Convenient synthesis of 2-substituted indoles from 2-ethynylanilines with tetrabutylammonium fluoride

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The cyclization reaction of various 2-ethynylanilines, which were easily synthesized from 2-haloanilines by the palladium-catalyzed reaction with terminal alkynes, with tetrabutylammonium fluoride (TBAF) to yield 2-substituted indoles proceeded at refluxing or room temperature in THF in excellent yields without affecting the bromo, chloro, cyano, ethoxycarbonyl, and ethynyl groups.

Introduction

The cyclization of 2-ethynylanilines is one of the most useful methods for the synthesis of 2-substituted indoles, because 2-ethynylanilines can be easily prepared from 2-haloanilines by the palladium-catalyzed cross-coupling reaction with terminal alkynes, and many synthetic methods for 2-haloanilines have been reported. For example, the preparation of 2-haloanilines is easily achieved by *ortho*-lithiation with alkyllithium.[1]

The cyclization of 2-ethynylanilines is promoted in the presence of metal species such as copper(I) halides,[2] $NaAuCl_4{\cdot}H_2O$[3] or palladium(II) species.[4] Another method is the cyclization of 2-ethynylphenylcarbamates with alkoxides.[5]

The cyclization reaction of 2-ethynylanilines is promoted with copper(I) chloride or iodide to give 2-unsubstituted and 2-substituted indoles, but the reaction proceeds at relatively high temperature (100–110 °C) in DMF.[2] Iritani and co-workers reported[3] the cylization of 2-ethynylanilines to 2-substituted indoles using $NaAuCl_4{\cdot}H_2O$ as catalyst. The palladium(II) species-promoted cyclization reaction of 2-ethynylanilines, which was first reported by Taylor *et al.*,[4a] was found to have wide applicability. Namely, *N*-unsubstituted, *N*-acyl-, *N*-alkoxycarbonyl-, and *N*-methylsulfonyl-2-ethynylanilines can be used as starting materials.

On the other hand, we have reported the cyclization reaction of 2-ethynylphenylcarbamates to indoles under basic conditions, sodium ethoxide in ethanol, without using a metal species.[3,4a–d] The reaction was utilized as a key reaction in the synthesis of some natural indole derivatives by Ogasawara *et al.*[5e–g] who reported that the cyclization of ethyl 2-dec-1-ynylphenylcarbamate also proceeded in the presence of lithium chloride in refluxing DMF,[5g] although the yield is inferior to the yield of the reaction using sodium ethoxide. The conditions of the indole cyclization reaction with alkali metal alkoxides were improved by using potassium *tert*-butoxide in *tert*-butyl alcohol,[5c–d] but there is a restriction that the substituents on the amino group were limited to alkoxycarbonyl groups, namely that only (2-ethynylaryl)carbamates were used as the starting materials.

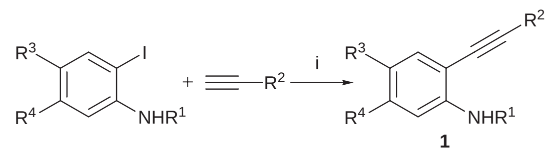
Based on the above background concerning the indole cyclization reaction and the availability of 2-ethynylanilines, we now report here the synthesis of various indoles from 2-ethynylanilines under mild conditions using TBAF in THF at refluxing or room temperature.

Results and discussion

Preparation of 2-ethynylanilines from 2-haloanilines by palladium-catalyzed reaction

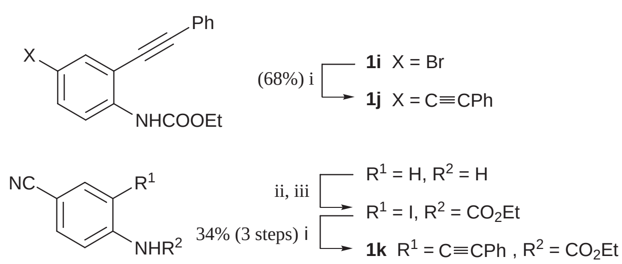
2-Ethynylanilines (**1a**,**c**–**f**,**i**,**l**–**o**) were prepared by the palladium-catalyzed reaction of 2-haloanilines with terminal alkynes using *N*-ethoxycarbonyl-, *N*-*tert*-butoxycarbonyl-, *N*-pivaloyl-, *N*-formyl-, and *N*-acetyl-2-iodoaniline derivatives as shown in Table 1. Ethyl 2,4-bis(phenylethynyl)phenylcarbamate (**1j**) was prepared from ethyl 4-bromo-2-(phenylethynyl)phenylcarbamate (**1i**) by palladium-catalyzed reaction with ethynylbenzene, and ethyl 4-cyano-2-(phenylethynyl)phenylcarbamate (**1k**) was prepared similarly from 4-iodobenzonitrile in 34% overall yield in 3 steps (Scheme 1).

Table 1 Palladium-catalyzed reactions of iodoanilines with terminal alkynes



Reagents: i, $PdCl_2(PPh_3)_2$, CuI, Et_3N.

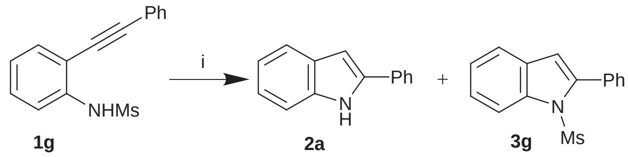
Compound	R^1	R^2	R^3	R^4	Time/ h	Yield (%)
a	H	Ph	H	H	3	95
c	CO_2Et	Ph	H	H	24	85
d	$CO_2{}^tBu$	Ph	H	H	24	80
e	CO^tBu	Ph	H	H	24	90
f	CHO	Ph	H	H	1.5	90
i	CO_2Et	Ph	Br	H	24	52
l	$CO_2{}^tBu$	Hex	H	Cl	1	80
m	CHO	$CH_2CH_2CO_2Et$	H	H	5	71
n	Ac	Ph	H	MeO	3	66
o	CO_2Et	Bu	H	H	12	94



Scheme 1 *Reagents and conditions*: i, ethynylbenzene, $PdCl_2(PPh_3)_2$, CuI, Et_3N; ii, I_2, 30% H_2O_2, MeOH; iii, $ClCO_2Et$, pyridine.

