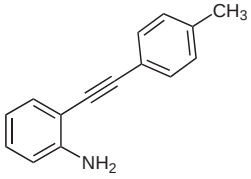
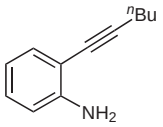
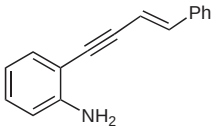
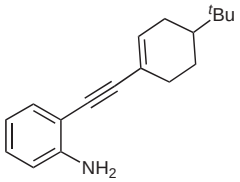
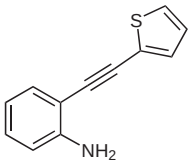
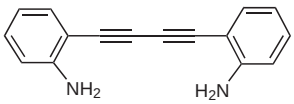
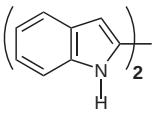
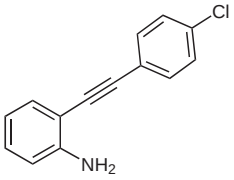
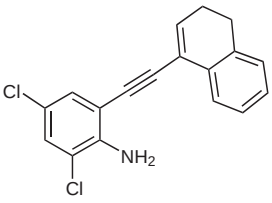
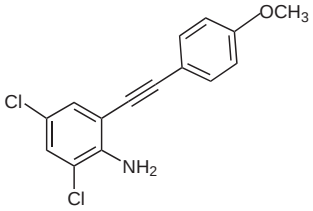
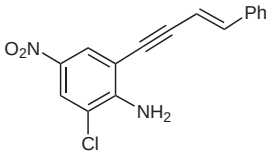
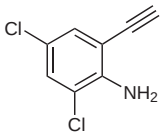
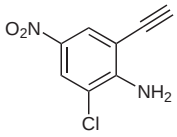
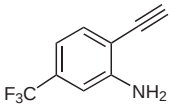
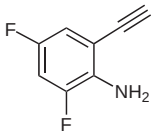
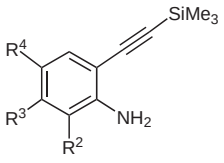
Entry	2-Alkynylaniline **1**	Solvent,[b] Time (h)	Indole **3**, Yield (%)
1	 **1b**	EtOH (2.5)	**3b** (80)
2	 **1c**	95:5 (4)	**3c** (74)
3	 **1d**	EtOH (4)	**3d** (70)
4	**1d**	95:5 (4.5)	**3d** (78)
5	**1d**	50:50 (7)	**3d** (75)
6	 **1e**	EtOH (2)	**3e** (83)
7	 **1f**	EtOH (4)	**3f** (80)
8	**1f**	50:50 (2.5)	**3f** (90)
9	 **1g**	EtOH (3)	 **3g** (70)[d]
10	 **1h**	EtOH (6)	**3h** (92)
11	 **1i**	EtOH (20)	**3i** (90)
12	**1i**	95:5 (20)	**3i** (77)

Table 2 Gold-Catalyzed Synthesis of Indoles **3** from 2-Alkynilanilines **1**[a] (continued)

Entry	2-Alkynylaniline **1**	Solvent,[b] Time (h)	Indole **3**, Yield (%)
13	 **1j**	50:50 (5.5)	**3j** (75)
14	 **1k**	EtOH (5)	**3k** (91)[e]
15	 **1l**	EtOH (7)	**3l** (79)
16	 **1m**	EtOH (16)	**3m** (66)
17	**1m**	50:50 (18)	**3m** (12)
18	 **1n**	EtOH (16)	**3n** (60)
19	 **1o**	EtOH (16)	**3o** (58)

[a] Reactions were carried out on a 0.35–0.75 mmol scale in 3–6 mL of solvent, at r.t. under N_2 using the following molar ratios: **1**/$NaAuCl_4 \cdot 2H_2O$ = 1:0.04.
[b] Numbers refer to ratio of EtOH–H_2O.
[c] Yields refer to single runs and are for pure isolated products.
[d] 6 mL of EtOH.
[e] Carried out at 70 °C.

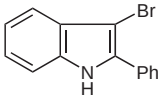
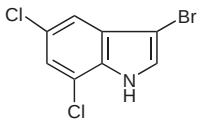
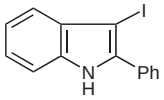
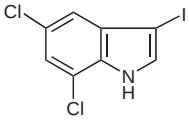
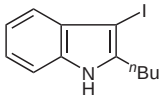
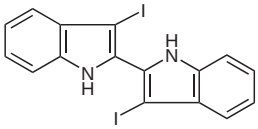
Melting points are uncorrected. ^1H NMR (200 MHz) and ^{13}C NMR (50.3 MHz) spectra were recorded on a Bruker AC 200 spectrometer in $CDCl_3$ (unless otherwise stated). EI (70 eV) mass spectra were recorded on a Varian Saturn 2100T/GC apparatus. IR spectra were recorded in KBr pellets or neat in NaCl disks using a Perkin-Elmer 683 spectrometer. 2-Alkynylanilines **1a**,**c**,**d**,**f**,**g**,[4] and **1b**,**e** [6d] are known products; **1h**,[6b] **1i**[21] and **1k**,**l**[20] were prepared from 2-ethynylanilines using reported procedures. 2-Ethynylanilines **1l**–**o** were obtained through desilylation of 2-ethynyltrimethylsilanyl anilines **1p**–**s** (Figure 1) which were in turn obtained by the Sonogashira reaction of commercially available 2-bromoanilines with ethynyltrimethylsilane.[21]



R^2	R^3	R^4	compound
Cl	H	Cl	**1p**
Cl	H	NO_2	**1q**
H	CF_3	H	**1r**
F	H	F	**1s**

Figure 1

Table 3 One-Flask Synthesis of 3-Halogenoindoles **4**[a]

Entry	Alkynylaniline **1**	3-Haloindole	Yield (%)[b]
1	**1a**	 **4a**	74 (75[c])
2	**1l**	 **4b**	80 (70[c])
3	**1a**	 **4c**	66
4	**1l**	 **4d**	64
5	**1c**	 **4e**	81
6	**1g**	 **4f**	56

[a] Reactions were carried out at r.t. under a N_2 atmosphere using the following molar ratios: **1**/$NaAuCl_4{\cdot}2H_2O$/Br_2 = 1:0.04:1 or **1**/$NaAuCl_4{\cdot}2H_2O$/I_2/KOH = 1:0.04:1:2.5.
[b] Yields refer to single runs and are for pure isolated products.
[c] Carried out using NBS (1.1 equiv) in place of Br_2

Preparation of 2-Trimethylsilanylethynylanilines 1p–s: Typical Procedure

To a solution of 2-bromo-4,6-dichloroaniline (1.363 g, 5.66 mmol) in DMF (1 mL) and Et_3N (4 mL) were added ethynyltrimethylsilane (1.205 mL, 8.48 mmol), $PdCl_2(PPh_3)_2$ (0.059 g, 0.084 mmol) and CuI (0.016 g, 0.084 mmol). The mixture was stirred at 50 °C for 8 h under N_2, then extracted with 0.1 M HCl (150 mL) and EtOAc (2 × 50 mL). The organic layer was dried (Na_2SO_4) and evaporated. Column chromatographic purification on silica gel (hexane–EtOAc, 98:2) afforded 2,4-dichloro-6-trimethylsilanylethynylaniline (**1p**).

Yield: 1.245g (85%); oil.

IR (neat): 3540, 3440, 2190 cm^{-1}.

^1H NMR: δ = 7.16 (s, 2 H, Ar), 4.58 (br s, 2 H, NH_2), 0.26 (s, 9 H, $SiCH_3$).

^{13}C NMR: δ = 143.5, 130.1, 129.4, 121.3, 118.9, 109.6 (Ar), 102.0, 99.6 (C≡C), –0.1 ($SiCH_3$).

MS: *m*/*z* (%) = 261 (14) [M^+ + 4], 259 (71) [M^+ + 2], 257 (100) [M^+], 207 (65).

2-Chloro-4-nitro-6-trimethylsilanylethynylaniline (1q)

Yield: 70%; mp 174–175 °C.

IR (KBr): 3500, 3390, 2140 cm^{-1}.

^1H NMR: δ = 8.13 (s, 2 H, Ar), 5.34 (br s, 2 H, NH_2), 0.29 (s, 9 H, $SiCH_3$).

^{13}C NMR: δ = 149.7, 137.6, 126.9, 125.6, 117.4, 107.7 (Ar), 103.4, 98.2 (C≡C), –0.2 ($SiCH_3$).

MS: *m*/*z* (%) = 270 (14) [M^+ + 2], 268 (46) [M^+], 253 (100).

5-Trifluoromethyl-2-trimethylsilanylethynylaniline (1r)

Yield: 66%; oil.

IR (neat): 3500, 3400, 2150 cm^{-1}.

^1H NMR: δ = 7.36 (d, *J* = 7.3 Hz, 1 H, Ar), 6.90–6.83 (m, 2 H, Ar), 4.41 (br s, 2 H, NH_2), 0.27 (s, 9 H, $SiCH_3$).