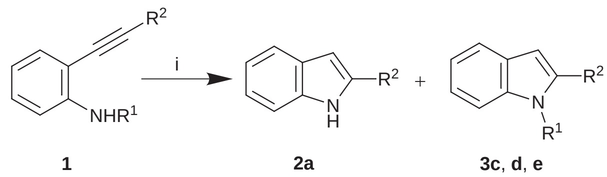
We have reported that the palladium-catalyzed reaction of *N*-(2-iodophenyl)methanesulfonamide with terminal alkynes gives 2-substituted indoles instead of the corresponding alkynyl derivatives (**1g**,**h**).[6] In order to examine the cyclization of **1g**

Table 2 Cyclization reaction of *N*-(2-ethynylphenyl)sulfonamides



	i				Yield (%)			
Entry	Solvent	Reagent (equiv.)	Time/h	Temp.	**2a**	**3g**	**2a** + **3g**	Recovery
1	THF	TBAF (0.5)	12	reflux	50	38	88	11
2	THF	TBAF (1)	12	reflux	81	5	86	5
3	THF	TBAF (2)	12	reflux	94	—	94	—
4	THF	TBAF (2)	12	rt	—	—	—	95
5	THF	K_2CO_3 (2)	24	reflux	—	—	—	75
6	THF	$NaHCO_3$ (2)	24	reflux	—	—	—	83
7	MeCN	K_2CO_3 (2)	24	reflux	—	75	75	15
8	MeCN	$NaHCO_3$ (2)	24	reflux	—	31	31	54

Table 3 Cyclization reaction of various *N*-substituted 2-phenylethynylanilines with TBAF

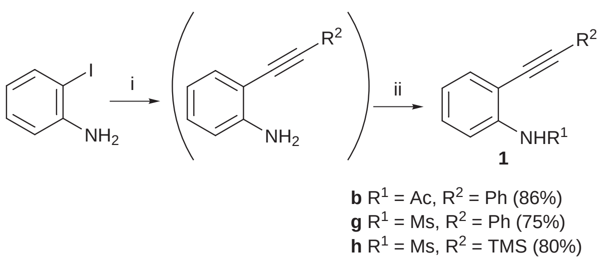


Reagents: i, TBAF, THF.

							Yield (%)		
Entry[a]	**1**	R^1	R^2	Temp.	TBAF (equiv.)	Time/h	**2a** + **3**	**2a**	**3**
1[b]	**b**	Ac	Ph	reflux	2	12	88	88	—
2	**b**	Ac	Ph	reflux	1	12	51	51	— (49)[c]
3	**c**	COOEt	Ph	reflux	2	12	100	43	57
4	**d**	Boc	Ph	reflux	2	2	100	22	78
5	**e**	CO*t*-Bu	Ph	reflux	2	12	82	26	56
6	**f**	CHO	Ph	reflux	2	2	96	96	—
7	**h**	Ms	TMS	rt	3	24	51	—	51[d] (46)[e]
8	**h**	Ms	TMS	reflux	3	3	100	100[f]	—

[a] The cyclization reaction of 2-(2-phenylethynyl)aniline (**1a**) did not proceed (recovery yield: 92%). [b] The cyclization reaction with K_2CO_3 in MeCN gave **2a** in 9% yield. [c] Values in parentheses are recovery yields of **1**. [d] Product: 1-methylsulfonylindole (**3q**). [e] Product: *N*-(2-ethynylphenyl)-methanesulfonamide (**1p**). [f] Product: indole.

and **1h** with TBAF, which were assumed to be intermediates of the indoles, **1g** and **1h** were prepared by the palladium-catalyzed reaction of 2-iodoaniline with terminal alkynes followed by sulfonylation with methanesulfonyl chloride. *N*-(2-Phenylethynyl)ethanamide (**1b**) was also prepared from 2-phenylethynylaniline (**1a**) with acetic anhydride.



Scheme 2 *Reagents and conditions*: i, ethynylbenzene or ethynyltrimethylsilane, $PdCl_2(PPh_3)_2$, CuI, Et_3N, 3 h; ii, MsCl or Ac_2O, pyridine.

Reaction conditions for the cyclization into indole

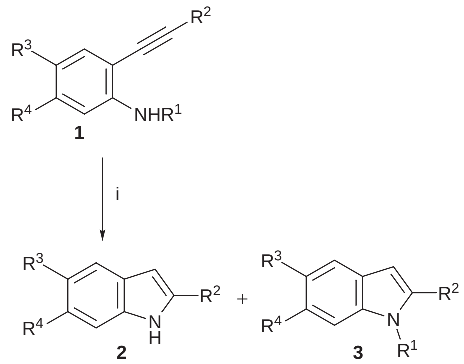
When a mixture of *N*-[2-(phenylethynyl)phenyl]methanesulfonamide (**1g**) with 2 equiv. of TBAF, K_2CO_3, or $NaHCO_3$ in THF was refluxed, the cyclization reaction with TBAF gave 2-phenylindole (**2a**) in 94% yield (Table 2, Entry 3), but the reaction with K_2CO_3 or $NaHCO_3$ in THF resulted in the recovery of **1g** in 75 or 83% yield (Table 2, Entries 5, 6). The cyclization reaction with the same alkali metal carbonates in acetonitrile gave **3g** in 75 and 31% yields, respectively (Table 2, Entries 7, 8).