^{13}C NMR: δ = 148.3, 132.6, 131.5 (q, *J* = 32 Hz, C_5), 123.9 (q, *J* = 270 Hz, CF_3), 114.0 (q, *J* = 3.8 Hz), 111.5 (q, *J* = 4.0 Hz), 110.8 (Ar), 102.2, 100.3 (C≡C), –0.1 ($SiCH_3$).

MS: *m*/*z* (%) = 257 (100) [M^+], 242 (65).

2,4-Difluoro-6-trimethylsilanylethynylaniline (1s)

Yield: 91%; oil.

IR (neat): 3510, 340, 2150 cm^{-1}.

^1H NMR: δ = 6.85–6.75 (m, 2 H, Ar), 4.08 (br s, 2 H, NH_2), 0.27 (s, 9 H, $SiCH_3$).

^{13}C NMR: δ = 153.6 (dd, J_1 = 237.8 Hz, J_2 = 12.3 Hz, C_4), 150.4 (dd, J_1 = 241.6 Hz, J_2 = 12.6 Hz, C_2), 133.7 (dd, J_1 = 13.6 Hz, J_2 = 2.8 Hz, C_1), 113.3 (dd, J_1 = 23.3 Hz, J_2 = 3.6 Hz), 109.5 (dd, J_1 = 10.8 Hz, J_2 = 6.5 Hz), 104.9 (dd, J_1 = 26.9 Hz, J_2 = 22.7 Hz, Ar), 102.1, 99.3 (t, *J* = 4.0 Hz, C≡C), –0.1 ($SiCH_3$).

MS: *m*/*z* (%) = 225 (70) [M^+], 210 (100).

Preparation of 2-Ethynylanilines 1l,m; Typical Procedure

To a solution of **1p** (0.570 g, 2.21 mmol) in MeOH (15 mL) was added KF (0.320 g, 5.52 mmol). The mixture was stirred at r.t. for 3 h, then extracted with water (150 mL) and Et_2O (2 × 50 mL). The organic layer was dried (Na_2SO_4) and evaporated. Column chromatographic purification on silica gel (hexane–EtOAc, 95:5) afforded 2,4-dichloro-6-ethynylaniline (**1l**).

Yield: 0.351g (86%); mp 90–91 °C.

IR (KBr): 3430, 3300, 2090 cm^{-1}.

^1H NMR: δ = 7.23 (d, *J* = 2.3 Hz, 1 H, Ar), 7.20 (d, *J* = 2.3 Hz, 1 H, Ar), 4.63 (br s, 2 H, NH_2), 3.45 (s, 1 H, C_{sp}-H).

^{13}C NMR: δ = 143.9, 130.5, 129.8, 121.4, 119.1, 108.4 (Ar), 84.2, 78.7(C≡C).

MS: *m*/*z* (%) = 189 (10) [M^+ + 4], 187 (63) [M^+ + 2], 185 (100) [M^+], 150 (31).

2-Chloro-6-ethynyl-4-nitroaniline (1m)

Yield: 78%; mp 189–190 °C.

IR (KBr): 3500, 3380, 3300, 2100 cm^{-1}.

^1H NMR (acetone-d_6): δ = 8.14 (d, *J* = 2.5 Hz, 1 H, Ar), 8. 09 (d, *J* = 2.5 Hz, 1 H, Ar), 6.32 (br s, 2 H, NH_2), 4.10 (s, 1 H, C_{sp}-H).

^{13}C NMR (acetone-d_6): δ = 152. 1, 137.7, 127.9, 126.6, 117.8, 107.0 (Ar), 87.1, 78.3 (C≡C).

MS: *m*/*z* (%) = 197 (37) [M^+ + 2], 195 (100) [M^+].

Preparation of 2-Ethynylanilines 1n–o; Typical Procedure

To a solution of **1s** (0.331 g, 1.29 mmol) in THF (5 mL) was added TBAF (1.5 mL of a 1.2 M solution in THF). The mixture was stirred

at r.t. for 0.5 h, then extracted with water (150 mL) and Et_2O (2 × 50 mL). The organic layer was dried (Na_2SO_4) and evaporated. Column chromatographic purification on silica gel (hexane–EtOAc, 95:5) afforded 2-ethynyl-5-(trifluoromethyl)aniline (**1n)**.

Yield: 0.190 g (80%); oil.

IR (neat): 3500, 3400, 3310, 2090 cm^{-1}.

^1H NMR: δ = 7.37 (d, *J* = 8.3 Hz, 1 H, Ar), 6.88–6.84 (m, 2 H, Ar), 4.14 (br s, 2 H, NH_2), 3.46 (s, 1 H, C_{sp}-H).

^{13}C NMR: δ = 148.6, 133.0, 131.7 (q, *J* = 31.9 Hz, C_5), 113.8 (q, *J* = 3.8 Hz), 110.6 (q, *J* = 3.9 Hz), 109.6 (arom); 123.8 (q, *J* = 272 Hz, CF_3), 84.4, 79.3 (C≡C).

MS: *m*/*z* (%) = 185 (100) [M^+], 166 (20).

2-Ethynyl-4,6-difluoroaniline (1o)
Yield: 70%; liquid; bp 200 °C (dec).

IR (neat): 3500, 3400, 3310, 2100 cm^{-1}.

^1H NMR: δ = 6.87–6.71 (m, 2 H, Ar), 4.14 (br s, 2 H, NH_2), 3.45 (s, 1 H, C_{sp}-H).

^{13}C NMR: δ = 153.7 (dd, J_1 = 237.7 Hz, J_2 = 12.1 Hz, C_4), 150.6 (dd, J_1 = 241.6 Hz, J_2 = 12.6 Hz, C_2), 134.2 (dd, J_1 = 13.9 Hz, J_2 = 2.9 Hz, C_1), 113.7 (dd, J_1 = 23.5 Hz, J_2 = 3.7 Hz), 108.3 (dd, J_1 = 10.9 Hz, J_2 = 6.9 Hz), 105.3 (dd, J_1 = 26.8 Hz, J_2 = 22.6 Hz, Ar), 84.4, 78.6 (t, *J* = 4.1 Hz, C≡C).

MS: *m*/*z* (%) = 153 (100) [M^+].

2-[(4-Chlorophenyl)ethynyl]aniline (1h)
To a solution of 2-ethynylaniline (0.193 g, 1.65 mmol) in DMF (1 mL) and Et_2NH (2 mL) were added 4-iodochlorobenzene (0.394 g, 1.65 mmol), $Pd(PPh_3)_4$ (0.038 g, 0.033 mmol) and CuI (0.013 g, 0.068 mmol). The mixture was stirred at r.t. for 4 h under N_2, then extracted with 0.1 M HCl (150 mL) and EtOAc (3 × 50 mL). The organic layer was dried (Na_2SO_4) and evaporated. Column chromatographic purification on silica gel (hexane–EtOAc, 98:2) afforded **1h**.

Yield: 0.310 g (82%); mp 116–117 °C.

IR (neat): 3460, 3360, 2200 cm^{-1}.

^1H NMR: δ = 7.40 (d, *J* = 8.7 Hz, 2 H, Ar), 7.35–7.30 (m, 1 H, Ar), 7.27 (d, *J* = 8.7 Hz, 2 H, Ar), 7.16–7.06 (m, 1 H, Ar), 6.73–6.64 (m, 2 H, Ar), 4.18 (br s, 2 H, NH_2).

^{13}C NMR: δ = 147.7, 134.0, 132.5, 132.1, 129.9, 128.6, 121.7, 117.9, 114.3, 107.4 (Ar), 93.5, 86.9 (C≡C).

MS: *m*/*z* (%) = 229 (34) [M^+ + 2], 227 (100) [M^+], 192 (11).

2,4-Dichloro-6-(3,4-dihydronaphthalen-1-ylethynyl)aniline (1i);Typical Procedure
To a solution of **1l** (0.108 g, 0.58 mmol) in DMF (0.5 mL) and Et_2NH (2 mL) were added 3,4 dihydronaphthalen-1-yl triflate (0.198 g, 0.71 mmol), $PdCl_2(PPh_3)_2$ (0.008 g, 0.011 mmol) and CuI (0.005 g, 0.026 mmol). The mixture was stirred at r.t. for 18 h under N_2, then extracted with 0.1 M HCl (150 mL) and EtOAc (3 × 50 mL). The organic layer was dried (Na_2SO_4) and evaporated. Column chromatographic purification on silica gel (hexane–EtOAc, 99:1) afforded **1i**.

Yield: 0.125g (69%); mp 79–80 °C.

IR (KBr): 3430, 3320, 2180 cm^{-1}.

^1H NMR: δ = 7.58 (d, *J* = 6.6 Hz, 1 H, Ar), 7.25–7.12 (m, 5 H, Ar), 6.57(t, *J* = 4.8 Hz, 1 H, C=CH), 4.63 (br s, 2 H, NH_2), 2.82 (t, *J* = 8.0 Hz, 2 H, CH_2Ar), 2.48–2.38 (m, 2 H, C=CCH_2).

^{13}C NMR: δ = 143.1, 136.7, 135.0, 132.2, 130.0, 129.1, 127.9, 127.6, 126.8, 124.8, 121.6, 121.3, 119.0, 110.1(Ar, C=C), 94.3, 84.8(C≡C), 27.0 (CH_2Ar), 23.7 (C=CCH_2).