The reaction of **1g** using 0.5, 1.0, or 2.0 equiv. of TBAF under reflux gave a mixture of **2a** and 1-methylsulfonyl-2-phenylindole (**3g**) in approximately 90% yields (Table 2, Entries 1–3). The results suggest that the cyclization reaction can proceed with a catalytic amount of TBAF. However, because TBAF is a good desulfonylating reagent for *N*-sulfonyl nitrogen-heteroaromatics and the desulfonylation reaction requires a stoichiometric amount of TBAF,[7] the amount of TBAF required for the cyclization reaction was more than 1 equiv.

Cyclization reaction of various *N*-substituted ethynylanilines

Although the cyclization reaction of **1g** with 2 equiv. of TBAF did not proceed at room temperature (Table 2, Entry 4), the reaction of *N*-[2-(trimethylsilylethynyl)phenyl]methanesulfonamide (**1h**) with 3 equiv. of TBAF at room temperature gave 1-methylsulfonylindole (**3h**) in 51% yield (Table 3, Entry 7). And

Table 4 Synthesis of various indoles substituted at the 2-position and benzene moiety from ethynylanilines with TBAF



Reagents: i, TBAF, THF.

Entry	1	R^1	R^2	R^3	R^4	Temp	Time (h)	Yield (%) 2 + 3	2	3
1	**i**	CO_2Et	Ph	Br	H	reflux	17	98	98	—
2	**j**	CO_2Et	Ph	≡–Ph	H	reflux	21	99	99	—
3	**k**	CO_2Et	Ph	CN	H	rt	12	100	100	—
4	**l**	$CO_2{}^tBu$	Hex	H	Cl	reflux	2	100	59	41
5	**m**	CHO	$CH_2CH_2CO_2Et$	H	H	reflux	3	51	51	—
6	**n**	Ac	Ph	H	MeO	reflux	24	88	88	—
7[a]	**o**	CO_2Et	Bu	H	H	reflux	4	100	42	58
8	**o**	CO_2Et	Bu	H	H	reflux	24	96	96	—
9	**p**	Ms	H	H	H	reflux	17	85	85	—

[a] THF–DMF (5:1) was used as a solvent. The cyclization reaction of **1n** in THF at refluxing for 48 h gave **2n** in 79% yield and the starting material was recovered in 16% yield.

at refluxing temperature, the cyclization of **1h** was faster than the cyclization of **1g** (Table 3, Entry 8). On the basis of the above results, we next examined the cyclization reaction of various *N*-substituted 2-(phenylethynyl)anilines, whose reactivity toward cyclization was lower than that of 2-(trimethysilylethynyl)anilines. As shown in Table 3, the cyclization reaction of *N*-substituted 2-(phenylethynyl)anilines (**1b**–**f**) with 2 equiv. of TBAF gave the corresponding indoles (**2** and **3**) in excellent yields. We previously reported[5b] that the cyclization of *N*-acetyl, *N*-pivaloyl, and *N*-formyl derivatives of 2-(trimethylsilylethynyl)aniline with sodium ethoxide–ethanol proceeded in low yields (17–34%), because the deacylation of the *N*-acyl-2-ethynylanilines occurred before the cyclization to form indoles, and that the 2-ethynylaniline did not give indole under these reaction conditions.

The cyclization of *N*-[2-(2-phenylethynyl)phenyl]ethanamide (**1b**) (Table 3, Entry 2) with 1 equiv. of TBAF gave only 2-phenylindole (**2a**) in 51% yield. However, the cyclization reaction of the phenylcarbamates (**1c**, **d**) and the 2,2-dimethylpropanamide (**1e**) gave the corresponding 1-acylindoles (**3c**, **d**, **e**) rather than **2a** in good yields.

Although the cyclization reaction of **1g** with K_2CO_3 in acetonitrile (Table 2, Entry 7) gave **3g** in 75% yield, the cyclization reaction of **1b** with K_2CO_3 gave **2a** in only 9% yield. The reaction of phenylethynylaniline (**1a**) with TBAF did not give **2a** similarly in the reaction using sodium ethoxide–ethanol.

Synthesis of indoles having various substituents at the 2-position and the benzene moiety

As shown in Table 4, the cyclization reaction of ethynylanilines (**1i**–**m**) with TBAF gave the corresponding indoles in good yields without affecting the bromo, chloro, cyano, ethoxycarbonyl, and phenylethynyl groups. Synthesis of 2-aryl- (*e.g.*, **2i**) and 2-alkylindoles (*e.g.*, **2l**) can be achieved using the corresponding ethynyl derivatives which were prepared by the palladium-catalyzed reaction with the terminal alkynes. Indoles without the functional group at the 2-position were synthesized from the 2-(trimethylsilylethynyl)aniline (Table 2, Entries 7, 8) or the 2-ethynylaniline derivative (Table 4, Entry 9).

The cyclization reaction of *N*-[5-methoxy-2-(phenylethynyl)-phenyl]ethanamide (**1n**) with TBAF in THF under reflux for a long time (48 h) gave the corresponding indole derivatives (**2n**) in 79% yield. However, when the reaction was carried out using THF–DMF (5:1) as a solvent, the yield of **2n** was improved to 88% in 24 h (Table 4, Entry 6).

Although ethyl 2-(hex-1-ynyl)phenylcarbamate (**1o**) was refluxed for 4 h to give a mixture of 2-butylindole (**2o**) and 2-butyl-1-ethoxycarbonylindole (**3o**) (Table 4, Entry 7), the cyclization reaction of **1o** at reflux in THF for 24 h gave only **2o** in 96% yield (Table 4, Entry 8). This deethoxycarboxylation reaction was found in many cases in the cyclization reaction.

It seems that the tendency to promote the cyclization reaction with TBAF depends on the acidity of the substituted amino groups. For example, the cyclization reaction of **1k**, which has an electron-withdrawing group on the benzene moiety, proceeded at room temperature (Table 4, Entry 3).

Conclusion

Because the cyclization reaction of 2-ethynylanilines with TBAF proceeds under milder conditions to give the corresponding indoles in excellent yields and does not require dry conditions and complicated operations, the reaction was found to be a useful synthetic method for indoles. Considering that many synthetic methods for haloanilines have been reported and that cyclization reaction with TBAF gave the corresponding indoles without affecting many functional groups, the synthesis of indoles with functional groups at any position except for the 3-position seems to be a widely usable method. Furthermore, the 3-position of indole is the most reactive position for electrophiles, and there are many reports that various functional groups can be introduced to the 3-position of indole.[8] The cyclization reaction of 2-ethynylanilines with TBAF can be concluded to have a wide usage for the synthesis of indoles having multi-functional groups.

Experimental

All melting points and boiling points are uncorrected. IR spectra were measured on a JASCO IR-810 spectrophotometer. ^{1}H NMR spectra were recorded on a Varian Gemini 2000 (300 MHz). Chemical shifts are expressed in δ (ppm) values with tetramethylsilane (TMS) as an internal reference, and coupling constants are expressed in Hz. Mass spectra and high resolution mass spectra were recorded on JMS-DX303 and JMS-AX500 instruments, respectively.

General procedure for the palladium-catalyzed cross-coupling reaction of 2-iodoanilines with terminal alkynes

A mixture of a 2-iodoaniline (1 mmol), an alkyne (1 mmol), $PdCl_2(PPh_3)_2$ (5 mol%), CuI (10 mol%), and Et_3N (5 ml) was refluxed for the time shown in Table 1. After removal of the solvent, the residue was diluted with H_2O and extracted with AcOEt. The AcOEt extract was dried over $MgSO_4$ and evaporated. The residue was purified by silica gel column chromatography using hexane–AcOEt as an eluent and recrystallization or distillation.

2-(2-Phenylethynyl)aniline 1a. Pale yellow prisms from hexane–acetone; mp 85–86 °C (lit.,[10] 92 °C) (Found: C, 86.82; H, 5.62; N, 7.15. $C_{14}H_{11}N$ requires C, 87.01; H, 5.74; N, 7.25%); ν_{max}(KBr)/cm^{-1} 3500, 2250, and 1620; δ_H 4.20–4.39 (br, 2 H), 6.79 (2 H, t, *J* 7.7), 7.14 (1 H, dt, *J* 7.9, 1.4), 7.32–7.39 (4 H, m), 7.51–7.56 (2 H, m); *m*/*z* 193 (M$^+$, 100%), and 165 (27).

Ethyl 2-(2-phenylethynyl)phenylcarbamate 1c. Pale yellow liquid; bp 170 °C/3 mmHg (lit.,[5a] 170–175 °C/3 mmHg); ν_{max}(KBr)/cm^{-1} 3400, 1730, and 1240; δ_H 1.34 (3 H, t, *J* 7.1), 4.26 (2 H, q, *J* 7.1), 7.02 (1 H, t, *J* 7.7), 7.32–7.58 (8 H, m), 8.18 (1 H, d, *J* 8.5); *m*/*z* 265 (M$^+$, 100%), 237 (2), 219 (11), 206 (25), 193 (41), and 165 (37) (Found: *m*/*z* 265.1096. Calc. for $C_{17}H_{15}NO_2$: 265.1103).

***tert*-Butyl 2-(2-phenylethynyl)phenylcarbamate 1d.** Colourless prisms from EtOH; mp 62–65 °C (Found: C, 77.71; H, 6.54; N, 4.84. $C_{19}H_{19}NO_2$ requires C, 77.79; H, 6.53; N, 4.77%); ν_{max}(KBr)/cm^{-1} 3395, 2370, and 1780; δ_H 1.55 (9 H, s), 7.00 (1 H, t, *J* 7.9), 7.30–7.57 (8 H, m), 8.16 (1 H, d, *J* 7.9); *m*/*z* 293 (M$^+$, 27%), 237 (100), 220 (10), and 193 (94).

***N*-[2-(2-Phenylethynyl)phenyl]-2,2-dimethylpropanamide 1e.** Colourless needles from hexane; mp 59–61 °C (Found: C, 82.36; H, 6.99; N, 5.03. $C_{19}H_{19}NO$ requires C, 82.28; H, 6.90; N, 5.05%); ν_{max}(KBr)/cm^{-1} 3400, 2350, and 1680; δ_H 1.36 (9 H, s), 7.07 (1 H, t, *J* 7.4), 7.33–3.41 (3 H, m), 7.48–7.56 (2 H, m), 8.48 (1 H, d, *J* 7.42), 8.42–8.50 (1 H, br); *m*/*z* 277 (M$^+$, 100%), 220 (15), and 193 (75).

***N*-[2-(2-Phenylethynyl)phenyl]methanamide 1f**. Colourless needles from hexane–acetone; mp 97–99 °C (Found: C, 81.33; H, 5.10; N, 6.13. $C_{16}H_{13}NO$ requires C, 81.43; H, 5.01; N, 6.33%); ν_{max}(KBr)/cm^{-1} 1690; δ_H 7.10–7.19 (1 H, m), 7.28–7.51 (4.35 H, m), 7.51–7.58 (3 H, m), 7.89–8.02 (1 H, br), 8.45 (0.65 H, d, *J* 8.5), 8.52 (0.65 H, s), 8.85 (0.35 H, d, *J* 11.5); *m*/*z* 221 (M$^+$, 100%), 193 (39), 179 (3), and 120 (4).