MS: *m*/*z* (%) = 317 (11) [M^+ + 4], 315 (60) [M^+ + 2], 313 (100) [M^+], 243(29).

Preparation of 2-Alkynylanilines 1j,k: Typical Procedure
To a solution of **1l** (0.146 g, 0.78 mmol) in DMF (1.2 mL) were added 4-iodoanisole (0.230 g, 0.98 mmol), piperidine (0.080 mL, 0.80 mmol), $PdOAc_2(PPh_3)_2$ (0.012 g, 0.016 mmol), and CuI (0.06 g, 0.031 mmol). The mixture was stirred at 60 °C for 7 h under N_2, then extracted with 0.1 M HCl (150 mL) and EtOAc (3 × 50 mL). The organic layer was dried (Na_2SO_4) and evaporated. Column chromatographic purification on silica gel (hexane–EtOAc, 90:10) afforded 2,4-dichloro-6-[(4-methoxyphenyl)ethynyl]aniline (**1j).**

Yield: 0.198g (87%); mp 81–82 °C.

IR (KBr): 3420, 3320, 2180 cm^{-1}.

^1H NMR: δ = 7.42 (d, *J* = 8.9 Hz, 2 H, Ar), 7.22 (d, *J* = 2.3 Hz, 1 H, Ar), 7.18 (d, *J* = 2.3 Hz, 1 H, Ar), 6.86 (d, *J* = 8.9 Hz, 2 H, Ar), 4.61 (br s, 2 H, NH_2), 3.80 (s, 3 H, OCH_3).

^{13}C NMR: δ = 160.0, 142.9, 133.1, 129.8, 128.9, 126.7, 121.6, 118.9, 114.1, 110.3 (Ar), 96.4, 82.7 (C≡C).

MS: *m*/*z* (%) = 295 (9) [M^+ + 4], 293 (44) [M^+ + 2], 291 (72) [M^+], 276 (100).

2-Chloro-4-nitro-6-[(3*E*)-4-phenylbut-3-en-1-ynyl]aniline (1k)
Yield: 79%; mp 168–170 °C.

IR (KBr): 3500, 3360, 2190 cm^{-1}.

^1H NMR (acetone-d_6): δ = 8.14 (d, *J* = 2.5 Hz, 1 H, Ar), 8. 10 (d, *J* = 2.5 Hz, 1 H, Ar), 7.58–7.53 (m, 2 H, Ar), 7.45–7.30 (m, 3 H, Ar), 7.22 (d, *J* = 16.3 Hz, 1 H, C=CH), 6.61 (d, *J* = 16.3 Hz, 1 H, C=CH), 6.52 (br s, 2 H, NH_2).

^{13}C NMR (acetone-d_6): δ = 151.5, 143.5, 136.9, 129.9, 129.7, 129.5, 129.4, 127.4, 127.2, 126.0, 108.0 (Ar), 97.2, 86.0 (C≡C).

MS: *m*/*z* (%) = 300 (35) [M^+ + 2], 298 (93) [M^+], 251 (100).

Preparation of Indoles 3; Typical Procedure
To a solution of 2,4-dichloro-6-ethynylaniline (**1l**) (0.140 g, 0.75 mmol) in EtOH (6 mL) was added $NaAuCl_4 \cdot 2H_2O$ (0.012 g, 0.030 mmol). The mixture was stirred at r.t for 7 h under N_2, then purified by chromatography on silica gel (hexane–EtOAc, 98:2) to give 5,7-dichloro-1*H*-indole (**3l**).

Yield: 0.110g (79%); mp 55–56 °C (Lit.[22] 53.5–54 °C).

IR (KBr): 3460, 1530 cm^{-1}.

^1H NMR: δ = 8.37 (br s, 1 H, NH), 7.51 (dd, J_1 = 1.8 Hz, J_2 = 0.7 Hz, 1 H), 7.28–7.25 (m, 1 H), 7.20 (dd, J_1 = 1.8 Hz, J_2 = 0.4 Hz, 1 H), 6.53 (dd, J_1 = 3.2 Hz, J_2 = 2.2 Hz, 1 H, H-3).

^{13}C NMR: δ = 131.7, 129.6, 126.1, 125.3, 121.4. 118.9, 116.9, 103.4 (C-3).

MS: *m*/*z* (%) = 189 (11) [M^+ + 4], 187 (72) [M^+ + 2], 185 (100) [M^+], 150 (23).

Anal. Calcd for $C_8H_5Cl_2N$: C, 51.65; H, 2.71; N, 7.53. Found: C, 51.63; H, 2.72; N, 7.54.