Ethyl 4-bromo-2-(phenylethynyl)phenylcarbamate 1i. Colourless needles from hexane; mp 105–106 °C (Found: C, 59.31; H, 4.11; N, 4.18. $C_{17}H_{14}BrNO_2$ requires C, 59.32; H, 4.10; N, 4.07%); ν_{max}(KBr)/cm^{-1} 3350, 2370, and 1700; δ_H 1.34 (3 H, t, *J* 7.1), 4.24 (2 H, d, *J* 7.1), 7.39–7.46 (4 H, m), 7.54–7.61 (3 H, m), 8.10 (1 H, d, *J* 9.3); *m*/*z* 345 (98%) 343 (M$^+$, 100), 273 (49), and 271 (50).

Ethyl 2,4-bis(phenylethynyl)phenylcarbamate 1j. Colourless needles from hexane; mp 121 °C (Found: C, 81.98; H, 5.28; N, 3.95. $C_{25}H_{19}NO_2$ requires C, 82.17; H, 5.24; N, 3.83%); ν_{max}(KBr)/cm^{-1} 3320 and 1700; δ_H 1.35 (3 H, t, *J* 7.1), 4.27 (2 H, q, *J* 7.1), 7.32–7.44 (6 H, m), 7.48–7.59 (6 H, m), 7.67 (1 H, d, *J* 1.9), 8.21 (1 H, d, *J* 8.8); *m*/*z* 365 (M$^+$, 100%), 319 (15), 293 (32), and 189(7).

***tert*-Butyl [5-chloro-2-(oct-1-ynyl)phenyl]carbamate 1l.** Yellow viscous oil; ν_{max}(KBr)/cm^{-1} 3400 and 1740; δ_H 0.91 (3 H, t, *J* 7.0), 1.31–1.66 (17 H, m), 2.49 (2 H, t, *J* 7.0), 6.89 (d, *J* 8.3, 1 H), 7.23 (1 H, d, *J* 8.3), 7.28 (1 H, s), 8.21 (1 H, s); *m*/*z* 335 (M$^+$, 23%), 279 (45), and 57 (100) (Found: *m*/*z* 335.1642. Calc. for $C_{19}H_{26}ClNO_2$ 335.1651).

Ethyl 5-[2-(formylamino)phenyl]pent-4-ynoate 1m. Colourless viscous oil; ν_{max}(KBr)/cm^{-1} 3330, 1730, and 1700; δ_H 1.29 (3 H, t, *J* 7.1), 2.65 (2 H, t, *J* 7.3), 2.78 (2 H, t, *J* 7.3), 4.19 (2 H, q, *J* 7.1), 7.03 (1 H, t, *J* 7.8), 7.20–7.43 (4.3 H, m), 8.43 (0.7 H, d, *J* 8.2), 8.53 (0.7 H, d, *J* 1.9), 8.57–8.68 (1 H, br), 8.82 (0.3 H, d, *J* 0.3); *m*/*z* 245 (M$^+$, 90%), 227 (8), 217 (14), 200 (34), and 144 (100) (Found: *m*/*z* 245.1031. Calc. for $C_{14}H_{15}NO_3$ 245.1051).

***N*-[5-Methoxy-2-(2-phenylethynyl)phenyl]ethanamide 1n.** Colourless needles from hexane–AcOEt; mp 122–123 °C (Found: C, 77.11; H, 5.58; N, 5.34. $C_{17}H_{15}NO_2$ requires C, 76.96; H, 5.70; N, 5.28%); ν_{max}(KBr)/cm^{-1} 3280 and 1660; δ_H 2.25 (s, 3 H), 3.85 (s, 3 H), 6.63 (1 H, dd, *J* 8.5, 2.5), 7.36–7.42 (4 H, m), 7.50–7.54 (2 H, m), 7.96–8.05 (1 H, br), 8.13 (1 H, d, *J* 2.5); *m*/*z* 265 (M$^+$, 100%), 223 (80), and 208 (42).

Ethyl 2-(hex-1-ynyl)phenylcarbamate 1o. Colourless liquid; bp 160 °C/2 mmHg (lit.,[5a] 170–175 °C/3 mmHg); ν_{max}(KBr)/cm^{-1} 3400 and 1740; δ_H 0.97 (3 H, t, *J* 7.1), 1.33 (3 H, t, *J* 7.1), 1.48–1.68 (4 H, m), 2.51 (2 H, t, *J* 6.87), 4.24 (2 H, q, *J* 7.1), 6.95 (1 H, t, *J* 7.3), 7.27 (1 H, t, *J* 7.3), 7.33 (1 H, d, *J* 7.3), 7.35–7.45 (1 H, br), 8.12 (1 H, d, *J* 7.5); *m*/*z* 245 (M$^+$, 93%), 216 (20), 156 (28), and 130 (100) (Found: *m*/*z* 245.1398. Calc. for $C_{15}H_{19}NO_2$ 245.1415).