2-Phenyl-1*H*-indole (3a)
Mp 186–188 °C (Lit.[5a] 185–187 °C).

2-(4-Methylphenyl)-1*H*-indole (3b)
Mp 213–215 °C (Lit.[6d] 210–212 °C).

2-Butyl-1*H*-indole (3c)
Mp 29–31 °C (Lit.[23] 28–29.5 °C).

2-[(*E*)-2-phenylvinyl]-1*H*-indole (3d)
Mp 197–199 °C (Lit.[6d] 198–201 °C).

2-(4-*tert*-butylcyclohex-1-enyl)-1*H*-indole (3e)
Mp 147–150 (Lit.[6d] 148–150 °C).

2-(2-Thienyl)-1*H*-indole (3f)
Mp 165–167 °C (Lit.[24] 167–168 °C).

2,2′-Bisindolyl 3g
Mp 294–296 °C (dec) [Lit.[4] 292–294 °C (dec)].

IR (KBr): 3420 cm^{-1} (Lit.[4] 3400 cm^{-1}).

2-(4-Chlorophenyl)-1*H*-indole 3h
Mp 209–211 °C (Lit.[25] 208–211).

5,7-Dichloro-2-(3,4-dihydronaphthalen-1-yl)-1*H*-indole (3i)
Oil.

IR (neat): 3440 cm^{-1}.

^{1}H NMR: δ = 8.32 (br s, 1 H, NH), 7.47–7.46 (m, 1 H), 7.33–7.28 (m, 1 H), 7.24–7.19 (m, 3 H), 7.17 (d, *J* = 1.8 Hz, 1 H), 6.54 (d, *J* = 2.2 Hz, 1 H, H-3), 6.41 (t, *J* = 4.8 Hz, 1 H, C=CH), 2.84 (t, *J* = 7.4 Hz, 2 H, CH_2Ar), 2.47–2.40 (m, 2 H, C=CCH_2).

^{13}C NMR: δ = 139.1, 136.9, 133.1, 131.1, 130.4, 129.9, 127.9, 127.8, 126.7, 125.5, 125.0, 121.3, 118.5, 116.5, 102.5 (C-3), 27.8 (*C*H_2Ar), 23.3 (C=*C*CH_2).

MS: *m*/*z* (%) = 317 (12) [M^+ + 4], 315 (64) [M^+ + 2], 313 (100) [M^+], 278 (21).

Anal. Calcd for $C_{18}H_{13}Cl_2N$: C, 68.81; H, 4.17; N, 4.46. Found: C, 68.78; H, 4.19; N, 4.47.

5,7-Dichloro-2-(4-methoxyphenyl)-1*H*-indole (3j)
Mp 158–159 °C.

IR (KBr): 3450, 1530 cm^{-1}.

^{1}H NMR: δ = 8.40 (br s, 1 H, NH), 7.58 (d, *J* = 8.9 Hz, 2 H), 7.44 (d, *J* = 1.5 Hz, 1 H), 7.14 (d, *J* = 1.5 Hz, 1 H), 6.98 (d, *J* = 8.9 Hz, 2 H), 6.65 (d, *J* = 1.5 Hz, 1 H, H-3), 3.86 (s, 3 H, OCH_3).

^{13}C NMR: δ = 159.9, 140.1, 131.1, 128.8, 126.8, 125.7, 124.0, 121.2, 118.4, 116.4, 114.6, 99.2 (C-3), 55.4 (OCH_3).

MS: *m*/*z* (%) = 295 (12) [M^+ + 4], 293 (67) [M^+ + 2], 291 (100) [M^+], 278 (59), 276 (81).

Anal. Calcd for $C_{15}H_{11}Cl_2NO$: C, 61.67; H, 3.79; N, 4.79. Found: C, 61.68; H, 3.78; N, 4.78.

7-Chloro-5-nitro-2-[(*E*)-2-phenylvinyl]-1*H*-indole (3k)
Mp 158–159 °C.

IR (KBr): 3400, 1520, 1330 cm^{-1}.

^{1}H NMR (DMSO-d_6): δ = 12.23 (br s, 1 H, NH), 8.48 (d, *J* = 2.0 Hz, 1 H), 8.01 (d, *J* = 2.0 Hz, 1 H), 7.61 (d, *J* = 16.5 Hz, 1 H), 7.63–7.59 (m, 2 H), 7.47–7.25 (m, 4 H), 6.98 (d, *J* = 1.7 Hz, 1 H, H-3).

^{13}C NMR (DMSO-d_6): δ = 142.3, 141.6, 137.7, 137.1, 131.9, 130.2, 129.5, 128.9, 127.2, 118.5, 116.8, 116.4, 116.1, 105.6 (C-3).

MS: *m*/*z* (%) = 300 [M^+ + 2], 298 (100) [M^+], 252 (41).

Anal. Calcd for $C_{16}H_{11}ClN_2O_2$: C, 64.33; H, 3.71; N, 9.38. Found: C, 64.35; H, 3.70; N, 9.39.

7-Chloro-5-nitro-1*H*-indole (3m)
Mp 176–177 °C.

IR (KBr): 3360, 1530, 1320 cm^{-1}.

^{1}H NMR (acetone-d_6): δ = 11.24 (br s, 1 H, NH), 8.55 (dd, J_1 = 2.0 Hz, J_2 = 0.7 Hz, 1 H), 8.05 (dd, J_1 = 2.0 Hz, J_2 = 0.3 Hz, 1 H), 7.67–7.64 (m, 1 H), 6.87 (dd, J_1 = 3.2 Hz, J_2 = 1.9 Hz, 1 H, H-3).

^{13}C NMR (acetone-d_6): δ = 143.1, 137.5, 130.8, 129.9, 118.0, 117.7, 117.3, 107.1 (C-3).

MS: *m*/*z* (%) = 198 (31) [M^+ + 2], 196 (100) [M^+], 150 (21).

Anal. Calcd for $C_8H_5ClN_2O_2$: C, 48.88; H, 2.56; N, 14.25. Found: C, 48.87; H, 2.57; N, 14.26.

6-(Trifluoromethyl)-1*H*-indole (3n)
Mp 79–81 °C.

IR (KBr): 3420 cm^{-1}.

^{1}H NMR: δ = 8.32 (br s, 1 H, NH), 7.70 (dd, J_1 = 8.3 Hz, J_2 = 0.7 Hz, 1 H), 7.62–7.61 (m, 1 H), 7.35 (dd, J_1 = 8.3 Hz, J_2 = 1.6 H, 1 H), 7.31–7.28 (m, 1 H), 6.60–6.57 (m, 1 H, H-3).

^{13}C NMR: δ = 132.8, 129.4, 126.8, 125.2 (q, *J* = 271 Hz, CF_3) 121.1, 116.5 (q, *J* = 3.6 Hz), 108.6 (q, *J* = 4.4 Hz), 102.9 (C-3).

MS: *m*/*z* (%) = 185 (100) [M^+], 166 (21).

Anal. Calcd for $C_9H_6F_3N$: C, 58.38; H, 3.27; N, 7.57. Found: C, 58.40; H, 3.25; N, 7.58.

5,7-Difluoro-1*H*-indole (3o)
Liquid; bp 208 °C.

IR (neat): 3480, 1590 cm^{-1}.

^{1}H NMR: δ = 8.07 (br s, 1 H, NH), 6.94–6.90 (m, 1 H), 6.82 (dd, J_1 = 9.1 Hz, J_2 = 2.2 Hz, 1 H), 6.52–6.39 (m, 1 H), 6.27–6.22 (m, 1 H, H-3).

^{13}C NMR: δ = 157.2 (dd, J_1 = 236.1 Hz, J_2 = 9.9 Hz, C_5), 148.9 (dd, J_1 = 246.0 Hz, J_2 = 14.4 Hz, C_7), 130.5 (dd, J_1 = 11.6 Hz, J_2 = 6.4 Hz), 126.5, 103.7 (dd, J_1 = 4.9 Hz, J_2 = 2.4 Hz), 101.4 (dd, J_1 = 23.2 Hz, J_2 = 3.9 Hz), 97.3 (dd, J_1 = 20.3 Hz, J_2 = 6.4 Hz).

MS: *m*/*z* (%) = 153 (100) [M^+], 126 (27).

Anal. Calcd for $C_8H_5F_2N$: C, 62.75; H, 3.29; N, 9.15. Found: C, 62.80; H, 3.27; N, 9.14.

Preparation of 3-Bromoindoles 4a,b; Typical Procedure
To a solution of 2,4-dichloro-6-ethynylaniline (**1l**) (0.099 g, 0.38 mmol) in EtOH (3 mL) was added $NaAuCl_4 \cdot 2H_2O$ (0.006 g, 0.015 mmol). The mixture was stirred under N_2 at r.t. for 7 h, then a solution of Br_2 (0.021 mL, 0.41 mmol) in EtOH (2 mL) was added dropwise. The mixture was stirred for further 2 h, then extracted with 5% sodium thiosulfate (100 mL) and EtOAc (2 × 50 mL). The organic phase was dried (Na_2SO_4) and evaporated. Column chromatographic purification on silica gel (hexane–EtOAc, 95:5) afforded 3-bromo-5,7-dichloro-1*H*-indole (**4b**).