***N*-[2-(Phenylethynyl)phenyl]methanesulfonamide 1g.** A mixture of 2-iodoaniline (20.0g, 91.3 mmol), ethynylbenzene (11.2 g, 0.1 mol), CuI (1.73 g, 9.13 mmol), $PdCl_2(PPh_3)_2$ (1.9 g, 2.7 mmol), and Et_3N (200 ml) was stirred for 1 h at room temperature. The reaction mixture was diluted with H_2O, and extracted with $CHCl_3$. The extract was dried over $MgSO_4$. The $CHCl_3$ extract was evaporated under reduced pressure. The residue was dissolved in pyridine–THF (1 : 2, 150 ml), and methanesulfonyl chloride (11.4 g, 0.1 mol) was added. The mixture was stirred for 24 h at room temperature. The reaction mixture was diluted with H_2O, extracted with $CHCl_3$ and dried over $MgSO_4$. The $CHCl_3$ extract was evaporated under reduced pressure. The residue was purified by silica gel column chromatography using hexane–AcOEt (5 : 1) as an eluent and recrystallized from acetone–hexane to give colourless needles. Yield 16.3 g (75%), mp 128–130 °C (lit.,[9] mp 128–130 °C); ν_{max}(KBr)/cm^{-1} 3340 and 2220; δ_H 3.03 (3 H, s), 6.80–7.80 (10 H, m); *m*/*z* 271 (M$^+$, 70%), 192 (100), and 165 (94).

***N*-[2-(Phenylethynyl)phenyl]ethanamide 1b.** This was prepared according to the procedure for the preparation of **1g**, using acetyl chloride (790 mg, 10 mmol) instead of methanesulfonyl chloride. Colourless needles from hexane–acetone; yield 2.0 g (86%). Mp 119–121 °C (lit.,[10] mp 122 °C); ν_{max}(KBr)/cm^{-1} 3300 and 1660; δ_H 2.24 (3 H, s), 7.07 (1 H, t, *J* 7.7), 7.26–7.56 (7 H, m), 8.41 (1 H, d, *J* 8.2); *m*/*z* 235 (M$^+$, 31%), 193 (100), and 165 (16).

***N*-[2-(Trimethylsilylethynyl)phenyl]methanesulfonamide 1h.** This was prepared according to the procedure for preparation of **1g**, using trimethylsilylacetylene (2.1 g, 10 mol) instead of phenylacetylene to give colourless plates from hexane. Yield 3.1 g (80%), mp 138 °C; ν_{max}(KBr)/cm^{-1} 3250, 2170, 1330, and 1160; δ_H 0.28 (9 H, s), 3.00 (3 H, s), 7.09 (1 H, br), 7.13 (1 H, t, *J* 8.0), 7.35 (1 H, dt, *J* 8.0, 1.4), 7.46 (1 H, dd, *J* 8.0, 1.4), 7.58 (1 H, d, *J* 8.0); *m*/*z* 267 (M$^+$, 67%), 252 (100), 189 (66), and 158 (69) (Found: C, 53.85; H, 6.53; N, 5.13. $C_{12}H_{17}NOSSi$ requires C, 53.90; H, 6.41; N, 5.24%).

Ethyl 4-cyano-2-(phenylethynyl)phenylcarbamate 1k. To an MeOH (30 ml) solution of 30% H_2O_2 (2.0 ml) and 4-aminobenzonitrile (2.4 g, 20 mmol), I_2 (5.05 g, 12 mmol) in MeOH (50 ml) was added, and the reaction mixture was stirred for 4 h at room temperature. After addition of 6 M $Na_2S_2O_3$, the mixture was extracted with $CHCl_3$ and evaporated under reduced pressure. The residue was dissolved in pyridine (100 ml) and ethyl chlorocarbonate (2.18 g, 20 mmol) was added. After stirring for 1 h at room temperature, the reaction mixture was diluted with H_2O, extracted with $CHCl_3$, and evaporated under reduced pressure. Ethynylbenzene (300 mg, 2.97 mmol), CuI (52 mg, 0.27 mmol), $PdCl_2(PPh_3)_2$, and Et_3N (30 ml) were added to the residue and the mixture was stirred for 1 h at room temperature. The reaction mixture was evaporated under reduced pressure. The residue was diluted with H_2O, and extracted with $CHCl_3$. The $CHCl_3$ extract was dried over $MgSO_4$ and evaporated under reduced pressure. The residue was purified by silica gel column chromatography using hexane–AcOEt (10 : 1) as an eluent and recrystallized from Et_2O–hexane to give colourless needles. Yield 1.74 g (34%), mp 110 °C (Found: C, 74.46; H, 4.87; N, 9.61. $C_{17}H_{14}N_2O$ requires C, 74.47; H, 4.86; N, 9.65%); ν_{max}(KBr)/cm^{-1} 3400, 2225, and 1740; δ_H 1.35 (3 H, t, *J* 7.14), 4.28 (2 H, q, *J* 7.14), 7.41–7.61 (7 H, m), 7.75 (1 H, d, *J* 2.2), 8.34 (1 H, d, *J* 8.8); *m*/*z* 290 (M$^+$, 100%), 262 (5), 245 (10), 231 (30), 218 (51), and 190 (26) (Found: *m*/*z* 290.1054. Calc. for $C_{18}H_{14}N_2O_2$ 290.1054).

General procedure for the cyclization reaction of 2-ethynylanilines with TBAF

A mixture of a 2-ethynylaniline (1 mmol), TBAF (1 M soln. in THF, 2 or 3 mmol) and THF (5 ml) was refluxed or stirred at room temperature for the time shown in Tables 2 and 3. After removal of the THF, the residue was diluted with H_2O and extracted with AcOEt. The AcOEt extract was dried over $MgSO_4$ and evaporated. The residue was purified by silica gel column chromatography and/or recrystallization.

2-Phenylindole 2a. Colourless scales from hexane–AcOEt; mp 185–187 °C (lit.,[11] 187–188 °C); ν_{max}(KBr)/cm^{-1} 3445 and 1655; δ_H 6.83 (1H, dd, *J* 1.1, 1.9), 7.12 (1 H, dt, *J* 7.1, 1.1), 7.20 (1 H, dt, *J* 8.2, 1.1), 7.22–7.48 (4 H, m), 7.62–7.68 (3 H, m), 8.28–8.42 (1 H, br); *m*/*z* 193 (M$^+$, 100%) and 165 (19).