Yield: 0.103g (80%); mp 97–98 °C.

IR (KBr): 3450 cm^{-1}.

^{1}H NMR: δ = 8.42 (br s, 1 H, NH), 7.46 (dd, J_1 = 1.8 Hz, J_2 = 0.7 Hz, 1 H), 7.28 (d, *J* = 2.6 Hz, 1 H), 7.24 (d, *J* = 1.8 Hz, 1 H).

^{13}C NMR: δ = 128.7, 126.5, 125.3, 122.8, 117.7, 117.2, 91.9 (C-3).

MS: *m*/*z* (%) = 269 (7), 267 (46), 265 (100), 263 (7).

Anal. Calcd for $C_8H_4BrCl_2N$: C, 36.27; H, 1.52; N, 5.29. Found: C, 36.30; H, 1.53; N, 5.28.

3-Bromo-2-phenyl-1*H*-indole (4a)
Mp 80–82 °C (Lit.[19b] 78–79 °C).

Preparation of 3-Iodoindoles 4c–f; Typical Procedure
To a solution of 2-hex-1-ynylaniline (**1c**) (0.070 g, 0.40 mmol) in EtOH (1.5 mL) was added $NaAuCl_4 \cdot 2H_2O$ (0.006 g, 0.015 mmol). The mixture was stirred under N_2 at r.t. for 3.5 h, then KOH (0.057 g, 1.02 mmol) and a solution of I_2 (0.104 g, 0.41mmol) in EtOH (1 mL) were added. The mixture was stirred for further 2 h, then extracted with 5% sodium thiosulfate (100 mL) and EtOAc (2 × 50 mL). The organic phase was dried (Na_2SO_4) and evaporated. Column chromatographic purification on silica gel (hexane–EtOAc, 95:5) afforded 2-butyl-3-iodo-1*H*-indole (**4e**).

Yield: 0.098 g (81%); oil.

IR (neat): 3400 cm^{-1}.

^{1}H NMR: δ = 8.00 (br s, 1 H, NH), 7.40–7.33 (m, 1 H), 7.18–7.13 (m, 3 H), 2.71(t, *J* = 7.3 Hz, 2 H), 1.61–1.50 (m, 2 H), 1.40–1.29 (m, 2 H), 0.92 (t, *J* = 7.2 Hz, 3 H).

^{13}C NMR: δ = 140.5, 135.9, 130.7, 122.3, 120.4, 120.3, 110.7, 58.6 (C-3) 31.3, 28.3, 22.2, 13.8.

MS: *m*/*z* (%) = 299 (100) [M^+], 256 (70), 172 (14).

Anal. Calcd for $C_{12}H_{14}IN$: C, 48.18; H, 4.72; N, 4.68. Found: C, 48.15; H, 4.71; N, 4.70.

3-Iodo-2-phenyl-1*H*-indole (4c)
Mp 68–70 °C (Lit.[19b] 70–71 °C).

5,7-Dichloro-3-iodo-1*H*-indole 4d
Mp 142–143 °C.

IR (KBr): 3410, 1620 cm^{-1}.

^{1}H NMR (acetone-d_6): δ = 11.25 (br s, 1 H, NH), 7.67 (s, 1 H), 7.33 (d, *J* = 1.8 Hz, 1 H), 7.30 (d, *J* = 1.8 Hz, 1 H).

^{13}C NMR (acetone-d_6): δ = 133.2, 132.9, 132.7, 126.4, 122.6, 119.6, 118.0, 56.5(C-3).

MS: *m*/*z* (%) = 315 (12) [M^+ + 4], 313 (75) [M^+ + 2], 311 (100) [M^+].

Anal. Calcd for $C_8H_4Cl_2IN$:C, 30.80; H, 1.29; N, 4.49. Found: C, 30.85; H, 1.27; N, 4.47.

3,3′-Diiodo-1*H*,1′*H*-2,2′-biindole (4f)
Mp 125–126 °C (dec.).

IR (KBr): 3420 cm^{-1}.

^{1}H NMR (acetone-d_6): δ = 11.78 (br s, 2 H, NH), 7.54–7.41 (m, 4 H), 7.31–7.14 (m, 4 H).

^{13}C NMR (acetone-d_6): δ = 133.8, 132.7, 131.4, 124.1, 121.4, 121.2, 112.7, 61.8 (C-3).

MS: *m*/*z* (%) = 484 (100) [M^+], 357 (42), 230 (13)

Anal. Calcd for $C_{16}H_{10}I_2N_2$: C, 39.70; H, 2.08; N, 5.79. Found: C, 39.85; H, 2.10; N, 5.77.

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