1-Ethoxycarbonyl-2-phenylindole 3c. Colourless viscous oil; δ_H 1.09 (3H, t, *J* 7.1), 4.24 (2 H, q, *J* 7.1), 6.60 (1 H, s), 7.24–7.46 (7 H, m), 7.56 (1 H, d, *J* 7.3), 8.20 (1 H, d, *J* 8.2); *m*/*z* 265 (M$^+$, 100%), 221 (10), 206 (44), 193 (72), and 165 (30) (Found: *m*/*z* 265.1087. Calc. for $C_{17}H_{15}NO_2$ 265.1102).

1-*tert*-Butoxycarbonyl-2-phenylindole 3d. Colourless scales from hexane–Et_2O; mp 75–76 °C (lit.,[12] 76–77 °C) (Found: C, 77.79; H, 6.50; N, 4.71. $C_{19}H_{19}NO$ requires C, 77.79; H, 6.53; N, 4.77%); ν_{max}(KBr)/cm^{-1}1720; δ_H 1.30 (9 H, s), 6.65 (1 H, s), 7.23–7.42 (7 H, m), 7.54 (1 H, d, *J* 8.2), 8.22 (1 H, d, *J* 8.2); *m*/*z* 293 (M$^+$, 22%), 237 (44), and 193 (100).

1-(2,2-Dimethylpropanoyl)-2-phenylindole 3e. Colourless viscous oil; ν_{max}(KBr)/cm^{-1} 1655; δ_H 1.39 (9 H, s), 6.14 (1 H, s), 7.20–7.26 (3 H, m), 7.29–7.41 (3 H, m), 7.57 (1 H, d, *J* 7.9), 7.69 (2 H, d, *J* 7.9); *m*/*z* 277 (M$^+$, 100%), 262 (18), 235 (19), 220 (33), and 193 (34) (Found 277.1445. Calc. for $C_{19}H_{19}NO$: 277.1466).

1-Methylsulfonyl-2-phenylindole 3g. Colourless needles from hexane–Et_2O; mp 115–116 °C (lit.,[6] 116–117 °C); ν_{max}(KBr)/cm^{-1} 1370; δ_H 2.74 (3 H, s), 6.73 (1 H, s), 7.35–7.45 (5 H, m), 7.56–7.63 (3 H, m), 8.15 (1 H, d, *J* 7.1); *m*/*z* 271 (M$^+$, 52%), 192 (100), and 165 (50) (Found 271.0662. Calc. for $C_{15}H_{13}NO_2S$: 271.0666).

5-Bromo-2-phenylindole 2i. Colourless scales from hexane; mp 196–198 °C (Found: C, 61.69; H, 3.72; N, 5.14. $C_{14}H_{10}BrN$ requires C, 61.79; H, 3.70; N, 5.15%); ν_{max}(KBr)/cm^{-1} 3430; δ_H 6.76 (1 H, s), 7.28 (2 H, s), 7.36 (1 H, d, *J* 7.4), 7.46 (2 H, t, *J* 7.4), 7.66 (2 H, d, *J* 7.4), 7.75 (1 H, s), 8.32–8.42 (1 H, br).

2-Phenyl-5-(2-phenylethynyl)indole 2j. Colourless scales from hexane–AcOEt; mp 225 °C (Found: C, 88.14; H, 5.11; N, 4.70. $C_{22}H_{15}N\cdot 1/3H_2O$ requires C, 88.27; H, 5.27; N, 4.68%); ν_{max}(KBr)/cm^{-1} 3420 and 2200; δ_H 6.83 (1 H, d, *J* 2), 7.25–7.40 (5 H, m), 7.46 (2 H, t, *J* 7.9), 7.56 (2 H, d, *J* 7.9), 7.68 (2 H, d, *J* 8.1), 7.85 (1 H, s), 8.39–8.44 (1 H, br); *m*/*z* 293 (M$^+$, 100%), 265 (5), 189 (8), and 146 (19) (Found: *m*/*z* 293.1196. Calc. for $C_{22}H_{15}N$: 293.1204).

5-Cyano-2-phenylindole 2k. Colourless needles from hexane; mp 195 °C (Found: C, 82.39; H, 4.81; N, 12.85. $C_{15}H_{10}N_2$ requires C, 82.55; H, 4.62; N, 12.84%); ν_{max}(KBr)/cm^{-1} 3320 and 2220; δ_H 6.88 (s, 1 H), 7.37–7.51 (m, 5 H), 7.68 (1 H, d, *J* 7.4), 7.98 (1 H, s), 8.60–8.72 (1 H, br); *m*/*z* 218 (M$^+$, 100%) and 190 (15).

6-Chloro-2-hexylindole 2l. Colourless scales from hexane; mp 178–180 °C (Found: C, 71.46; H, 7.75; N, 5.91. $C_{14}H_{18}ClN$ requires C, 71.33; H, 7.70; N, 5.94%); ν_{max}(KBr)/cm^{-1} 1730; δ_H 0.94 (3 H, t, *J* 7.3), 1.31–1.69 (17 H, m), 2.97 (2 H, t, *J* 8.0), 6.30 (1 H, s), 7.16 (1 H, d, *J* 8.4), 8.14 (1 H, s); *m*/*z* 235 (M$^+$, 40%), 178 (28), and 164 (100).

1-*tert*-Butoxycarbonyl-6-chloro-2-hexylindole 3l. Colourless plates from hexane; mp 78–79 °C (Found: C, 67.78; H, 7.79; N, 4.06. $C_{19}H_{18}ClNO_2$ requires C, 67.54; H, 7.80; N, 4.17%); ν_{max}(KBr)/cm^{-1} 3400; δ_H 0.82–1.75 (11 H, m), 2.72 (2 H, t, *J* 7.3), 6.20 (1 H, s), 7.02 (1 H, d, *J* 8.2), 7.27 (1 H, s), 7.40 (1 H, d, *J* 8.2), 7.80–7.94 (1 H, br); *m*/*z* 335 (M$^+$, 19%), 279 (66), and 57 (100).

Ethyl 3-indol-2-ylpropanoate 2m. Colourless scales from hexane; mp 82 °C (Found: C, 71.75; H, 7.03; N, 6.29. $C_{13}H_{15}NO_2$ requires C, 71.87; H, 6.96; N, 6.45%); δ_H 1.27 (3 H, t, *J* 7.3), 2.72 (2 H, t, *J* 6.7), 3.07 (2 H, t, *J* 6.7), 4.18 (2 H, q, *J* 7.3), 6.24 (1 H, s), 7.03–7.14 (2 H, m), 7.31 (1 H, d, *J* 7.5), 7.51 (1 H, d, *J* 7.5), 8.44–8.64 (1 H, br); *m*/*z* 217 (M$^+$, 80%), 171 (45), and 144 (100).

6-Methoxy-2-phenylindole 2n. Colourless scales from hexane–AcOEt; mp 171–172 °C (Found: C, 80.60; H, 5.87; N, 6.21. $C_{15}H_{13}NO$ requires C, 80.69; H, 5.87; N, 6.27%); ν_{max}(KBr)/cm^{-1} 3400; δ_H 3.87 (3H, s), 6.76 (1 H, d, *J* 1.5), 6.80 (1 H, dd, *J* 8.5, 2.1), 6.91 (1 H, d, *J* 1.5), 7.29 (1 H, t, *J* 7.1), 7.43 (2 H, t, *J* 7.1), 7.50 (1 H, d, *J* 8.5), 7.62 (2 H, d, *J* 7.14), 8.22–8.30 (1 H, br); *m*/*z* 223 (M$^+$, 100%) and 208 (91).

2-Butylindole 2o. Colourless liquid; bp 160 °C/3 mmHg (lit.,[5a] 155–160 °C/4 mmHg); ν_{max}(KBr)/cm^{-1} 3400; δ_H 0.95 (3 H, t, *J* 7.3), 1.42 (2 H, sextet, *J* 7.3), 1.71 (2 H, quintet, *J* 7.3), 2.76 (2 H, t, *J* 7.3), 6.23 (1 H, s), 7.06 (1 H, t, *J* 7.2), 7.13 (1 H, t, *J* 7.2), 7.31 (1 H, d, *J* 7.2), 7.53 (1 H, d, *J* 7.2), 7.80–7.92 (1 H, br); *m*/*z* 173 (M$^+$, 57%) and 130 (100).

1-Ethoxycarbonyl-2-butylindole 3o. White solid; bp 180–190 °C/3 mmHg, mp 35 °C (Found: C, 73.22; H, 7.77; N, 5.80. $C_{15}H_{19}NO_2$ requires C, 73.44; H, 7.81; N, 5.71%); ν_{max}(KBr)/cm^{-1} 1730; δ_H 0.97 (3 H, t, *J* 7.4), 1.49–1.51 (5 H, m), 1.64–1.74

(2 H, m), 3.01 (2 H, t, *J* 6.8), 4.52 (2 H, q, *J* 7.4), 6.37 (1 H, s), 7.17–7.24 (2 H, m), 7.44 (1 H, d, *J* 5.9), 8.11 (1 H, d, *J* 8.2); *m*/*z* 245 (M^+, 84%), 203 (100), 174 (29), and 130 (75).

Indole (Table 3, Entry 8). Colourless scales from EtOH; mp 54 °C (lit.,[13] 53 °C); ν_{max}(KBr)/cm^{-1} 3030 and 1700; δ_H 6.57 (1 H, s), 7.10–7.23 (4 H, m), 7.40 (1 H, d, *J* 8.2), 7.65 (1 H, d, *J* 7.7), 8.02–8.30 (1 H, br).

Reaction of 1h with TBAF at room temperature (Table 3, Entry 8)

According to the general procedure for the cyclization reaction of 2-ethynylanilines with TBAF, the mixture of **1h** (535 mg, 2 mmol) and TBAF (1 M soln in THF, 6 ml, 6 mmol) in THF (30 ml) was stirred at room temperature for 3 h. The reaction mixture was purified by silica gel column chromatography. The first eluent gave 1-methylsulfonylindole (**3q**) (200 mg, 51%) and the second eluent gave *N*-(2-ethynylphenyl)methanesulfonamide (**1p**) (180 mg, 46%). **3q**; colourless liquid; bp 170 °C/3 mmHg (lit.,[5] 140 °C/0.5 mmHg); δ_H 3.10 (3 H, s), 6.73 (1 H, d, *J* 3.6), 7.31 (1 H, t, *J* 7.5), 7.38 (1 H, t, *J* 7.5), 7.38 (1 H, d, *J* 3.6), 7.92 (1 H, d, *J* 7.3); *m*/*z* 195 (M^+, 51%) and 116 (100); **1p**; colourless needles from hexane; mp 105 °C (Found: C, 55.47; H, 4.69; N, 7.09. $C_9H_9NO_2S$ requires C, 55.37; H, 4.65; N, 7.17%); ν_{max}(KBr)/cm^{-1} 3300 and 2250; δ_H 3.03 (3 H, s), 3.50 (1 H, s), 6.98–7.06 (1 H, br), 7.14 (1 H, t, *J* 7.7), 7.40 (1 H, t, *J* 7.7), 7.46 (1 H, d, *J* 7.7), 7.62 (1 H, d, *J* 7.7).

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